STUDIES ON THE EFFECTS OF
DRUGS ON SLEEP

by

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Thesis presented for the Degree of Doctor of Philosophy in the University of Edinburgh.

May, 1969.
SUMMARY

Section 1: A brief review of the physiological and psychological difference of the two types of sleep, rapid eye movement (REM) and orthodox (NREM), is followed by a review of the evidence of a need for the each type. The effects of commonly used psychoactive drugs on sleep is reviewed with particular emphasis on the effects on REM sleep.

Section 2: Problems in the clinical evaluation of hypnotics are discussed.

Section 3:
A) The EEG sleep technique is outlined and the rationale of the experimental design is discussed. The experimental studies presented are summarised as follows.

B) Administration of 200mg. sodium amytal for a period of 3 weeks demonstrated that the sleep EEG technique was sensitive to REM sleep changes brought about by small doses of drug. It also demonstrated that withdrawal phenomena were apparent from small doses. The sleep of a patient dependent upon Tuinal was also studied. Discussion is centered on the clinical implications of the results. It is suggested that hypnotics allow sleep to be "borrowed" and that patients being withdrawn even from small dose and short courses of therapy should be supported.

C) In drug withdrawal there is not only an increase in the amount of REM sleep but an increase in the vividness of the patient's dreams. It has been shown that both these events are associated with an increased profusion of/
of eye movements during REM sleep. This study confirmed this latter finding during withdrawal from nitrazepam though a decrease in profusion during nitrazepam administration when REM time was not demonstrated.

D) The data in the literature on the effects of chlorpromazine on sleep are either incomplete or contradictory. This study demonstrated a dose-response effect of chlorpromazine on REM sleep: 25mg. suppressed and 100mg. enhanced REM sleep. It is argued that this could account for the seeming contradictions in previous studies. It is also pointed out that unlike many psychoactive drugs, chlorpromazine does not show an immediate increase of REM sleep on withdrawal, and that this is probably due to its slow clearance rate from body tissue. This lack of REM withdrawal increase may in part account for chlorpromazine's lack of clinical withdrawal effects.

E) A review of the history of the treatment of drug withdrawal states suggests that all the drugs used have in common the property of suppressing REM sleep. The effects of chlorpromazine and chlorpromethiazole, both commonly used in the treatment of drug withdrawal, were studied in barbiturate withdrawal. Both drugs blocked the REM sleep increase on stopping amytal administration. On stopping chlorpromazine, no REM sleep increase was observed over the 45 subsequent nights. Withdrawal of chlorpromethiazole however resulted in a small REM sleep increase i.e. this drug ameliorated the amytal withdrawal. It is suggested that these experiments give further evidence to the hypothesis of a common mechanism underlying REM sleep and the/
the paranoid delirium of drug withdrawal states.

F) It has been variously stated that withdrawal from the tricyclic antidepressants does not lead to a REM sleep increase. The sleep of three patients each of whom had taken an overdose of a tricyclic anti-depressant was monitored. A large increase in REM sleep was observed. In discussing this observation, it is pointed out that some slow brain recovery process must be operating to account for the slow return to normal of REM sleep values following withdrawal of many drugs. It is hypothesised that this involves intra-neuronal protein synthesis. The results are also relevant to the theory of the action of tricyclic antidepressants.

G) Anti-obesity drugs are amphetamine derivatives and amphetamine is a well-known disturber of sleep. However, fenfluramine is thought to have "sedative" rather than "stimulant" properties even though it is an amphetamine derivative. In a comparative study with several other amphetamine derivatives it was demonstrated that fenfluramine had both sedative and stimulant properties while the others were all more akin to amphetamine.

H) It has been suggested that drugs of addiction cause suppression of REM sleep followed by immediate withdrawal increase. However, there is no good evidence of the effects of the "hard" drugs. This study considered the effects of subcutaneously injected heroin in normal volunteers. It was found that there could be an immediate withdrawal REM increase but that this was subject to considerable individual differences. The results are discussed in the light of/
Evidence of altered protein synthesis during morphine tolerance.

I) On withdrawing sleeping pills from patients there are frequent complaints of bad sleep. In this study subjective estimates of sleep parameters were compared with EEG estimates and it was found that subjects were not accurate in their estimates. There was a greater divergence of the two measures during drug withdrawal than during the control period. The implications of these results for the design of clinical trials is discussed.

Section 4: A) The results of the experiments are discussed in terms of the hypothesis that drugs of addiction cause a suppression of REM sleep and an immediate REM sleep increase on withdrawal. 

B) In the experiments it was emphasised that return of REM sleep to pre-drug levels consequent to drug withdrawal takes several weeks. It is hypothesised that this time course reflects some slow repair process in the brain and that this is likely to involve intra-neuronal protein synthesis.

Co-operative Studies

The following studies, included in this thesis, were carried out jointly with Drs. I. Oswald and J.I. Evans.

1. A demonstration of the sensitivity of the sleep EEG technique and of its use with patients. (Section III.B).

2. Dose effects of chlorpromazine (Section III.D).

3. Two studies of the treatment of drug withdrawal (Section III.E).
4. Overdose of tricyclic antidepressants and deductions concerning their cerebral action. (Section III.F).

5. Heroin and human sleep (Section III.H).
INTRODUCTION

According to Roth (1964), the term "psychopharmakon" was first used by Reinhardus Lorichius of Hadamar. In 1548, Lorichius edited a collection of prayers of comfort in preparation for death under the title "Psychopharmakon, hoc est: medicine animae". However, the dawn of modern psychopharmacology was not until some four centuries later with the introduction of chlorpromazine in 1952. The "psychopharmakon" of the Renaissance and the twentieth century differ from each other in concept and meaning: the spiritual support in times of anxiety and fear has been largely replaced by drugs which "tranquillise" the agitated and brighten the depressed. Thus the pioneering discovery by Daley et al., (1952) of the usefulness of phenothiazines in schizophrenics, followed by the report of Loomer et al., (1957) of the anti-depressant effects of iproniazide and Kuhn's (1957) observation of the thymoleptic property of imipramine triggered the 'new look' in psychiatry. Subsequently numerous new psychopharmaka have been introduced. Parallel with this development, the interest in experimental behaviour research which began to utilise the newly discovered, or in some cases rediscovered, drugs grew rapidly. Coincident with this growth in the availability of psycho-active drugs was the work of Aserinsky and Kleitman (1953, 1956). Their observations of sleeping babies resulted in the reassertion that there were two types of sleep. While Kleitman and his colleagues, Aserinsky and Dement, made the distinction on the basis of eye movements/
Movements and associated brain electrical phenomena, McWilliams (1923) had suggested that there were two types of sleep on the basis of his studies of blood pressure changes during the sleep of cardiac patients. Even earlier, a Glasgow physician stated "Sleep exists in two states: in the complete and incomplete. The former is characterised by a torpor of the various organs which compose the brain, and by that of the external senses and voluntary motion. Incomplete sleep, or dreaming, is the active state of one or more of the cerebral organs while the remainder are in repose....." (McNish, 1838).

"Out of the mouths of babes......." is undoubtedly a truism. It may be paraphrased in the context of sleep to "out of the eyes of babes......." for no-one apparently was interested in considering sleep as anything other than a "temporary metaphysical death" until babies revealed their rapid eye movements. It appeared that at last the psychoanalyst had at his disposal a means of knowing when his patient was dreaming for Dement and Kleitman (1957) described the high incidence of dream recall obtained by waking a person when his eyes are moving. While there had been advances in the physiology of sleep with animals using modern implant electrode techniques, the impetus to study sleep in man came with Aserinsky's observation. The growth of psychopharmacological interest, the world-wide increase in the consumption of drugs to make people sleep or in smaller doses to allay their waking anxiety, and the new-found approach to the study of sleep in man all/
all contributed to the increasing flood of research papers on the effects of drugs on sleep. The studies included in this dissertation are but a drop in what Koella (1967) has called the "ever increasing 'hypoplethora'".
ACKNOWLEDGEMENTS

I would wish to express my considerable gratitude to many colleagues. My interest in sleep and in particular the effects of drugs on sleep stems from a chance meeting with Dr. Ralph Berger while still a very lowly undergraduate. At that time I was game to try anything and volunteered for sleep experiments. Gradually over the many visits to the sleep laboratory while Drs. Berger, Oswald, Evans and Priest stuck electrodes on my face and hypodermic needles in my rear - all in the course of science! - my interest was caught. When looking for a project for an undergraduate dissertation, Dr. Oswald became not only supervisor but mentor. With his infectious enthusiasm for sleep - in the research sense - it seemed logical that I should, after graduation, continue in this area of research. That enthusiasm has never failed to spur me on when often I have felt like giving up.

Dr. Evans and I have co-operated in several of the studies reported here and as testimony to the harmoniousness of the co-operation, several more are being planned. It is, however, impossible to acknowledge all who have helped, for much of the help has come from coffee and lunchtime discussions. Many of these discussions have helped clarify my ideas, some indirectly by causing confusion and forcing me to think again.

Over the past four years, I have been a "guest" in the Department of Psychiatry. As a non-clinical psychologist...
/psychologist, I was really an outsider. However, I was never made to feel anything less than a member of the Department. Credit for this must go to Professor Carstairs whose encouragement and hospitality were always freely available.

The deciphering of the manuscript and the typing of the end product of four years study has been borne by Miss C.M. Robb. Her knowledge of orthography coped admirably with my cecographical script.

It is customary to conclude acknowledgements with a courtesy reference to one's wife. In this instance, however, it is genuine appreciation of her long-suffering forebearance without a word of complaint. She has suffered a husband who, just after they were married, took an overdose of barbiturates and eventually spent a week as a 'junkie' — all for the sake of science! Not only that, she has had to suffer 'night starvation' on an average of two nights a week, on many occasions every night of the week and consequently an irascible spouse recovering from sleep deprivation.

"Then seal her eyelids, gentle sleep, whilst cares of her mine open keep, lock up, I say, those doors of day, which with the morn for lustre strive, that I may look on her, and live".
### IV. GENERAL DISCUSSION

| A. | Addictive Drugs cause Suppression of Paradoxical Sleep with Withdrawal Rebound | 127 |
| B. | Possible Mechanisms Involved in the Effects of Drugs on REM Sleep | 134 |

### EPILOGUE

### REFERENCES

**Published Papers**

1. Drug Withdrawal State: An EEG Sleep Study
2. Sleep and Barbiturates: some Experiments and Observations
3. Sleep Patterns during Afternoon Naps in the Young and Elderly.
4. Learning While Asleep.
To his bed.

My bed, the rest of all my cares,
the ende of toilyng paine;
Which bryngest ease and sollace sweetes,
while darknesse dooth remaine,
My bedde, yelde to me slumber sweet,
and triflyng dreams repell;
Cause carkyng care from sobbyng breast
to part, where it doeth dwell.
All mockeries of this wretched worlde,
put cleane from out my mynde:
Doe these, my bedde, and then by thee
much comfort shall I finde.

Translated from the Latin
of Dr. Haddon by Timothy Kendall,
1577.
I. SLEEP and DRUG EFFECTS: REVIEW
I.A.i. **TWO KINDS OF SLEEP**

The central tool of sleep research, the electroencephalogram, was available in the 1930s. At that time Loomis *et al.* (1957) described stages of sleep based on the presence or absence of the alpha rhythm and the amount of high voltage slow wave activity. However the realisation that sleep was not a unitary state arose from the pioneering work of Aserinsky, Kleitman and Dement (Aserinsky and Kleitman, 1953, 1955; Dement and Kleitman, 1957; Dement, 1958), though, in 1923, MacWilliam had hinted at the possibility from his studies of blood pressure changes during sleep.

There are available several reviews of the physiology and psychology of the two types of sleep (Oswald, 1962; Jouvet, 1965; Murray, 1965; Foulkes, 1966; Hartmann, 1967; Koella, 1967; Oswald, 1968).

The two states are commonly known as NREM (non-rapid eye movement), orthodox, fore-brain or slow-wave sleep and as REM (rapid eye movement), paradoxical, hind-brain or "fast" sleep. (Hartmann (1967) lists some 32 synonyms for this latter state). Terms such as "light" and "deep" have been used based on studies of arousal threshold but as the terms are relative and since the EEG features of the two states would reverse the terminology, the terms have now been largely dropped.

NREM or orthodox sleep is characterised by EEG slow waves and spindles and in man is customarily divided into stages 1, 2, 3 and 4 (Rechtschaffen and Kales, 1968). The state is characterised by regularity of respiration, heart/
/heart rate and blood pressure; the skeletal musculature is greatly but not fully relaxed; the eye balls are motionless or at most have a slow rolling motion and mental life is mundane and described as "thinking".

If subjects are wakened from REM or paradoxical sleep, they more often categorise their immediately preceding mental life as "dreaming", the descriptions being much less reality orientated, more vivid and lengthier. Research in this area has served to illustrate the primary process thinking of dream work (Berger, 1963). Perhaps because of this association with emotional experience, REM sleep has proved so fascinating that orthodox sleep tends to have been neglected.

The EEG during REM sleep is of low voltage, in man containing much slower frequencies than waking but in the cat closely resembling wakefulness, being made up chiefly of 4-10 c/sec. waves. The rapid, jerky, saccadic-like movements of the eyes occur in intermittent bursts and are commonly preceded by a second or two of 2-3 c/sec. "saw-tooth" waves. In the cat the bursts of eye movements are associated with ponto-geniculo-occipital (PGO) spikes. Each period of REM sleep in man lasts about 20 minutes and the two types of sleep alternate throughout the night with a REM sleep periodicity of about 90 mins. This type of sleep accounts for approximately 23% of all human nocturnal sleep. It is interesting to note that although the sleep-wakefulness cycle can be altered fairly readily, the ultradian rhythm of REM-NREM sleep appears to be particularly stable (e.g. Baekeland, 1967; Fisher, 1967).
If NREM sleep is characterised by regularity, then REM sleep is characterised by irregularity. Heart rate, respiration and blood pressure are each subject to sharp and frequent fluctuations during REM sleep (Snyder, 1963; Snyder et al., 1964). Although in REM sleep brief major body movements are more frequent than in NREM sleep (Oswald, et al., 1963), the loss of muscle tone is otherwise much more profound (Berger, 1961; Jacobson et al., 1964). More detailed study has shown this loss in muscle tone to be a representation of paralysis caused by descending inhibitory impulses acting on the spinal anterior horn cells (Pompeiano, 1967), causing a loss of electrically induced reflexes (Hodes and Dement, 1965) in man in whom the inhibitory impulses are carried by the anterior columns (Shimizu et al., 1966).

Cerebral blood flow and temperature also show changes in REM sleep. Blood flow in some sub-cortical region is much greater than during wakefulness (Baust, 1967; Reivich, et al., 1968). Likewise, cerebral temperature at REM onset shows a more sudden rise than does the onset of wakefulness. Conversely, the start of NREM sleep is accompanied by a fall in temperature to below waking levels (Kawamura and Sawyer, 1965). A further concomitant of REM sleep is penile erection in the male and increased vaginal blood flow in the female (Shapiro et al., 1968) though this latter finding is perhaps questionable in view of the technique used. (Attempts to observe vulval temperature changes in the Edinburgh Laboratory have not been successful for technical reasons).
I.A.ii. The Need for Each Type of Sleep

Sleep has, since the time of Hippocrates, been considered to have a restitutive function. The differences between the two types of sleep might be considered to be suggestive of their subserving different, albeit unknown, restitutive functions. Whatever the function of sleep, experimental evidence certainly points to there being a need for each type. The results of the first such study was interpreted as being indicative of a "need to dream" rather than as a "need for REM sleep". Dement (1960) woke subjects every time a REM period started and kept them awake for a couple of minutes before allowing them to go back to sleep. Since NREM sleep always precedes REM sleep, except in certain special cases such as narcolepsy (Rechtschaffen et al., 1963; Hishikawa et al., 1968), the subjects became progressively and selectively deprived of REM sleep. As a consequence, the REM sleep periodicity became shorter, as if there was a build up in REM "pressure". When normal, undisturbed sleep was again permitted, a greater than base-line proportion of the night was spent in REM sleep. This continued for several nights and over these nights the percentage of REM sleep gradually returned to base-line values, as if what had been lost had been made up. A similar disturbing procedure was carried out during NREM sleep when no subsequent compensation was observed. These findings have been amply confirmed in both humans and animals but in no study has it been shown that more than a fraction of the loss is retrieved. This is in distinction to the findings on recovery from/
from pharmacological REM deprivation where the "rebound" accounts for more than 100% of the loss. (These studies will be described in later sections of this introduction and the implications of the differences in section IV.)

Evidence for specific need is not confined to REM sleep. NREM sleep is commonly divided into stages as mentioned previously. The four stages are not evenly distributed throughout the night, stage 4 being almost wholly confined to the first four hours of sleep. This alone would suggest that there is some urgent priority of whatever function this stage of sleep may serve. Total sleep deprivation leads, as mentioned above, on recovery nights to an excess of REM sleep. 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; Williams et al., 1964). Again this is suggestive of restorative priority. People totally deprived of sleep are, naturally, very sleepy as are those being withdrawn from amphetamine. However, it is worth noting at this point, that unlike behavioural deprivation subjects, withdrawal from amphetamine leads to an immediate REM sleep excess (Oswald and Thacore, 1963).

Comparable to the selective deprivation of REM sleep is the study by Agnew et al. (1964). Every time a subject entered NREM stage 4 sleep he was deliberately nudged out of this stage. The disturbance was not sufficient to arouse him and he therefore became selectively deprived of stage 4 sleep. As with REM sleep deprivation, there was subsequent excess of this NREM sleep stage.
On the basis of the amount and amplitude of slow wave activity and changes in the arousal threshold, it can be argued that the NREM sleep stages lie on a continuum of depth or possibly "worthwhileness" of NREM sleep. If this were so then it would follow that loss of stages 2 and 3 would lead to an increase in stage 4 by way of rapid and non-specific compensation. To test this hypothesis, Dement and Greenberg (1966) restricted sleep over a period of several nights to about 5 hours nightly. (Normally after 5 hours NREM sleep is almost entirely made up of stage 1, 2 and 3). The procedure had the predicted effect of increasing the absolute duration of stage 4 in the night and they suggested that stage 4 "is worth more" than stage 2. Similar observations have been made by others (Webb and Agnew, 1965) and (Baekeland and Lasky, 1966) have shown that physical exercise promotes stage 4.

There is thus evidence that both kinds of sleep are necessary. That lack may subserve a different function is evidence in the statement by Williams and Williams (1966): "a chronic deficit in stage REM leads to personality disorders, whereas chronic loss of slow-wave sleep (i.e. stages 3 and 4) leads to impaired performance." Studies of such effects are in their infancy and many of the studies of performance change due to sleep loss have been carried out without EEG control (Wilkinson, et al., 1966). One study (Williams and Williams, 1966) studied the effects of sleep deprivation on performance after classifying subjects as "restless" or "quiet" sleepers on the basis of the EEG profiles. Those/
Those called "restless" sleepers, i.e. those with a smaller amount of stage 3 and 4, more body movements, more awakenings, more transitions from stage to stage and longer sleep latencies, had a greater performance decrement after sleep deprivation. Despite the differences between the groups, it was found that all subjects within a group had highly systematic sleep stage cycles and that for both groups the within cycle stage sequence formed a Markov chain of at least order 1. It is not unreasonable then to suggest that if a drug were to distort the normal proportions of the two kinds of sleep, or the stages of NREM sleep alone, the effect could properly be regarded as an undesirable or adverse one. Examples of both kinds of distortion will be outlined below.

I.A.iii. Measures of the two kinds of sleep.

Having suggested that drugs affect the amount and type of the two kinds of sleep, it would be appropriate to give a general outline of the technique and measures used in the assessment of drug effects on sleep. In many fields of psychological study the effect of novelty is well known and steps are taken to counteract the "false" results obtained from the subject in a novel situation. So it is in sleep research. It is generally accepted that results from the first night in the laboratory should be discarded. It has been shown that novelty this night gives rise to an increased number of awakenings and a reduction in REM sleep (Agnew et al., 1966; Mandela and Hawkins, 1967).

The experimental paradigm most commonly used is one involving the recording of a series of base-line or pre-drug/
/pre-drug nights to give a measure of a subject's variability and mean percent REM. A small number of investigators have considered not just the "on" effect of the drug but also its "off" effect. Although it is desirable to follow through this withdrawal period, it can persist for many weeks and demand on labour and time can often preclude this phase of the study. There are many non-specific effects of experimental adaptation and so a late series of base-line records would be desirable recorded many months after the "off" effects have stopped. However, as nearly all subjects are volunteers the practical difficulties of maintaining them at a base-line condition i.e. abstention from alcohol and late nights over a period prior to the recordings, is difficult. These same problems are present during the whole of the experimental period and it is therefore unlikely that the ideal in experimental control is ever achieved.

A further problem is that few studies of drug effects on sleep utilise anyone other than normal healthy volunteers. It is not inconceivable that effects such as anxiety or depression interact with the drug to modify the latter's effect on sleep. For example, Akindele (1969) in a study of phenelzine in normal volunteers, found that this drug increased the amount of stage 2 sleep in the whole night and that stage 2 time gradually returned to normal values. However, in a depressed patient, Akindele found that the amount of stage 2 sleep initially was reduced. With continued administration of phenelzine there was not just a return to control values but a large overshoot which gradually subsided.
Whether this is a function of the depressive illness or of the individual is unclear but it would be more likely that the effect found by Akindela in the patient was an interaction between the drug and the illness. The interaction may possibly be mediated through some alteration in biogenic amine metabolism (Ashcroft et al., 1966).

There are now internationally recommended schemes for the recording and scoring of all-night EEG and eye-movement records, (Rechtschaffen and Kalas, 1968), which will be described in a later section. The concomitant recording of muscle tonus can assist in the discrimination of REM and NREM periods (Berger, 1963; Jacobson et al., 1964).

Heart rate and body temperature normally fall during sleep (Feinberg, 1965); skin electrical resistance normally rises during sleep (Monroe, 1967). Simultaneous recording of these variables would also be worthwhile in the assessment of an hypnotic for there is evidence to suggest that what is subjectively "poor" sleep is associated with a lesser fall of heart rate and body temperature and, paradoxically, with a greater rise of skin resistance than in sleep subjectively assessed as "good" (Monroe, 1967). However, it has to be borne in mind that the more paraphanalia that is plastered about the subject, the more anxiety provoking is the situation and hence the further removed from 'normal' sleep is the record. This is of course with the proviso that laboratory sleep is different from home sleep anyway, as shown by the finding that 'home' dreams are "spicier" than those recorded in the laboratory (Domhoff, 1967).
The common feature of all studies, be they physiological or behavioural, using drugs and live subjects, is the presence of a placebo period. While it is undoubtedly preferable to give subjects blank medications on base-line nights, there has been widespread agreement amongst sleep researchers that suggestion influences the REM and NREM distribution minimally. Deliberate attempts to try to effect the proportion of REM sleep by means of a reward gave a positive but very small effect (Rechtschaffen and Verdene, 1964).

In all the studies reported here, the whole night's sleep was recorded. This naturally gave maximum information but in some instances the essential information can be obtained from only the first 2 or 3 hours of sleep. While a subject is taking barbiturates, for example, the REM time for the early part of the night is low while in withdrawal the proportion of REM sleep is very high (Oswald and Priest, 1965). Further, as will be shown in the study of amphetamine derivatives reported here, some drug effects can be masked when whole night data is considered in isolation. This is presumably due to a rapid fall in active drug levels due either to rapid metabolism and excretion or to the dose administered being small. Equally of course the effects of a drug which is slowly absorbed will not be observed in the early part of the night.

Where subjects are used as their own controls, as is the usual paradigm, there are few problems in interpreting the changes in say percent REM, during or after drug/
/drug administration. Standard statistical methods, with minor modifications, can be used as is demonstrated in the study of dose effects of chlorpromazine reported here. Studies using patients, however, often depend on a large element of opportunism as patients are often only briefly available and there can be little hope of achieving a neat experimental design. In such cases, arbitrary limits of normality may be useful.

A mean of 23 percent is usually taken as normal and the published results from many laboratories have shown remarkable uniformity. However, the range of normality is difficult to assess as there is a lack of published information. Furthermore, it was not until after several studies had been published using normal subjects that it was appreciated that the effects of drugs, including alcohol, exerted an influence for more than a short time. If studies prior to this appreciation are taken into consideration the upper end of normality can be extended into what is now regarded as abnormal. Equally, the lower end of the range can be extended by the incorporation of results from short nights. It would appear from the normal records produced in the Edinburgh Laboratory that the total sleep time is related to absolute REM time in a sigmoid fashion, with the linear relationship existing between about 290 minutes and 490 minutes of total sleep (unpublished observations).

In 1963, Oswald and Thacore suggested a lower time limit to the first eye movement of the night from the first sleep spindle of the night. This they claimed was unlikely to be less than 45 minutes more than once or twice per/
per hundred records. Although this delay or latency is negatively correlated with REM percent, it is not a one-to-one relationships. The delay is certainly increased with the administration of hypnotics when REM time is low and conversely is lowered when hypnotics are withdrawn and REM time high. However, the frequency distribution of this parameter is bimodal, the first mode being around 60 minutes and the second around 110 minutes and there have been many instances in the laboratory's experience when either of these delays have been obtained and the difference in REM percent of the order of 1 or 2 percent (Lewis and Oswald, unpublished observations). Nevertheless, it does appear that the delay to the first REM period of the night is sensitive to increased REM times. For instance, it has been reported that it is shortened in occasional cases of severe depression (Mendels and Hawkins, 1968) or chronic insomnia, occasional cases of schizophrenia and organic dementia (Feinberg, 1967) or drug withdrawal delirium (Greenberg and Pearlman, 1967; Evans and Lewis, 1968). The reliability of this lower limit of 45 minutes can be judged from the fact that the laboratory has recently reviewed 185 recent normal recordings in which only 3 instances of the delay being less than 45 minutes were found 36, 38 and 42 mins respectively (cf. Oswald and Thacore, 1963), in which there was every confidence in the subjects not having had alcohol or sleeping pills or anything else of like nature in the weeks preceeding these records. Similar findings have been reported from other laboratories./
Rechtschaffen and his colleagues, reporting on 80 normal records found the shortest delay to the first REM period to be 46 minutes (Rechtschaffen and Verdons, 1964). They state elsewhere that "according to our knowledge of nocturnal sleep, subjects do not have REM periods before 45 minutes of NREM sleep have elapsed", (Maron et al., 1964). While Rechtschaffen was speaking of nocturnal sleep, it would appear that the value of 45 minutes held also for napping sleep (Maron et al., 1964; Lewis, 1969). It is possible that the limit set is relevant only to young adults as it is this group of people who have been most often studied. Feinberg et al., (1967) who have studied the elderly, reports some short latencies though Kales et al., (1967) do not. However, in any study using elderly people, there is a greater risk of there being contamination from drugs as the proportion of the population taking pharmaceutical preparations for sleep increases markedly after age 45 (McGhie and Russell, 1962). The sensitivity of the parameter to prior drug taking may be one of its drawbacks in clinical studies as shortened latencies have been reported up to 3 weeks after stopping barbiturates (Oswald and Priest, 1965).
Heptobarbitone 400mg orally reduced the amount of paradoxical sleep when the drug was taken at bedtime (Oswald et al., 1963). Not only did the drug reduce the proportion of REM sleep, it also reduced the number of eye movements per unit time. (Actually, no-one has attempted to give a drug during the day, say first thing in the morning, and observe the effect on the night’s sleep. Would there be a rebound in both these measures of suppressed REM sleep?) Using pentobarbitone, Baekeland (1967) while confirming the resultant depressed REM sleep, pointed out that the periodicity in the cyclic alternation of the two kinds of sleep appear unaffected. In other words, REM sleep appeared in the night when it was expected but each appearance was of shortened duration. Confirmation of unaltered underlying cyclic activity has been given by Fisher (1967) who showed that the penile erections of REM sleep may appear at the expected times despite depression of eye movements and other signs of REM sleep.

Longitudinal studies of the effects of drugs on sleep are costly of both time and energy. Consequently, such studies have tended to use only two or three subjects. Such a study was that of Oswald and Priest (1965) in which the effects of administration and withdrawal of up to 600mg amyllobarbitone was considered in two young adults. The return to "normal" REM percent was described over a three week period of drug administration. On withdrawal there were abnormally short delays to the first REM period associated with high REM percentages, especially in the/
In the early part of the night. The sleep of the two subjects was not thought to return to normal (i.e., pre-drug) until some five weeks after stopping the amytal. Three nights of 100mg. pentobarbitone also leads to a similar REM "rebound" on withdrawal (Kales et al., 1968).

As mentioned, Oswald et al. (1963) reported a reduction in the number of eye movements per se during heptobarbitone administration. The withdrawal of barbiturates leads not only to an increase in the amount of REM sleep in the night but also to an increase above base-line in the number of eye movements per unit time (Kales, 1969; Oswald, 1969). There is therefore a physiological increase in REM intensity. Moreover, there is in the immediate drug withdrawal period an increase in the psychic phenomenon of which REM sleep is a concomitant, i.e. dreaming, for at this time dreams are more vivid and frequently described as nightmares (Kales and Jacobson, 1967; Oswald and Priest, 1965). Thus in drug withdrawal there is a physiological and psychological increase in intensity of REM sleep manifest as increased amount of paradoxical sleep, increased number of eye movement and increased intensity of dreams.
Chlorpromazine and thioridazine are often employed as hypnotics especially in geriatric practice, and when used as tranquillizers it is not uncommon to find that the patient complains of sleepiness. Yet evidence of their intimate effects on sleep are sparse and, possibly because the effects may be dose related, what reports as are available are conflicting.

If isolated clinical case reports are excluded, then consideration is confined to chlorpromazine. This phenothiazine in one study (Toyoda, 1964) was given in doses of 12.5 to 50mg, to 8 subjects. An increase in REM sleep was reported especially in two neurotic patients. There can be many criticisms of this study. For the two neurotic patients, no past history of chemotherapy is given and in particular no mention is made of whether or not hypnotics had previously been given. This obviously raises the possibility of a withdrawal state existing. Further, the sleep of all eight subjects is compared to a single night of placebo only. In six subjects this single night was the first night in the laboratory and hence an abnormally low REM time would be probable (Agnew et al., 1966; Mendels and Hawkins, 1967). Nevertheless, Toyoda’s conclusion that REM sleep time is increased with chlorpromazine is consistent with the findings of Lester and Guerrero-Figueroa (1966). They found that 100mg. chlorpromazine given orally decreased the delay to the first REM period and increased the length of the first REM period. These two phenomena, as discussed above, can be associated/
associated with raised percent REM sleep in the whole night and so it is probable that, at least in the early part of the night, chlorpromazine enhances REM sleep. Although theirs was a carefully controlled study, it is unfortunate that Lester and Guerrero-Figueroa did not record over the full night as it is possible that this early night enhancement of REM sleep was due to a small dose before full absorption had taken place (III.D). However, there is evidence from animal studies (Hishikawa et al., 1965) that 2mg/kg (something of the order of 140mg, equivalent for an adult male) can shorten the latency to REM sleep. At the same time, Hishikawa et al., (1965), Jewett and Norton (1966) and Jouvet (1967) all present evidence that large doses of chlorpromazine can reduce REM sleep time over the full night in the cat.
Barbiturates and amphetamines have long been considered to have opposite effects: barbiturates are hypnotics, amphetamines stimulants. The appearance on the market of mixtures of barbiturates and amphetamines e.g. Drinamyl, therefore appeared nonsensical. However, studies on the effects of amphetamines on sleep brought to light some similarities of action.

The induction of wakefulness by amphetamines is legendary. There are many stories, no doubt apocryphal, of students before examinations, taking Dexedrine so that they might work throughout the night but the clearest indication of their sleep preventing action was provided by Kornetsky et al. (1959). Williams et al., (1959) had demonstrated that sleep loss caused measurable impairment in vigilance tasks and that in tasks where the rate of working was imposed by the experimenter errors of omission were frequent. "Microsleeps" were hypothesised as the cause for these brief falls in vigilance, which falls in turn lead to errors. 15mg. dextro-amphetamine, however, halved the impairment in "paced" tasks following 68 hours of sleep loss and in "unpaced" tasks the impairment was abolished (Kornetsky et al., 1959). The student, before examinations is working in a situation which is a mixture of a "paced" and "unpaced" task and probably will gain reasonable return for his all-night vigil. However, unless more amphetamine is taken the next morning he is liable to be in a withdrawal state which with amphetamine is lethargy and apathy; his night's work will have been to no avail.
Rechtschaffen and Maron (1964) using 10 volunteers demonstrated that 10 or 15mg. dextro-amphetamine increased the delay to the first REM period, decreased the proportion of REM sleep and increased the number of body movements. The results were complicated however, by the drug's disturbing effect. Two subjects did not reach the criterion of 75 minutes sleep with no awakenings of 5 minutes or more. It could be argued then that amphetamine per se did not reduce REM sleep but that the reduction was due to increased sleep disturbance. To overcome the problem of increased wakefulness and general disturbance during sleep, these workers gave other subjects pentobarbitone 100mg. during the control period and a mixture of dextro-amphetamine 15mg. and pentobarbitone 100mg. During the control period REM sleep averaged 18.4% but only 9% when amphetamine was added. The REM sleep decrease could therefore not be accounted for in terms of increased sleep disturbance. This conclusion has been confirmed by Baskeland (1967).

Withdrawal of barbiturates and other hypnotics characteristically decrease total sleep time but withdrawal of amphetamine, a mixture of amphetamine and amylobarbitone (Drinamyl) or phenmetrazine hydrochloride (Preludin) increases total sleep time. The effect of withdrawal of any of these drugs, like barbiturates increases REM percent and decreases the latency to the first REM period. Re-administration of the drugs immediately abolished these abnormalities and when medication is again withheld, the abnormalities persist for up to 2 months. These observations were made on/
on patients with long-standing addiction to the drugs by Oswald and Thacore (1963) who also noted that when the patients were first recorded the REM percent was normal. It is interesting to note at this point that Kales et al., (1969a, b) have found that in patients addicted to glutethimide, pentobarbitone or Tuinal, the first recordings show a percent REM sleep at the lower limit of normal, about 15%.

In a small-scale withdrawal study of phenmetrazine, using normal volunteers, Oswald et al., (1960) confirmed the rebound of REM sleep. Included in this study was a derivative of amphetamine, diethylpropion (Tenuate) which has been used as an anorexiant, as have many other amphetamine derivatives. This too on withdrawal resulted in all the signs of REM rebound. Administration of diethylpropion 50mg. to normal volunteers resulted in NREM sleep disturbance similar to those found with amphetamine. It was also found that not only was there increased awakening, there was an increase over placebo in the number of shifts from all other stages to NREM sleep stage 1 (drowsiness). Fenfluramine, on the other hand, in equivalent anorexic dose to diethylpropion disturbed sleep only in that it increased the number of shifts to, and amount of time in, stage 1 sleep. It did not affect REM sleep or the number of brief awakenings. Also unlike other amphetamine derivatives, there are no reports in the literature of addiction to fenfluramine even though it has been on the European market for several years. (Munroe et al., 1966).

Another new amphetamine derivative to be marketed/
/marketed as an anti-obesity agent is (Meta-
trifluoromethylphenyl)-1 [p(benzoyloxy) ethyl] -amine-2
propane, (JP992). A preliminary study of this drug
suggested that it was like fenfluramine in that it did not
affect REM sleep in the whole night. However, closer
analysis demonstrated a REM suppressant effect in the early
part of the night with intra-night rebound (Oswald, 1969a).

The effects of two other amphetamine derivatives on
sleep have been studied. A tranylcypramine (Parnate)
addict was studied by Oswald and his colleagues (Le Gassicka
et al., 1965), when it was found that this patient frequently
had no REM sleep after taking the drug but showed a rebound
increase of up to 75% on withdrawal. As with all studies
of patients addicted to drugs it is often difficult to assess
the validity of all but the general results as patients
frequently have their own supplies of the drug. However,
both the REM suppressant effect of tranylcypramine and
rebound increase in withdrawal have been confirmed (Cramer
and Ohlmeier, 1967; Rechtschaffen, 1968). Methylphenidate
hydrochloride (Ritalin) also suppresses REM sleep,
(Baekeland, 1966), but no information is available about
its withdrawal though presumably there would be a rebound.
I.E. TRICYCLIC ANTI-DEPRESSANTS

Imipramine (Tofranil) has been shown to decrease REM sleep in man and to enhance EEG sleep spindles in orthodox sleep (Toyoda, 1964). Delayed onset of the first REM period, reduced REM percent and increased total sleep time have been described in cats (Hishikawa et al., 1965) and rabbits (Khazan and Sawyer, 1966) with imipramine. There would appear to be no dose effects as Hishikawa's study considered dose of 4mg/kg and 2mg/kg imipramine in an excellent study using 5 animals and many recording periods. Desmethyliminipramine (Perfofran) on the other hand would seem to have some dose relationship, 4mg/kg showing all three of the effects found with imipramine while half the dose did not increase total sleep time (Hishikawa et al., 1965). Jouvat (1967) without stating the number of animals or the number or duration of recordings, mentions a suppression of REM sleep in the cat with 5-10 mg/kg imipramine and also states that there is no subsequent rebound on withdrawal. Amitriptyline (Tryptizol) withdrawal too, it has been suggested, is not associated with REM increase though 75mg. nocte does reduce the amount and delay the appearance of REM sleep (Hartmann, 1968).

The REM depressant effect of desmethyliminipramine found by Hishikawa et al., (1965) in cats has been confirmed in humans, given 25mg. t.i.d. for four consecutive days (Zung, 1969). The study used 17 adults and compared 4 consecutive drug nights to an equal number of control nights recorded prior to administration of desmethyliminipramine. Zung also found that stage 4 was increased with the drug/
drug and that there was a reduction in the number of intervening periods of wakefulness.

The most important clinical use of these drugs is in the treatment of depression but both imipramine and desmethyliimipramine have been suggested for the treatment of idiopathic narcolepsy (Hishikawa, et al., 1966). The patient with idiopathic narcolepsy is liable to fall asleep directly into REM sleep. There is debate as to whether the appearance of REM sleep without prior orthodox sleep is dependent on the concurrence of cataplexy with narcolepsy (Roth, 1969). Without discussing this area of sleep research further, it is as well to recall that during REM sleep there is a paralysis of most skeletal musculature (Jacobson et al., 1964). It has been proposed that the cataplectic attacks of the narcoleptic represent a partial REM sleep state and it has been found that imipramine and desmethyliimipramine are effective in reducing the cataplectic aspect of the sleep attack though they do not reduce the full sleep attack (Hishikawa et al., 1966).
MORPHINE

The opium alkaloids have been used since time immemorial to induce sleep. They were the early therapeutic agents used in the treatment of drug withdrawal delirium. (This aspect of these drugs will be discussed in a later section). Despite this long recognition of their ability to induce sleep, there is singularly little information about the EEG aspects of these alkaloids on sleep.

Khazan et al., (1967) using rats on a self-maintained morphine addiction schedule described an initial reduction of all sleep and an almost total elimination of all REM sleep. Tolerance was demonstrated to be almost complete after three days. Unfortunately, these workers did not consider the withdrawal period. However, Kay et al., (1968) using humans (post-addicts from the Drug Addiction Research Center, Lexington) found readministration of morphine depressed REM sleep and withdrawal resulted in what he called "a delayed REMs rebound".

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I.G. \textbf{ALCOHOL}

Ethyl alcohol in substantial doses (1g/kg) reduces REM sleep in man (Gresham \textit{et al.}, 1963). Using the same dose of alcohol in 3 men over 5 successive nights, Yules \textit{et al.}, (1966) found a reduction in REM sleep on the first night and a rise on subsequent nights. This study gives the only data which suggests that REM sleep can show an "escape" phenomenon. Normally continued administration of a drug leads to REM percent returning to and remaining at pre-drug levels and an excess of REM sleep is only found on stopping the drug. However, in the Yules \textit{et al.} study, one man had a REM time of 50% on the fifth night of alcohol administration. No satisfactory explanation of this finding can be given and it is an isolated instance though there is a report of occasional high REM times in heavy drinkers taking alcohol during the day (Greenberg and Pearlman, 1967). Rebound of REM sleep was observed in all three subjects in this study when no alcohol was given on the sixth night.

The study by Knowles \textit{et al.}, (1968) is interesting in that it mimics in the experimental setting a common drinking pattern. These workers had subjects take alcohol for one or two nights, stop for a night or two and restart alcohol again repeating this pattern several times. As would be expected, on the nights when no alcohol was taken an excess of REM sleep was apparent and the re-administration of alcohol reduced REM sleep. The data available from this study does not indicate whether the rebounds become/
/become successively smaller or whether on drug nights there was any tendency, despite intervening withdrawal, for REM time to return to normal values.
In common with barbiturates, nitrazepam (Mogadon) 15mg. reduced the signs of REM sleep (Oswald and Priest, 1965; Oswald and Haider, personal communication) though there is a report to the contrary (Tissot, 1965). However, details of the experimental procedure in this last study are not at all clear. Glutethimide (Doriden) and methypyrilone (Noludar) were studied in doses of 500mg. and 300mg. respectively (Kales et al., 1968) and were found also to reduce REM sleep as has been found with meprobamate (Equanil) (Freeman et al., 1965; Oswald et al., 1969). Chloral hydrate, one of the older hypnotics, on the other hand, is said to have little effect on REM sleep (Kales et al., 1968).

Withdrawal studies have been carried out on all the above drugs except chloral hydrate. Although drug administration has been for a variable length of time, from 3 to 14 nights, withdrawal of nitrazepam, glutethimide or methypyrilone results in an excess of REM sleep. Unfortunately, the full extent of the rebound is not known except for nitrazepam which has been the most adequately studied. It was noted that during the rebound from nitrazepam there was a decreased delay to the first REM period and that it took several weeks for REM sleep to return to pre-drug levels. A decreased delay to the first REM period has also been noted for nitrazepam by Lob et al., (1966) in 12 psychoneurotic patients. Although Lob et al., did not find an overall reduction in REM sleep it should be mentioned that their single drug night was subsequent/
/subsequent to a single placebo night. The arguments against such a procedure have been discussed.

In common with barbiturate withdrawal, nightmares were a feature of the immediate post-drug period with nitrazepam (Oswald, 1965) and methyprylon (Kales et al., 1968).

Two other benzodiazepine derivatives have been studied: chlordiazepoxide (Librium) and Ro5-6901 (Dalmane). 10 normal adult volunteers were used and the doses were 100mg. chlordiazepoxide and 30mg. Ro5-6901 (Hartmann, 1968). No significant effects were found with either drug when compared with 5 placebo nights. However, larger doses may have lead to significant effects on REM sleep since the results obtained by Hartmann indicated an increase in delay to REM sleep of 30 minutes and a decreased percent REM sleep with both drugs in comparison with placebo. Kales et al. (1969c) too have reported that there is no significant affect on REM sleep with 30mg. Ro5-6901 but a larger dose did decrease the proportion of this type of sleep in the whole night.
II. THE ASSESSMENT OF HYPNOTICS

The division between hypnotics and tranquillisers seems to be one of dose for many of the drugs used as hypnotics are also prescribed in smaller doses to reduce daytime anxiety. Like nearly all chemotherapeutic agents, their popularity is subject to fashion. Methylpentynol (Dormison) for example, no longer enjoys the vogue of 15 years ago; thalidomide has made a somewhat less than gracious exit; while barbiturates have retained pride of place, chloral derivatives in solid form have gained some popularity. There are several non-barbiturates now in common use, e.g. glutethimide (Doriden), methyprylon (Noludar), ethchlorvinol (Arvynol) methaqualone (Quaalude), nitrazepam (Megadon) and increasingly a mixture of methaqualone and diphenhydramine (Mandrax).
II. The Assessment of Hypnotics
II.A. THE CLINICAL ASSESSMENT

The advent of the Dunlop Committee has, it is to be hoped, introduced a considerable degree of reliability and standardisation into the pre-clinical testing of drugs. However, when it comes to the controlled double-blind trial in which neither the patient nor the immediate medical or nursing staff are supposed to know whether the patient has received placebo or an active drug, either the experimental drug or a standard, there is still much that is open to criticism. In practice the ideal of a completely "blind" study is not achieved for a variety of reasons which have been discussed by Joyce (1963). They include the patients' ability to distinguish on the basis of taste between the placebo and the active tablet. Though the trials of Exton-Smith et al., (1963) and of Parsons (1963) are well designed, they will be taken as examples to illustrate some of the problems of clinical trials.

On the grounds that the function of hypnotics is symptomatic treatment, Exton-Smith gave the greatest weight to the patient's overall assessment of his night's sleep. Four drugs - amobarbitone, 200mg., dichloralphenazone, 1.3g., promazine resinate, 50mg., and meprobamate 800mg. - were compared with each other and with placebo. They were administered in random order by the day nursing staff while the night nurses made hourly assessments for the presence of sleep. The 65 patients were in a female geriatric unit and were co-operative enough at 8.00 a.m. to answer questions put by the day nurses about their previous night's sleep. None were receiving daytime sedatives and all were/
were intelligent enough to mark a four-point rating scale. The nurses used the same scale to describe the patient's sleep.

The patients showed a significant preference for dichloralphenazone and for meprobamate while the nurses' scores showed similarity between all four drugs compared with placebo, although only promazine and meprobamate were significantly different from placebo. An additional finding was that both the nurses' and the patients' ratings suggested a progressive improvement in sleep over the five nights. Further, there was a correspondence between what the patients called a good night and what the nurses called a good night. This would not be expected since it is well known that clearly defined categories on a rating scale of something as subjective as sleep tend not to have the same meaning for two individuals. The agreement obtained by Exton-Smith may have been due to there being only four categories.

The morning hangover experienced by the patients after amylobarbitone resulted in an adverse report and so the authors concluded that, for elderly patients at least, the barbiturate, though inducing sleep, was not a satisfactory hypnotic.

Parsons (1963) concluded from his study that there were no clinical grounds for distinguishing between long-, intermediate-, and short-acting barbiturates. This categorisation had been suggested from animal studies. The technique of Parsons was radically different to that used by Exton-Smith for instead of using a rating scale,
The method of paired comparisons was employed. One of two "identical white tablets" was given on successive nights. After the second, the patient was asked to state "On which of the last two nights did you have the better sleep?" and "Have you had any hangover on waking after either of these two days?". There were six successive paired comparisons. Trial one found that quinalbarbitone 100mg. was preferred to placebo, while the second suggested that there was no important difference between 100mg. quinalbarbitone and 100mg. phenobarbitone. The overall conclusion was that at a dose of 100mg. there were no differences between phenobarbitone, butobarbitone, and quinalbarbitone though the three barbiturates could be placed in the order butobarbitone, phenobarbitone and quinalbarbitone in terms of increasing likelihood of morning hangover.

It is at this point appropriate to comment on the problem of rating. As mentioned, what is a "good night's sleep" to one individual may only be a moderately good night for another. In an attempt to remove the restrictions implied by the label, Aitken et al., (1969) have used an analogue scale. They have found that having nurses and patients mark a 100mm line with only the extremes labelled as "best" and "worst" that there is no distinction between amylobarbitone and nitrazepam in the eyes of either patient or nurse. The rationale for the use of this analogue scale has been outlined by Aitken (1969).
II.B. LIMITATIONS

i) The time of evaluation. Few demands are made on peoples’ skills and initiative immediately after waking in the morning yet it is common in clinical trials of hypnotics to have a patient assess his night’s sleep at 8.00 a.m. and to take no more interest in the patient – from the trial point of view – until 8.00 a.m. the next morning. This approach to clinical trials persists despite increasing information about the more prolonged and subtle effects of hypnotics and tranquillizers on human skills. For example, Kornetsky et al. (1959a) using nurses’ assessments found chlorpromazine either 100mg. or 200mg. and quinalbarbitone 200mg. significantly increased sleep time compared with placebo. Although there were apparently no noticeable effects of the drug once the patient was awake in the morning, his performance on the digit-symbol substitution test, symbol copying test, and tapping were all still significantly impaired at lunch-time i.e. 14-15 hours after drug administration.

With the ever increasing proportion of the population taking hypnotics and day-time tranquillizers, it is becoming more and more imperative that clinical trials of hypnotics do not merely ask about the patient’s sleep, but that they start considering what the effect of the drug will be on such skills as driving during the following day. The typical approach of the clinical drug trial is illustrated by Parsons (1963) when he states that “the resumption of sleep after breakfast has not been included as hangover because the patients did not usually consider it unpleasant.”
It has not yet become recognised in the medical profession at large that there are modern behavioural techniques of assessing the extent of impaired performance after small amounts of drug (Summerfield, 1964).

ii) **Coma Potential.** The pharmaceutical industry and the clinician take considerable cognisance of the LD<sub>50</sub>, the ED<sub>50</sub> and the difference between these values, of a drug. What they tend not to take into consideration to the same extent is the ease with which a drug will induce coma and the ease with which the tissue drug level can be artificially reduced. These considerations are increasingly important in the assessment of hypnotics and tranquillizers, as well as many other classes of drug, with the increasing incidence of self-administered non-fatal overdose. In Edinburgh, its frequency has increased about tenfold in as many years (Matthew, 1966). The rise has been roughly the same in Western Australia (Oswald, 1966). Since coma caused by phenobarbitone has a much greater duration than coma after an equivalent hypnotic dose of an intermediate-acting barbiturate, it is regrettable that authors such as Parsons should encourage the prescription of phenobarbitone as an hypnotic. The duration of a coma is related to the rate of elimination of the drug and Butler *et al.*, (1954) using human subjects reported that the phenobarbitone eliminated from plasma in the course of 24 hours represented only 11-23 percent.

iii) **Non-independence of successive nights.** Another assumption of the usual clinical trial is that successive nights and successive drugs are independent of one another. Although Exton-Smith *et al.*, (1963) made no comment about/
prior therapy of the patients, it was clear that over five nights of the trial there was some complicated interaction since both nurses and patients reported a progressive improvement in sleep over these nights. Tolerance to hypnotics is well known and EEG sleep studies would suggest that there is probably cross-tolerance. Belleville and Fraser (1957), using nurses' assessment of the patients' sleep, found that within 10 days there was some degree of tolerance to quinalbarbitone and pentobarbitone. They also found that there was no significant difference between control and drug sleep time after the 30th day of administration.

There is no reason to suppose that all the changes in the EEG features of sleep indicating disturbance on drug withdrawal described in section I would not be apparent after a single dose. As a consequence, in the standard clinical trial on which placebo nights are randomly interspersed with the nights on which the active drug is given, the night with placebo will be reported as "bad" as a direct result of active tablets on preceding nights. Since the majority of patients included in any trial will have been receiving hypnotics for some time, merely having the placebo first in every case will not help.

iv) The patient's report. Lasagna (1954) has pointed out that "subjective evaluation (of sleep) is important, if for no other reason than that the clinical use of hypnotic agents is most frequently concerned with alleviation of patients' complaints". While this is undoubtedly true, subjective evaluation may not be the most appropriate/
appropriate standard. For example, a report of "good" sleep after, say, heroin would not be taken as a recommendation for its widespread nightly employment.

The patient's introspective report of "bad" sleep when her sleeping pills are stopped must be held responsible for the majority of the so-called therapeutic addiction to hypnotic drugs. Dependence on sleeping pills is well documented, for example: barbiturates, glutethamide, methylpropion, ethchlorvinol, bromureide hypnotics, methaqualone, meprobamate and to drugs such as chlordiazepoxide more commonly used for daytime sedation.

The sense of satisfaction expressed by patients may not be due to improved sleep but to the anxiety-reducing properties which are characteristic of drugs which have hypnotic and dependence-inducing actions. This sense of "well-being" was shown with secobarbital 100mg. by Smith and Beecher (1960) who found that the impaired performance of college athletes was subjectively perceived as unusually good. It is not unreasonable then to suggest that the patient with significant quantities of barbiturate in their nervous system at 8:00 a.m. would attribute objectively unwarranted merit to their sleep.

As more sensitive psychological tools become available for the study of the abstinence syndrome there is likely to develop a situation analogous to that which arose with EEG sleep studies of withdrawal. It has been variously stated that clinically observable withdrawal signs only follow fairly heavy dosage of barbiturates (Fraser, 1957)/
(Fraser, 1957) and that 0.2g daily of pentobarbitone for a year results in no signs of an abstinence syndrome. Yet, it will be shown that 200mg. amylobarbitone for 3 weeks gives rise to a significant withdrawal effect in REM sleep.

v) Observer judgement. The usual procedure used by nurses when assessing sleep is to make observations at intervals of about one hour throughout the night, using such cues as respiration and stillness to determine the presence or absence of sleep. However, there are flaws in this technique. For example, heroin has long been thought to induce a "deep" sleep but using EEG techniques it can be shown that heroin in fact causes a considerable disturbance of sleep. However, taken overall, provided the nurses genuinely have no knowledge of whether an active drug was administered, these nurse evaluations must be taken as valid even if rather crude. In the Exton-Smith et al., (1963) study, tablets of different sizes were used; patients are very liable to comment on the size, colour, shape and taste of their tablets. A study of accuracy of nurses' assessments in relation to all-night EEG records is needed. It is possible that nurses could be trained to become better assessors by using the EEG to determine the type of sleep and then have the nurse observe the patient in the light of this knowledge.

vi) Other limitations. Exton-Smith et al., (1963) rightly pointed out that their results applied to elderly patients only. Elderly patients have often been quoted as showing a poor response to barbiturates especially in terms of morning hangover and confusion. Chlorpromazine and/
and thioridazine, both of which have been reported as effective hypnotics and are not known to be dependence-inducing, may give a lower incidence of unpleasant side-effects in the elderly.

Patients are individuals but little attention is given to individual differences in clinical trials. Costello and Smith (1963) reported that, according to nurses' ratings, equal doses of "sedatives" were more effective in prolonging sleep in introverts than in extroverts (who in any case slept longer without drugs).
II.C. **SOME OTHER TECHNIQUES OF ASSESSMENT**

The greater the objectivity and reliability desired in the assessment of an hypnotic, the greater is the amount of apparatus required. While EEG techniques give the greatest amount of information about the effect of a drug on sleep, the technique is laborious and not applicable to large numbers of subjects. Compromising between the rating approach and the EEG approach have been studies using body motility. This technique is based on the fact that in general, people in bed asleep move less than those in bed awake. Hinton (1963) in comparing 6 barbiturates and placebo pointed out that there were very large individual differences and that these were often in excess of inter-drug differences. Oswald *et al.* (1963) compared body motility discrimination of heptobarbitone 400mg. and placebo with EEG discrimination. Both methods of assessment were used simultaneously. It was found that body motility discriminated feebly while the EEG discrimination was much more sensitive.

One of the most unusual and intriguing behavioural techniques devised for the assessment of length of action of an hypnotic is that used by Isaacs (1957). He persuaded volunteers to drink a considerable quantity of cold water before retiring to bed. The measure of hypnotic effect was the difference in the length of time before the subject had to waken to empty his bladder after placebo and after the hypnotic. There would seem to be many imponderable intervening variables in this/
this technique and so far as can be ascertained no-one else has made use of the method.
III. THE EXPERIMENTAL STUDIES
III.A: GENERAL METHODOLOGY

The subjects who took part in these studies were, unless otherwise stated, male adults of good physical and mental health. All were over 21 years of age and none was chosen because he considered himself to be a "good" or "poor" sleeper. Indeed, none was ever asked about their sleep prior to their inclusion in an experiment.

All subjects were volunteers obtained most often from the senior medical undergraduate population of the University and senior design students of Napier Technical College. The usual procedure was that following a lecture on sleep given by the author or one of his supervisors, the names of those willing to take part in a study of the effects of drugs on sleep were obtained. It was pointed out that the drugs used were in common clinical use and that throughout the period of the study subjects would have to refrain from taking any drugs, including alcohol, other than the experimental one and to maintain reasonably regular bed-times. They were also told that they would be paid for their co-operation. Since co-operation was so essential, particularly since some of the studies lasted many weeks, they were paid thirty shillings per recording.

Before a subject was finally included in a study, he was informally interviewed by one of the research team to assess his personality and motivation.

There are several reports suggesting that volunteers are "different" to non-volunteers though the exact nature/
/nature of the differences seem to depend on the nature of the experiment, the perceived role of the person calling for the volunteers and the method of asking for the volunteers. These studies have been reviewed by Rosenthal (1965). From the review by Lewis (1968) it is apparent that, as would be expected, personality influences dream content as does mental ill-health. However, there is no evidence available to suggest that variations within normal personalities effects the EEG sleep patterns, though it would of course be expected that the more anxious the individual, the longer they would take to settle to sleeping in the laboratory. This would give rise to a prolongation of the first-night effect as it is described by Agnew et al. (1966). The first-night effect results in a lowered proportion of % REM sleep and of stage 3 + 4 sleep, increased proportions of stage 1 and stage 2 sleep and an increased number of shifts to stage 1 or wakefulness.

As part of a study not reported here, 19 of the subjects included in the current series of studies completed the 16 Personality Factor (16PF) questionnaire forms A and B. The mean profile for these subjects is shown opposite and it is seen that apart from factor B (intelligence) these subjects have scores within the normal range on all factors. The high score on factor B is to be expected since the subjects were university students. It can also be seen that they were not anxious, the second-order factor. Subjects reported to the laboratory in the late evening when silver disc electrodes were attached to the frontal/
/frontal bosses and outer canthi for eye movement monitoring. Electrodes in the mid-line, \( F_z - C_z - P_z \) distribution of the international 10/20 system of electrode placement, gave a global EEG record while electrodes over the submental muscles were occasionally used to record muscle tone (fig. 1). The subjects retired to a dark, quiet air-conditioned bedroom and data collection was continuous from approximately 23.30 hrs to 06.00 hours. In all experiments the electroencephalograph used was a 14-channel Alvar-Reega XIV.

Over a period of several weeks prior to any experimental manipulation baseline records were obtained. Despite the comment earlier about the lack of placebo response, dummy tablets were administered during this baseline period. Subjects were instructed to keep regular hours and to refrain from taking any drugs, including alcohol, from at least two days prior to the first control record till the end of the end of the experiment. The first record for every subject was discarded in view of the first-night effect.

During drug administration, recordings were taken on successive nights or at intervals as indicated in the details of each experiment. The drug was given routinely half an hour prior to retiring and on non-recording nights subjects were asked to take the drug at approximately the same time, keep the same hours and not to nap during the day.

All records were read page by page and analysed according to the international criteria (Rechtschaffen and Kales, 1968). Examples of the two types of sleep, REM and
FIGURE 1
Position of electrodes.

**EOG:** Right and left outer canthus to contralateral frontal boss.

**EEG:** Frontal boss to anterior scalp ($F_z$).

**EEG:** Anterior scalp ($F_z$) to posterior scalp ($P_z$).

**EMG:** Submental region.

**Heart rate:** Carotid artery.
/and NREM, are shown in Fig. 2. Briefly, the criteria for the NREM stages of sleep are as follows:

Stage 1: A low voltage desynchronised EEG with slow rolling eye movements.

Stage 2: A low voltage EEG record containing some theta activity, high-voltage slow wave complexes and sleep spindles. There are no eye movements.

Stages 3 and 4: The general features of these two stages are as in stage 2 but a minimum of 20% of any epoch is occupied by high voltage (greater than 75 uV) delta and theta waves. The differentiation of stage 3 and stage 4 is based on the amount of this high voltage slow wave activity.

Three other measures obtainable from the EEG were also noted. They were:

a) The delay to sleep onset: this was the time in minutes from the start of the recording which was coincident with switching out the lights, to the first spindle (a fusiform burst of 14 c.p.s. waves) of the night.

b) The Total Sleep Time was the time in minutes from the first spindle of the night to the end of the recording excluding any periods of wakefulness (indicated by the EEG) of 20 seconds or more.

c) The delay to the first REM period of the night was the time from the first spindle of the night to the first eye movement of the first REM period excluding any periods of wakefulness of 20 seconds or more.

The reading of EEG records is notoriously subjective. Although the international scoring criteria for sleep records was rigidly adhered to, an ad hoc check was kept on scoring. In experiments where a great many records were obtained, each record was read as soon as possible after the end of the recording session. There could theoretically be regular shifts in the scoring criteria. To overcome this,
FIGURE 2  Two Kinds of Sleep

Upper traces demonstrate the presence of EEG slow waves and spindles, the lack of eye movements, the presence of muscle tone and the regularity of the heart rate in NREM sleep.

Lower traces demonstrate the low voltage fast EEG, rapid eye movements, loss of muscle tone and irregularity of the heart rate of REM sleep.
This, a previously read record was reread blind and the re-scoring checked for consistency. Any discrepancies were discussed with colleagues. Further, during the course of any study, occasional records were read simultaneously by the author and a colleague. Any disagreements as to the exact point of change of sleep stage was resolved. In shorter experiments, no record was read until the completion of the study after which records were read in random order.
III. Ai.ii. RATIONALE OF THE EXPERIMENTAL DESIGN

The general design of most of the studies reported here is an intensive one, i.e. a design using repeated measures on one or at most a few subjects. The other general model of research is the extensive design in which the basic unit of variability is the individual subject. In the completely randomised design, for example, the percentage of patients who improve on drug A can be compared with the corresponding percentage in a presumably matched group of patients on drug B. There are many variations of this extensive design, the most common being a simple cross-over design.

Just as the extensive model is based upon variation between subjects, with average and percentage relating to the group, the intensive model is based on within-subject averages. An intensive design for the purpose of testing a drug effect with respect to a given subject will therefore consist of a sequence of treatment weeks and corresponding observations over a period of perhaps several months. One of the major limitations of extensive designs lies in its general failure to relate treatment effects to the individual and therefore to associate drug effects with contingent subject-characteristics. The question then arises as to what design would enable the investigator to determine whether a true drug effect, as distinct from a placebo or related effect, had taken place within a given individual.

In an attempt to answer this question, the example will be taken of a clinician in practice trying to decide whether a newly administered medication is effective in a given patient. Assume that the patient has been on an/
an older medication for some time with no apparent effect. He is transferred to some new drug and an assessment of any improvement is made. If there is improvement then it may be decided that this is possible evidence of an efficacious pharmacological activity of the drug in that patient. There must however, be the reservation that the patient may have improved over the treatment period without the drug. If there is sustained improvement, then the physician may decide to withdraw medication with the idea that it is no longer required (or perhaps never was). If the patient now relapses and is put back on to the drug with contingent improvement, then this can be taken as additional evidence of the effectiveness of the drug. Of course, the improvement may still be a placebo reaction or some related phenomenon such as physician expectation and the communication of this expectation to the patient as has been argued by Shapiro (1968). In the controlled clinical research setting, such effects can be substantially counter-balanced by using successive alterations of treatment sequence within a double-blind framework. This in essence represents the technique of intensive design applied to drug evaluation.

Assuming that the above procedure yields a statistically significant drug effect over placebo, then several points have been demonstrated which are qualitatively different from the same result obtained by an extensive design./
First, it has been demonstrated with statistical validity that a true effect has taken place in a particular patient. With the extensive model it is logically impossible to specify any given patient in the test-medication group as having benefited from the pharmacological properties of the medication. This is because there is no way of distinguishing from among the test group those whose improvement took place on a pharmacological basis and those who improved by mechanisms through which improvement took place in the control group. Hence, the characteristic of patient specification of the intensive model overcomes one of the major difficulties of the extensive, or patient-group averaging approach. The degree of heterogeneity of patient-characteristics generally makes it difficult to narrow down patient-variables associated with a significant effect in a clinical investigation based upon an extensive model. However, in the individual case, all the relevant and identifiable patient-characteristics in whose context the effect took place can be specified. An excellent example of the use of the intensive design is the study by Smith (1963) of the treatment of narcolepsy.

The vagueness of the population about which inferences from an extensive design sample can be drawn in terms of subsequent applications is one of the weaknesses of the design. The opposite argument against the over-specification of the population of the intensive study, to the extent that statistical inferences are strictly valid only with/
/with respect to the single case itself is of course correct. However, if the intensive design data are considered as a function of all patients relevant characteristics (and a random component), then the statistical population with which the single case is identified can in theory be defined in terms of these characteristics. To the extent that no two patients can possibly have exactly the same set of characteristics which may be considered a priori as relevant, no two such populations can be said to be identical. However, in the clinical setting and in the process of learning from experience, it is not usual to demand that the present patient's relevant variables all be identical to those of the earlier patients whose treatment is being used as a precedent. The decisions are necessarily based on similarities, rather than complete identities. That is, with respect to the single-case population, the application of the results of the sampling of such a population to other single-case populations must be performed in terms of similarities of relevant characteristics. From the point of view of purposeful research design, the systematic application of the intensive model to increasing numbers of subjects selected for similarities and dissimilarities in particular patient characteristics then becomes a logical-statistical approach toward identifying the factors most relevant to the success of a given treatment in terms of the a priori hypothesis.

Hence, the population of reference from the intensive/
/intensive data of the single case is so well specified that it is ideal for the testing of hypotheses, concerning treatment effects in relation to the influence of various specific subject-characteristics, with a directness which can hardly be approached in the use of the extensive model.

Despite the points that have been made with regard to the two approached there is often the feeling that there must be particular merit in the extensive design simply on the basis that the hypotheses tested in the extensive model are relevant to a "whole population" of cases and are based on a sample of 50 or 100 subjects. Conclusions concerning treatment effect, it is argued, based on the intensive design apply to just one, or, at most, a few cases. It is to be remembered in this connection that a significant effect obtained in an extensive model may actually reflect a true effect in a very few subjects. Thus it may take 50 subjects to demonstrate a true differential treatment effect in just one, two, three or four subjects and again which these particular subjects are is unknown.

Sleep research should turn to the intensive model but for practical reasons this is not always possible. The study of the effects of amylobarbitone sodium and nitrazepam on sleep by Oswald and Priest (1965) demonstrated that there is a residual effect of the drug on REM sleep lasting for many weeks after the last dose of the drug. This is the rebound phenomenon. The majority of the studies reported here are particularly concerned with the/
the rebound phenomenon. To study this fully, yet taking into consideration economy of time, labour and cost and subject co-operation, it is possible to consider only one placebo-drug-placebo sequence. Such a sequence usually occupies a minimum of six weeks. If, on the other hand, the concern is not with the rebound but is with the immediate effects of the drug, it is more likely that the intensive design would be a viable one. However, the prolonged sequelae to any administration again raises problems other than those of cost and co-operation. For example, administration of a drug on a second occasion too soon after the first period of administration means that it is acting in a situation of high REM sleep times. Its apparent immediate effect in terms of magnitude is therefore going to be altered. Even if sufficient time is left between the first and second drug periods for the rebound to have disappeared, it is still likely that the effect of the drug will not be the same on both occasions. This is possible since it has been shown for some drugs using measures other than sleep, that one dose of the drug will alter the physiological response to the drug though not necessarily the behavioural response. The most expedient design therefore, is one using a few subjects studied over a prolonged period of time. Such an approach permits consideration of both drug effects and withdrawal effects.
It has been mentioned that prior to any drug administration, several placebo-night records are obtained. If the proportions of REM sleep over these nights showed a trend conclusions about the effects of the drug would have to take this into consideration. To test for this, a trend analysis (Winer, 1962) was carried out on the percent REM sleep over the four base-line nights of 12 subjects. The F-ratios for the various components were:

i) Linear $F = 1.03$ (df 1,44)
ii) Quadratic $F = 2.05$ (df 1,44)
iii) Cubic $F = 12.01$ (df 1,44)

Only the cubic component is significant ($p < 0.01$) but since there are only four points on the abcissa, the result has no meaning as a cubic equation can always be fitted to four points.

A similar analysis was carried out for three other subjects for whom there was data for five control nights. The F-ratios were as follows:

i) Linear $F = 1$ (df 1,10)
ii) Quadratic $F = 2.15$ (df 1,10)
iii) Cubic $F = 1$ (df 1,10)
iv) Quartic $F = 1.40$ (df 1,10)

The conclusion therefore must be that no trend exists in the base-line proportion of REM sleep.

A further problem inherent in the analysis of the results is that REM time in minutes is related to the total sleep time as shown by a product-moment correlation of $+0.45$ obtained from 80 control records. To take account of any change in total sleep time due to drug/
/drug administration, an analysis of covariance would be appropriate. However, the data available in each study is limited and so a correction was made by calculating the expected REM time from a regression equation. From the 80 control records the regression equation was found to be

\[
Y = 0.2609 \times (X) - 11.3
\]

where \(Y\) is the expected REM time and \(X\) the observed total sleep time.

The 80 control records were composed of four records from each of 20 subjects and each datum point for the regression equation was the mean of these four records.

For the records from which this equation was obtained, the mean difference between expected and observed REM time was, of course, zero. The expected REM time for each subject in the present study was calculated from the total sleep time for each night both on and off the drug.

Also, the mean difference between observed and expected REM time for all control nights for each subject was calculated. Hence the comparison for the assessment of change due to drug administration or withdrawal was between the mean control night (observed - expected) REM time and the corresponding mean difference for the drug or withdrawal nights.

Therefore, to test the null hypothesis that drug has no effect, a t-test for correlated means is used in which the estimate of variance is:

\[
\frac{n(\sum D_i^2) - (\sum D_i)^2}{n^2(n-1)}
\]

where \(D_i = \bar{D}_i - \bar{C}_i\) and \(\bar{D}_i\) and \(\bar{C}_i\) are the mean \((R_{obs} - R_{exp})\) differences for the drug (or withdrawal) and control nights respectively for the \(i\)th person.
III. B. A demonstration of the sensitivity of the sleep EEG technique and of its use with patients.

In the past decade drugs have become the focus of attention of many groups in society. Doctors have become more aware of their side-effects, prolonged actions, effects on foetal development, and the possibility of addiction and overdose. Society has become anxious over the questions of abuse and addiction, and these anxieties have produced a number of standing committees in an effort to control this complex problem. The need for such control is apparent even when the quantity of drugs consumed for therapeutic reasons is appreciated. Ministry of Health (1964) statistics show that hypnotics, analgesics, and tranquillizers constitute 22.6% of all prescriptions. Of this group barbiturates are the largest contributors, making up 8.1% of all prescriptions, and the amount increases annually. Other indices confirm the increasing use and abuse of these drugs. Overdosage by hypnotics has increased steadily as a means of attempting suicide (Kessel, 1965), and delirium due to abrupt withdrawal is a frequent hazard (James, 1963).

Many doctors were taught that whatever else they could not do for their patients they could at least provide sleep. This expectation seems to have passed on to the patients, as doctors often complain that they feel under pressure to prescribe hypnotics.

One of the criticisms of the study of barbiturates on sleep by Oswald and Priest (1965) is that the dose used, up to 600mg, is in excess of that normally taken by the/
THE non-hospitalised patient. This study considered
the effects of a more usual "general practitioner" dose.

III. Bi. Study of a low dose of sodium amytyal on human sleep.

Experiment 1

Two female subjects were used as their own controls.
Over a period of six weeks seven baseline recordings were
made at irregular intervals. Subjects then received 200mg.
of sodium amylobarbitone at 23.00 hours each night for 26 nights.
Recordings were taken at intervals over the next two weeks
until all variables were within the normal range. During
the initial 15 days of the withdrawal period 8 recordings
were obtained (Fig. 4).

Results

The immediate effect of the drug was to decrease
the delay to sleep and prolong the total sleep time (Fig. 4).
REM sleep was depressed (Fig. 4) and orthodox sleep was
enhanced. REM sleep continued below the baseline for five
nights. Tolerance then occurred and REM values rose to
baseline values or a little above it. The rise above
the baseline was not statistically significant. During
this period of tolerance the drug still promoted and enhanced
orthodox sleep so that total sleep time remained raised.
The delay to the first REM period was increased by the drug
though gradually returning to pre-drug levels with continued
drug administration. When the barbiturate was stopped,
total sleep time fell abruptly for the first three nights
and the delay to sleep was prolonged. The delay to the
first REM period became abnormally short (less than 45/
Effect of sodium amylo barbitone 200mg. on the paradoxical sleep of two subjects.

Effects of Sodium Amylobarbitone 200mg. nocte on sleep of two female subjects.
/45 minutes) during this period, and REM sleep was increased - up to 31% of the night. The proportion of REM sleep subsided towards baseline levels in a fluctuant manner over the next fortnight.

III. Bii. The effects of chronic use of Tuinal on sleep.

This subject had been taking 600mg. of Tuinal nocte (quinalbarbitone sodium 300mg. and amylobarbitone sodium 300mg.). Over a period of three years after a hospital admission for treatment of a post-gastrectomy anaemia he had built up his consumption from 200mg. to 600mg. of this drug. He reported that after several months at each dose level the drug "lost effect" and he had had to increase the dose. When he tried to stop the drug he claimed that he did not sleep at all. The recording procedure was as previously outlined though no drug-free baseline nights were possible.

During the experiment the subject was asked to estimate his delay to sleep and total sleep time.

Results

While taking drugs this subject slept between 90 and 100% of the time available (Fig. 5). He regularly underestimated his total sleep and similarly over-estimated his delay to sleep by a regular amount (Figs. 5 & 6). Percent REM sleep was consistently at low normal levels (Fig. 7). On night 12, the drugs were stopped. The amount of REM sleep doubled and the first REM sleep period was abnormally early. Total sleep time fell to 76% of that available and the number of awakenings increased. The delay to sleep was over 90/
Total Sleep Time in a man addicted to Tuinal expressed as a percentage of total available time for sleep.

Solid line: EEG estimate of total sleep time.
Dotted line: Subjective estimate of total sleep time.
FIGURE 6. Delay to Sleep Onset and Number of Awakenings in a man addicted to Tuinal.

Solid line: EEG estimate of the delay to sleep onset.
Dotted line: Subjective estimate of the delay to sleep onset.

The number of awakenings were calculated from the EEG.
FIGURE 7  REM Sleep in a man addicted to Tuinal. Note the low normal % REM sleep at the start of the graph despite the fact that the patient had been taking Tuinal continuously for 3 years.
This disturbed night caused the subject to maintain adamantly that he had not slept at all. Over the next three nights of withdrawal, REM sleep remained increased, and the delay to sleep continued to be increased and total sleep time remained shortened. The subject continued to under-estimate seriously the extent of his sleep and complained of fatigue and restlessness. His REM sleep was very intense; not only were the periods of REM sleep longer but the eye movements themselves were more intense even on simple inspection. This increase in "activity" has been shown to occur in withdrawal from other hypnotics (III.C). Under these circumstances nightmares have been shown to occur (Oswald and Priest, 1965; Evans and Oswald, 1966).

At the subject's request the hypnotics were restarted at night 16. The amount of REM sleep fell to its former low normal level, and total sleep time and delay to sleep onset returned to previous drug night values. The subject's estimates returned to their previous reasonably accurate level.

Hypnotics were stopped again at night 20. The effects were similar to the previous withdrawal period and the irregularity of the onset of delay to sleep and total sleep time continued while the REM time remained raised, though fluctuating, between high normal and frankly abnormal values.

Discussion

These experiments demonstrate the effects of barbiturates as well as some of the problems which accompany their use. A single tablet of sodium amylobarbitone promotes the early/
early onset of sleep and enhances NREM sleep while depressing REM sleep. The body responds immediately and attempts to restore the amount of REM sleep to normal values. After a week on the drugs the principal effects are in shortening the delay to sleep and promoting continuous sleep. However, even while the drug continues there are times when the delay to sleep increases, total sleep time falls and REM time is raised above the baseline. Though in III.Bi this tendency was not severe, an "escape" phenomenon of this type may be the reason why patients increase the dose of hypnotics. Greenberg and Pearlman (1967) in their work on alcohol, which is very similar to barbiturates in its effect on sleep, also found that REM time could increase after a period of suppression though the alcohol continued in full doses. It is possible that over a longer period total sleep time would fall and delay to sleep increase, as patients report (Belleville and Fraser, 1957).

It is interesting to note that chronic use of hypnotics over years appears to result in an incomplete recovery in REM time since the proportion of REM sleep in the patient was low normal. Similar findings have been reported by Kales et al. (1969b) from two subjects also taking Tuinal. These results are in contrast to the findings with short term use of hypnotics are reported here and by Oswald and Priest (1965). While this persistent low normal REM percent may be a feature of patients' psychopathology or due to incomplete tolerance, no entirely satisfactory explanation can be offered.
Stopping the drug allows the overswing of REM sleep. This is experienced as an increase in intensity of dreams by the patient, who may suffer from frightening dreams and frequently wakes up during REM periods. The REM activity, increase in the delay to sleep, and number of awakenings lead to a serious under-estimate of the quantity of sleep, and the situation where the patients complain of total insomnia, while relatives or nurses differ in their opinion.

The temptation is to restart the tablets at the same or higher dose, and this, as seen in III.Bii, puts the patient back to previous drug values. However, while the withdrawal effect of 200mg. of sodium amylobarbitone takes almost two weeks to clear, Oswald and Priest (1965) found that 600mg. of sodium amylobarbitone took five weeks to subside. Thus, by increasing the dose of hypnotics the patient's eventual withdrawal state will be prolonged. Although there is an end to these withdrawal effects the patient's desire to return to the drug is understandable.

If tolerance and withdrawal are the hallmark of addiction, then only one tablet taken for a week could be considered addicting. However, the withdrawal is not severe. Serious withdrawal problems are not likely to occur until 800mg. to 1 g. of barbiturate is being regularly consumed. The literature confirms that almost all hypnotics, if taken in sufficient dose and for long enough, when stopped abruptly bring on a severe insomnia and a paranoid hallucinating state/
Identical with delirium tremens (de Clerambault, 1910; Hudson and Walker, 1962; James, 1963; Ewart and Priest, 1967). Recent work has shown that REM sleep is grossly increased in delirium owing to alcohol and barbiturate withdrawal (Gross et al., 1966; Greenberg and Pearlman, 1967; Evans and Lewis, 1968). Thus it seems likely that all hypnotics have these effects on REM sleep in some measure. These experiments demonstrate that 1 tablet of barbiturate does promote sleep. However, there is some cost. In many ways hypnotics allow sleep to be "borrowed", and this must be paid back during withdrawal. It seems advisable to tail off hypnotics slowly, even from small doses, to minimize the withdrawal state, but it is also necessary to support the patient through the period of withdrawal, which is, after all, a limited event. It would be better perhaps to consider hypnotics as a course of treatment, with a beginning and, as soon as circumstances permit, a definite end. It may also be more logical to prescribe intermittent courses of hypnotics so that withdrawal effects may be dissipated periodically and excessive build up of drugs prevented. It is an old criticism that doctors are good at starting and continuing treatment but not so good at stopping.
Dement and Wolpert (1958) have shown that the profusion of eye movements during a REM period was directly related to the "activity" of the dream events. This finding was confirmed by Berger and Oswald (1962). Pivik and Foulkes (1966) showed that selective deprivation of paradoxical sleep, using Dement's method of repeated awakenings, led not only to rebound increase of paradoxical sleep time, but to an increase of both profusion of eye movements and the vividness of the dream content. On rescrutinising the records from the amytal experiment (Oswald and Priest, 1965), it has been shown that on comparing the immediate post-drug nights, when REM time was high and subjects were spontaneously reporting nightmares, with the pre-drug nights the withdrawal nights contained a significantly increased number of epochs with eye movements (Oswald, 1969). The reverse situation is also true: when drugs are being administered and REM time is low, there is a decrease in the profusion of eye movements (Oswald et al., 1963; Baskeland, 1967).

Method

The eye movements occurring during the paradoxical phase of sleep have several characteristic features (Fig. 6). For the purposes of this study one of the most important features is that the pen deflection 'take-off' is always very sudden, the maximum rise-time for an input of 20 uV being about 500 m sec. As with most electrophysiological recording under such 'free' conditions as the sleep EEG,
FIGURE 6

Two Varieties of Rapid Eye Movements.

Upper traces show short bursts of low amplitude eye movement potentials during the control period. Lower traces show continuous high amplitude eye movement potentials after withdrawal of 15mg. nitrazepam.
/EEG, there are slow shifts in the base-line potential. An artificial base-line was therefore drawn parallel to the edge of the paper to facilitate recognition of the eye movements. A cursor with a series of 80° angles (equivalent to a rise-time of 500m sec. for 20 uV) marked on it was moved along this base-line. Any deflections in the eye monitoring channels out of phase with potentials in the 'occipital' EEG channel and of higher voltage than in-phase potentials in the 'frontal' EEG channel, were counted.

The experiment from which the records were obtained was the one reported by Oswald (1965) and Oswald and Priest (1965) which studied the effects of 15mg. nitrazepam (Ro5-4360). Nitrazepam delays the onset of the first REM period. Furthermore, the first REM period in both control and drug records tends to be short (of the order of 5-10 mins.) and to be interspersed with stage 2 sleep. In order that there would be compatibility between the periods used in the counting, it was decided to limit the period of counting to the middle 5 minutes of the first REM period to occur after 4.00 a.m. This REM period was of the order of 15-45 minutes long in all phases of the study.

*This study was included in the dissertation presented by S.A. Lewis as part fulfilment of the B.Sc. Honours examination in the University of Edinburgh, 1965.
Table 1
Analysis of REM count for 20-second intervals of a 5-minute sample from the 1st REM period after 0400 hours.

<table>
<thead>
<tr>
<th></th>
<th>Pre-drug</th>
<th>During-drug</th>
<th>Post-drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of ranks</td>
<td>254.0</td>
<td>307.0</td>
<td>556.0</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>254.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During-drug</td>
<td>307.0</td>
<td>53.0</td>
<td></td>
</tr>
<tr>
<td>Post-drug</td>
<td>556.0</td>
<td>302.0</td>
<td>269.0</td>
</tr>
</tbody>
</table>

*p < 0.01

Table 2
F ratios for standard deviations

<table>
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<tr>
<th>Standard deviation</th>
<th>df</th>
<th>Variance</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-drug</td>
<td>1.56</td>
<td>14</td>
<td>0.1343</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>During drug</td>
<td>1.6</td>
<td>14</td>
<td>0.1143</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Post-drug</td>
<td>3.23</td>
<td>14</td>
<td>0.2307</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
Analysis of REM count for 1 minute intervals of a 5 minute sample from the 1st REM period after 0400 hours.

<table>
<thead>
<tr>
<th></th>
<th>Pre-drug</th>
<th>During drug</th>
<th>Post-drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29.5</td>
<td>25.5</td>
<td>65</td>
</tr>
<tr>
<td>Same of Ranks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-drug</td>
<td>29.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During drug</td>
<td>25.5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Post-drug</td>
<td>65</td>
<td>35.5*</td>
<td>39.5*</td>
</tr>
</tbody>
</table>

*p < 0.01
FIGURE 10.

MEAN NUMBER OF EYE MOVEMENTS DURING SUCCESSIVE 20 SECOND PERIODS OF 5 MINUTES OF A RAPID EYE MOVEMENT PHASE OF SLEEP

- ■ CONTROL
- □ DURING 2ND NIGHT OF ADMINISTRATION OF 15 mg ROCHE 5-1360
- □ DURING 2ND NIGHT AFTER CESSION OF ADMINISTRATION OF ROCHE 5-1360

TOTAL MEAN FOR 20 SECONDS

CONTROL CORING 2ND NIGHT OF ADMINISTRATION OF 15 mg ROCHE 5-1360 DURING 2ND NIGHT AFTER CESSION OF ADMINISTRATION OF ROCHE 5-1360

FIGURE 9.

CHARGE IN MEAN NUMBER OF EYE MOVEMENTS FOR A 5 MINUTE PHASE OF SLEEP
Results

A cumulative count of the number of eye movements per 20 second epoch over the selected 5 minute period is shown in Fig. 9. The rapid eye movements occurred in bursts and the plateaux represents periods with few eye movements. On simple inspection it was obvious that the withdrawal period contained many more eye movements than either the pre-drug or drug periods. Fig. 10 shows the mean number of eye movements per 20 second epoch per minute over the 5 minute analysis period and Table 1 gives the analysis of these counts using the Kruskal-Wallis non-parametric analysis of variance. As can be seen, there was a significant increase in the number of eye movements in the post-drug period over both the pre-drug and drug periods. What was perhaps unexpected was that despite the reduction in the percent REM sleep in the whole night while the subjects were receiving the drug, the REM period was no less 'active' than during the pre-drug period (Table 1). It was possible that the significant withdrawal effect was due to an increase in the variance of the count per unit time i.e. that the eye movements came spasmodically and that each burst contained more eye movements. To test this hypothesis, an F-test for standard deviations was applied (Table 2). The hypothesis can be rejected. Regrouping the data into minute epochs rather than 20 second epochs did not alter the observed difference (Table 3).

Discussion

There is little doubt that there is a relationship/
relationship between raised percent REM and the profusion of eye movements during REM sleep (Pivik and Foulkes, 1966; Oswald, 1969). This study has confirmed this relationship over samples of short time intervals. However, it was not possible to confirm the findings of Oswald, et al., (1963), Baekeland (1967) or Allen et al., (1968) that reduced REM percent is associated with reduced REM 'activity'.

Sleep during drug withdrawal is frequently accompanied by nightmares (Oswald and Priest, 1965, 1965, Kales and Jacobson, 1967). Although an experimenter cannot say anything about a dream unless the subject is wakened it would seem that, from the already demonstrated relationship between eye movements and dream content (Dement and Wolpert, 1958; Berger and Oswald, 1962) and the present findings, an experimenter would be able to draw conclusions about the vividness or the activity involved in the sleepers' dream.

However, manual counting of eye movements is both time consuming and tedious. In an attempt to automate the counting of eye movements, an analogue computer was used in association with a simulated input. The criteria used were as in this study. As this appeared to give satisfactory results, the Electrical Engineering Department of Napier Technical College has undertaken to design and build a counter which will discriminate between potentials recorded on the eye channels of cerebral origin and those of ocular origin. It is hoped that such a counter will enable a greater sensitivity in the study of the long term effects of drug withdrawal.
III.D. **Dose Effects of Chlorpromazine on Human Sleep**

Over the years there has been a wealth of studies into the pharmacological mechanisms involved in and clinical effects of chlorpromazine (Guth and Spirtes, 1964; Ban, 1966). However, there has been little investigation into the drug's effect on sleep despite the well-recognised side-effect of sleepiness with some phenothiazines.

In cats and rabbits, chlorpromazine appears to have a predominately suppressant effect on REM sleep while increasing total sleep time (Hishikawa et al., 1965; Khazan and Sawyer, 1964). On the other hand, Toyoda (1964) suggests that in humans REM sleep is enhanced with chlorpromazine though the situation seems complicated by dose effects. Fisher (1966) in a single case study appears to support this enhancing effect in that trifluoperazine in "large doses" led to a very early REM onset. However, it was found that trifluoperazine severely reduced this activity in moderate dosage in a patient with high REM time. While many of these discrepancies could be due to species differences, it is also possible that there is a dose-response effect. This study was designed to investigate the latter possibility.

III.Di. Two young females and two young males were the subjects. Four base-line nights were recorded from the females and seven base-line nights from the males.

These recordings were spread over several weeks prior to the administration of chlorpromazine, the first dose of which was given on the night immediately following the last/
### Table 4

**Distribution of recordings nights**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Number of Subjects</th>
<th>Sex</th>
<th>Total Base-line Nights</th>
<th>Drug Nights *</th>
<th>Withdrawal nights</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPZ</td>
<td>25mg</td>
<td>2</td>
<td>F</td>
<td>4</td>
<td>1,2,3,4,6(6)</td>
<td>1,2,3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>3</td>
<td>1,2,3,4,5,7(7)</td>
<td>1,2,3</td>
</tr>
<tr>
<td>CPZ</td>
<td>100mg</td>
<td>3</td>
<td>M</td>
<td>3</td>
<td>1,2,3(3)</td>
<td>1,2,3</td>
</tr>
</tbody>
</table>

*Drugs were administered on non-recording nights. Number in brackets indicates total number of drug nights. The last base-line and the first drug night were successive nights as were the last drug night and first withdrawal night.*

*CPZ = chlorpromazine.*
/last base-line night. 25mg. chlorpromazine was administered orally for six successive nights in the case of the females and seven nights with the males. Table 4 gives the nights on which recordings were obtained. It should be noted that on drug nights when there was no recording, the subjects took the drug at home at approximately the same time, 30 minutes before retiring, as on recording nights. Following the drug nights, three withdrawal night recordings were obtained the first of which was the night immediately following the last drug night.

III.Dii. Essentially the same procedure as in III.Di was used here with three young male subjects. After three base-line nights, three nights on which 100mg. chlorpromazine was administered orally were recorded. Three withdrawal nights followed. Again, Table 4 gives the distribution of the recording nights.
b) III.Dii. The administration of 25mg. chlorpromazine resulted in a rise in % REM sleep (Fig. 11). There was also a corresponding increase in total sleep time confirming the hypnotic action of the drug. Using the technique of analysis outlined above, the rise in REM time was significant \( (t = 4.0403; \ p < 0.05) \) after correction for change in total sleep time.

As can be seen from Fig. 11, the females show a greater change than the males. This difference is significant \( (F = 9.4629; \ p < 0.05) \). However, the males alone show a significant increase in REM time after correction for changes in total sleep time \( (t = 15.9283; \ p < 0.05) \) and so the overall rise was not due entirely to the larger rise seen in the two female subjects. No withdrawal rebound was observed.

c) III.Diii. The effect of administering 100mg. chlorpromazine on % REM sleep is shown in Fig. 12. There was an initial depression of REM sleep. While this depression was small it was significant \( (t = 3.6301; \ p < 0.01) \). No significant change was observed in the delay to sleep onset or the delay to the first REM period. There was, however, a 20 minute increase in the mean total sleep time though this was not significant.

In the withdrawal phase of the experiment, total sleep time decreased but again this was not significant; nor was the change in REM sleep.

Discussion

This investigation has shown that the effect of/
Effect of 100 mg Chlorpromazine on Rapid Eye Movement Sleep

FIGURE 12

Effect of 25 mg chlorpromazine on rapid eye movement sleep

FIGURE 11
of chlorpromazine on human REM sleep is dose dependent; 100mg. (approximately 1.5mg/kg) suppressing and 25mg. (approximately 0.5mg/kg) enhancing this type of sleep. While there was a sex difference with the 25mg. dose, the difference was of magnitude and not of direction of change. This difference may have been due to the phase of the menstrual cycle during the experiment (Hartmann, 1966).

The possibility of a dose effect has been indicated by others. Jouvet (1967b) states that at a dose of 5mg/kg in cats, chlorpromazine does not affect REM sleep but that at 10mg/kg there is suppression of REM sleep. Hishikawa et al. (1965) agree with there being a suppressant effect but at a dose of 4mg/kg. However at a lower dose (2mg/kg) he showed a decrease in latency to the first REM period of the night, an effect which has been shown to correlate with an increased total REM time for the whole night (Oswald and Priest, 1965) under certain circumstances.

Working with rabbits, Khazan and Sawyer (1964) reported a marked reduction in REM sleep with chlorpromazine (2.5-5mg/kg) and Kawakami et al. (1966), also in the rabbit, suggest that 1.5mg/kg results in a slight reduction. The difference in dose level necessary to produce a change in REM sleep with chlorpromazine suggests that there may be a species as well as a dose difference.

In humans Toyoda (1964) has demonstrated a reduction in REM sleep with 12.5 - 50mg. chlorpromazine. However, his subjects were patients and no indication is given regarding prior therapy with hypnotics. At least one of his subjects/
/subjects had a grossly abnormal base-line REM time and was said to be schizophrenic. It has also been shown that the effects of withdrawal from hypnotics can last for several weeks (Oswald and Priest, 1965), even from small doses (III.Bi). Further, it has been demonstrated that 100mg. of chlorpromazine will block the withdrawal effects of hypnotics (III.Eii). Furthermore, for the majority of Toyada's subjects there was only one "placebo" night at the beginning of the experiment. As this was the subject's first night in the laboratory, the REM times would be unreliable (Agnew et al. 1966). However, in a well designed study, Lester and Guerrero-Figueroa (1966) showed that 50-100mg. chlorpromazine in humans decreased the latency to the first REM period. As mentioned previously this may indicate an increased whole night REM time. This finding, which appears to contradict the present data, unfortunately does not give whole night data.

There is clinical debate as to whether stopping chlorpromazine can lead to withdrawal symptoms (e.g. Garfield et al. 1966; Gross et al. 1960). It was pointed out earlier (section I) that many psychoactive drugs on withdrawal result in a marked rise in REM sleep. From this, it has been argued that the hallmark of addicting drugs is a suppression and tolerance of REM sleep during drug administration followed by immediate "rebound" on withdrawal (Oswald et al. 1968, see IV.A). In the present study, 100mg. chlorpromazine showed depression and tolerance but no immediate REM sleep rebound. This lack of immediate rebound may be due to/
chlorpromazine's very slow clearance from body tissues (Dubost and Pascal, 1965) and could well account for there being at most, only minimal clinical withdrawal symptoms.

If, as would seem likely, chlorpromazine has a suppressant effect at high doses and an enhancing effect at low doses on human REM sleep, it would be of interest to observe the dose level at which there was no apparent effect.
III.E. Two studies of the treatment of drug withdrawal.

i) General Introduction

In almost any field of clinical medicine, the practitioner is faced with a plethora of possible chemotherapeutic agents. Each drug has its advocates and its detractors. It is interesting to wonder to what extent fashion and patriarchal culture play a role in the choice of therapeutic agent. The treatment of delirium associated alcohol and hypnotic drug abuse may be taken as a case in point. Delirium associated with the abuse of alcohol was delineated from the group of 'phrenites' at the end of the eighteenth century. Excellent clinical descriptions of this syndrome were given by clinicians such as Lettsom (1787), Pearson (1807), Sutton (1813) and Armstrong (1816) and each was struck by the patient's restlessness, "dreadful nocturnal dreams", insomnia, hallucinations and tremors all of which improved with the "critical sleep". Opium was seen as curative and that "the measure of its beneficial efficacy is by producing sleep". Although a chronic illness could result it was recognised that delirium was frequently an acute and self limiting disorder, and Ware (1831) reported excellent results from nothing more than careful nursing and supervision, an 'expectant' treatment. Frequently active treatment with opium, alcohol, quinine or mercurials was used as well as the traditional anti-phlogistic remedies of bleeding, emetics and vesications./
In this early period the association of this drug-withdrawal type of delirium, which Sutton (1813) called delirium tremens, with insomnia and bad dreams, together with the curative qualities of sleep, was emphasised. Later in the century, the Victorian preoccupation with toxins and intoxication absorbed from the gut or some other infected site, largely obscured these associations. Treatment with purgatives, emetics and dehydrating measures including spinal drainage, were advised although opium was still in use.

Despite this change in England, evidence of the persistence of 18th century views came from the Continent; Laseque (1881) wrote a paper entitled "Alcoholic delirium is not a delirium but a dream". He saw this state as consisting of variations in visual experience from increasing wildness of night dreams to day time hallucinations which he called "awake dreaming". These views were however out of touch with the dominant clinical ideas of the period.

There was still a great deal of argument about this disorder. Was it a state of alcoholic intoxication? Was it an alcoholic withdrawal syndrome? Was it a secondary intoxication from gut? Perhaps it was a state of cerebral oedema, "wet brain", or perhaps due to more permanent cerebral damage. The appreciation of the more chronic delirium of Korsakow confirmed some of these suspicions (Korsakow, 1890).

Nevertheless, the recognised value of promoting sleep in these disturbed patients led to the use of the available/
/available agents and paraldehyde (Bumke 1901) came to replace morphia or opium. Barbiturates and bromide were also used.

Early in the twentieth century there was a return to the use of alcohol itself occasioned by the popularity of the theories of Professor Jauregg of Vienna who was presumably influenced by the coming of the antibody-antigen theory. As reported by Astley Cooper in 1913, Jauregg hypothesised that there was developed in the body an "anti-alcohol". This increased in amount over a period of time and produced the phenomenon of tolerance. In abstinence the anti-alcohol could act alone to produce delirium, but then gradually decreased in amount as its "antigen" was no longer present, over a period of days. Alcohol administered during the delirium would oppose this effect. Further abstinence, with the resulting decay in the anti-alcohol, lowered the patient's tolerance to alcohol and Jauregg suggested that individuals with greater tolerance would be more prone to delirium when their alcohol consumption was abruptly curtailed. Astley Cooper therefore suggested that alcoholics should be 'weaned off' their alcohol and early symptoms of delirium treated with alcohol.

In the 1930s, the growth of knowledge of the vitamins and their associated deficiency diseases led to an increased awareness of the physical manifestations of alcoholism. Peripheral neuritis was frequently found in alcoholics (Romano 1937) and alcoholic pellagra was reported by/
by Spiers in 1938. Bowman (1939) used large doses of thiamine and nicotinomide to treat Korsakow states with some success. The appreciation that a Korsakow syndrome could occur in other disorders as far removed from each other as diabetes and pregnancy also influenced thinking so that it seemed logical to regard the delirium as the effect of alcohol or its lack or some intermediate process which could be influenced by other diseases.

It became clinical practice to use supplementary vitamins to treat the peripheral neuritis or perhaps to prevent the Korsakow state. However there was much discussion as to which vitamin was most effective. Rosenbaum (1940), though failing to find vitamins alone effective in delirium, thought that patients on vitamins needed less sedation. Sydenstriker (1941) gave large doses of nicotinamide to an acutely psychotic pellagrous patient who responded dramatically and Seliger (1948) gave 600mg. of thiamine daily to patients in delirium together with sedatives.

Armstrong and Gould (1954, 1955), advocated high dosage poly-vitamin therapy in delirium with satisfactory results and this approach to treatment on both clinical and theoretical grounds still has many adherents.

The most recent advance in the treatment of drug withdrawal delirium has been brought about by the introduction of the major tranquillisers in the 1950s. Reserpine (Wells, 1957) was rapidly replaced by chlorpromazine. This seemed to be a very logical choice. It was an/
/an anti-emetic; it promoted sleep which was not so profound as the sleep produced by paraldehyde and barbiturates, thus making nursing easier; and its anti-psychotic effects which were becoming recognised, enhanced its reputation in the treatment of delirium (Mitchell, 1955; Cohen, 1955). Initial difficulties due to hypotension were accepted. However, the association of chlorpromazine with jaundice, which was only later recognised as an obstructive jaundice (Cohen, 1955; Graham, 1957), made clinicians wary of using this drug in alcoholics with evidence of liver disease. Furthermore, some workers (Barrett, 1958; Frazekas et al., 1957) thought that convulsions were more frequent when delirium was treated with chlorpromazine.

Under the misconception that the chlorine radicle of chlorpromazine was the hepato-toxic part of the molecule and responsible for the jaundice, other phenothiazine derivatives gained favour. Promazine was the most frequently used alternative (Mitchell, 1956; Figuralli, 1958).

Comparison of chlorpromazine with paraldehyde (Friedhoff and Zitrin, 1959) suggested that paraldehyde was much quicker in its action although both were effective. Hart (1962) however, found promazine apparently more effective than paraldehyde and so presumably more effective than chlorpromazine. During this most recent period, almost all the tranquillisers including meprobamate (Leraboulet, 1960) and chlordiazepoxide (Lawrence et al., 1960), have at some time been advocated.

Glatt (1959) however was not convinced that/
that chlorpromazine, promazine or reserpine were any more efficient than placebo in the treatment of alcohol withdrawal.

In the Scandinavian countries another drug has been used in the treatment of alcoholic withdrawal. This is chlormethiazole. Its origins are of interest as its use would suggest that the full circle has been run. It is derived from thiamine and was developed because it was found that the thiazole portion of the thiamine molecule had sedative and anti-convulsant properties. This latter property is clinically useful; sedation has always been advocated; and presumably its vitamin association has psychological benefits for the clinician even supposing it does not help in the alleviation of the alcoholic's physical ailments (Laborit, 1957, Osterman, 1959, Salum, 1966). Glatt (1965) investigated this drug and found it more effective than placebo in the treatment of alcoholic withdrawal syndromes of all degrees. At the same time it should be remembered that for most of the drugs which have been used to treat delirium tremens reports have appeared which have shown that the drug, if taken in sufficient dose for long enough, was abruptly stopped, it could produce a syndrome identical with delirium tremens.

Sutton (1813) was aware that "opium proves a cure to the ravages of a disease brought on by fermented liquor. Yet it may be observed that in theory and practice the effects of opium have been acknowledged to be analogous and similar to them". Paraldehyde withdrawal was described by/
Barbiturate withdrawal delirium was produced experimentally in post addicts by Isbell and the Lexington workers in 1950. These workers have shown (Isbell et al., 1955) beyond doubt that alcohol withdrawal led to a delirium identical to barbiturate withdrawal. Indeed one can say that for every known hypnotic there is a case report that abrupt withdrawal from a high sustained dose has produced delirium (James, 1962; Hudson, 1962; Wood, 1965).

The list of agents used in the treatment of alcoholic withdrawal delirium is extensive. How much can fashion and placebo effects explain this situation or can it be that many of these diverse drug treatments have some common physiological effect?

III. Eii Chlorpromazine and Drug Withdrawal.

Assuming the excess of REM sleep in drug withdrawal, chlorpromazine administered immediately after stopping, for example, a barbiturate could have one of three possible effects: (i) The chlorpromazine could have no effect on REM sleep and the rebound could continue. (ii) The chlorpromazine could have a delaying effect on the rebound such that it would appear after the chlorpromazine had been withdrawn. (iii) Chlorpromazine could block the rebound completely.

The results of a previous study (III.Dii) makes the first hypothesis unlikely and the slow clearance of chlorpromazine from body tissues (Dubost and Pascal, 1955)/
Table 5

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Sex</th>
<th>Number of Baseline nights</th>
<th>Drug</th>
<th>Drug†</th>
<th>Withdrawal**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>6</td>
<td>Amobarbital</td>
<td>1,2,4,7,8,9,10</td>
<td>15,16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11,14</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorpromazine</td>
<td>17,18,19,21</td>
<td>22,23,25,28,30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32,35,37,39,42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46,51,53,59,62</td>
</tr>
</tbody>
</table>

* This excludes the first adaptation night record.
† Drugs were administered on successive nights even though a record was not obtained each night.
** The first withdrawal night was the night immediately succeeding the last drug night.

Table 6

Effect on Sleep

<table>
<thead>
<tr>
<th></th>
<th>Total Sleep Time (min)</th>
<th>Delay to Sleep Onset (min)</th>
<th>Delay to 1st REM period (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Control</td>
<td>446.7 ± 5.8</td>
<td>21.0 ± 2.6</td>
<td>76.5 ± 15.0</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>445.4 ± 5.0</td>
<td>45.0 ± 13.9</td>
<td>65.9 ± 15.0</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>455.0 ± 4.5</td>
<td>31.4 ± 22.8</td>
<td>86.9 ± 22.9</td>
</tr>
</tbody>
</table>
coupled with clinical evidence suggests that the last hypothesis (iii) is the most likely.

The present study was designed to test these hypotheses using barbiturate withdrawal as the model.

**Method**

Six base-line night records were obtained from each of two healthy young male subjects over a period of weeks prior to the administration of the drugs. 400mg. amylobarbitone sodium was administered for 14 consecutive nights, recordings being taken on 9 of these as shown in Table 5. On non-recording nights, the subjects took the drug at approximately the same time, 30 minutes before retiring.

Following the last "amytal night" there were two non-drug nights. These two nights were followed by 5 nights on which the subjects received 100mg. chlorpromazine orally approximately 30 minutes before retiring. Four recordings were obtained, night 4 being omitted though, as before, the subjects still received the chlorpromazine. On stopping the chlorpromazine, their sleep was monitored on fifteen of the first forty-five "withdrawal" nights. The nights on which recordings were obtained are indicated in Table 5.

**Results**

The initial stage of this experiment, the administration of 400mg. amylobarbitone sodium nocte, was to enable the later induction of a drug withdrawal state. Although records of the subjects' sleep were obtained, little comment on the results of this stage is necessary since they followed exactly those obtained by Oswald and Priest (1965). There was the expected depression of % REM sleep and tolerance with continued administration (Fig. 13). On withdrawing the amylobarbitone the initial stages of the expected/
FIGURE 13  The administration of 100mg. chlorpromazine as a substitute for 400mg. sodium amytal blocks the REM sleep rebound. Subsequent withdrawal of chlorpromazine does not result in a REM sleep rebound.
expected rebound were seen.

Fig. 13 shows that after 5 successive nights of chlorpromazine no rebound was seen despite the sampling over forty-five subsequent withdrawal nights.

Using the technique of analysis outlined previously (III, A) it was found that chlorpromazine, after fourteen nights of amylobarbitone, does not result in REM sleep time (in minutes) being significantly different from the control values. Further, despite the significant ($t=2.5714, p<0.01$) decrease in total sleep time (Table 6) the mean REM time during chlorpromazine administration was not significantly different from that to be expected for the observed total sleep time (obtained from the regression equation of III.D).

It was noticed in the process of this analysis that on the first two nights on which the subjects received chlorpromazine, the observed REM time was greater than the expected, while the reverse was true for the 3rd and 5th nights. However, neither of these pairs of nights was significantly different from control or from each other.

The significant decrease in total sleep time during chlorpromazine administration can be accounted for in terms of the increased delay to sleep onset (Table 6) ($t=3.3069, p<0.01$). In withdrawal this parameter was not significantly different from either the control or chlorpromazine stages. This was also true of total sleep time.

During the administration of chlorpromazine, the delay to the onset of the 1st REM period of the night decreased but not significantly (Table 6) with respect to the control values.
Table 7

Distribution of Recording nights.

<table>
<thead>
<tr>
<th>Drug 1 (dose)</th>
<th>Drug 2 (dose)</th>
<th>Number of subjects</th>
<th>Sex</th>
<th>No. of control records (excluding 1st adaptation night for each subject)</th>
<th>1st Drug nights on which records obtained*</th>
<th>2nd Drug nights on which records obtained*</th>
<th>Withdrawal nights on which records obtained*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amytal (400mg.)</td>
<td>Chioromethiazole (400mg.)</td>
<td>2</td>
<td>M</td>
<td>1,2,4,6,9,11</td>
<td>1,2,3,5,7</td>
<td>1,2,3,5,7</td>
<td>1,2,3,5,7</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
<td></td>
<td>(11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine (400mg.)</td>
<td></td>
<td>1</td>
<td>M</td>
<td>1,2,4,6,9,11</td>
<td>1,2,3,5,7</td>
<td>1,2,3,5,7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(11)</td>
<td></td>
<td></td>
<td>(7)</td>
</tr>
</tbody>
</table>

*The subjects received each drug on successive nights even though a record was not obtained each night. The first withdrawal night was always the night immediately succeeding the last drug night.
values (t=1.3955, p > 0.05) while in withdrawal it was significantly increased when compared to drug values (t=2.4266, p < 0.05).

III.Eiii: Chlormethiazole and Drug Withdrawal.

Drug administration and recordings: The three subjects who took part in this study received 400mg. sodium amytal nocte for eleven nights. Two of the subjects immediately transferred to 400mg. chlormethiazole nocte for seven successive nights while the third was administered 400mg. thiamine for the same number of nights. Both subjects and experimenter were kept ignorant of which subject received thiamine. It should be noted that unlike the last experiment, there were no intervening withdrawal nights between the "addicting" drug and the "treatment" drug. All subjects were studied over the first seven "treatment" withdrawal nights. The distribution of recordings is shown in Table 7).

Results

The effects of the treatments on % REM sleep (Fig. 14). showed that thiamine apparently did not block the REM rebound. However, as only one subject received thiamine it was not possible to carry out any meaningful statistical analysis for this drug. On the other hand, it was possible to compare thiamine with chlormethiazole.

Comparing the total sleep times of the subject receiving thiamine with the total sleep times of those receiving chlormethiazole, it was found that there was/
Table 8

Effect of administration of sodium amytal on total sleep time and of chloromethiazole and thiamine immediately after amytal withdrawal on total sleep time.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean total sleep time (mins)</th>
<th>S.D.</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amytal</td>
<td>470.0</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloromethiazole</td>
<td>456.5</td>
<td>14.3</td>
<td>2.5815</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Amytal</td>
<td>470.0</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine</td>
<td>437.7</td>
<td>14.1</td>
<td>5.0077</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chloromethiazole</td>
<td>456.5</td>
<td>14.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine</td>
<td>437.7</td>
<td>14.1</td>
<td>2.2554</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Ferguson, 1959.
Effect of Chlormethiazole and Thiamine on Rapid Eye Movement (REM) Sleep in Amytal Withdrawal

(a) 2 Subjects received Chlormethiazole; 1 Subject received Thiamine
(b) Both Chlormethiazole subjects had grossly disturbed sleep on withdrawal night 1
(c) One of the Chlormethiazole subjects was not available for nights 5 and 7 of withdrawal

FIGURE 14 The administration of chlormethiazole as a substitute for sodium amytal blocks the REM sleep rebound but subsequent withdrawal of chlormethiazole results in a small REM sleep rebound. Thiamine does not block REM sleep rebound.
was a significant difference between drugs during the period of drug administration (Table 8, \(t=2.2554, \ p<0.05\)). Also comparing the total sleep times during thiamine and amytal administration in the same subject, there was again a significant difference (Table 8, \(t=5.0077, \ p<0.001\)). Chlorothiazole too was ineffective in preventing the reduction in total sleep time though this manifestation of sleep disturbance was less marked (Table 8, \(t=2.5813, \ p<0.05\)) than with thiamine.

It should be noted, however, that on the first night of chlorpromiazole withdrawal both subjects had particularly disturbed nights, one subject having a total sleep time of only 157 mins. while the other slept for a total of 253 mins. despite both being in bed for 455 mins. This total sleep time reduction resulted in a gross reduction in % REM sleep as noted in Fig. 14.

Differences in the delay to sleep onset and the delay to the 1st REM period were also apparent (Table 9). While thiamine was only partially successful in stopping the increase in delay to sleep onset, which other experiments would predict for the withdrawal phase, chlorpromiazole did block this aspect of the sleep disturbance. Similarly, thiamine did not prevent there being a decrease in the delay to the 1st REM period while chlorpromiazole did.

Analysing the REM sleep time during chlorpromiazole administration using the technique outlined in the study of dose effects of chlorpromazine (III.D), it was found/
Table 9

Effect of sodium amytal, thiamine and chlormethiazole on the delay to sleep onset and the delay to the 1st REM period.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean delay to sleep onset (mins.)</th>
<th>SD</th>
<th>t</th>
<th>p</th>
<th>Mean delay to 1st REM period (mins.)</th>
<th>SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amytal</td>
<td>13.5</td>
<td>8.4</td>
<td></td>
<td></td>
<td>149</td>
<td>76.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine</td>
<td>24.4</td>
<td>12.3</td>
<td>1.5097</td>
<td>N.S.</td>
<td>64</td>
<td>21.3</td>
<td>2.2544</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Amytal</td>
<td>11.9</td>
<td>6.7</td>
<td></td>
<td></td>
<td>149.5</td>
<td>90.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>10.2</td>
<td>7.2</td>
<td>&lt; 1.0</td>
<td>N.S.</td>
<td>143.4</td>
<td>38.4</td>
<td>&lt; 1.0</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

*Ferguson, 1959.*
found that this dose (400mg.) of chlormethiazole was effective in maintaining REM sleep time at control levels, (t=7.6696). The rise in % REM sleep on cessation of chlormethiazole administration was not significant (t=1.2476). As previously remarked, there was a gross reduction in total sleep time on withdrawal night 1 in both subjects and so this night was not included in the REM time analysis.

The only meaningful comparison of REM sleep that could be made between chlormethiazole and thiamine administration was the comparison between the (expected-observed) REM times. On this comparison, the two drugs were found to be not significantly different (t=1.8464). This was presumably due to the decreased % REM sleep on nights three and five of thiamine administration. While the ability to depress REM sleep in this way may be a property of thiamine, it should be remembered that only one subject received thiamine.

Discussion

It has been shown that barbiturates initially suppress REM sleep and that on withdrawal there is a greatly increased proportion of REM sleep in the night (Oswald and Priest, 1965). The same effects have been shown for alcohol (Yules et al. 1966). Within the clinical definition of addiction is implicit the concept of tolerance to the drug and that D.Ts develop only if tolerance is complete. However, it has been shown (III.Bi) that the changes in REM sleep are sensitive to changes due to small amounts of/
of drug. It is this sensitivity that has permitted laboratory investigations of drug withdrawal states using normal volunteers and the effects of two drugs used in the treatment of such states.

When a drug is administered subsequent to withdrawal of an "addicted" drug, there can be one of three effects on REM sleep. It can, of course, have no effect. This was probably the effect with thiamine, though only one subject was studied, and although it has been advocated for the treatment of delirium tremens, its effect may be due to the often overlooked simultaneous administration of hypnotics.

The alternative effects that could be expected from drug substitution are (a) a complete blockage of the REM sleep rebound or (b) a delay in the rebound. The experiment in which chlorpromazine was substituted for amyotal demonstrated the complete block effect. 100mg. chlorpromazine when given alone depressed REM sleep (III,Di) but was found to maintain the amount of REM sleep in the night at normal levels during withdrawal. The lack of any rebound on stopping administration of chlorpromazine can be explained on the basis of the drug's slow clearance from the body tissues. It is well known that traces of the chlorpromazine can be found in urine several months after the last dose was administered (Dubost and Pascal, 1955).

Chloromethiazole demonstrated the delaying effect of a drug on the rebound phenomenon. This drug, having sedative properties, reduced REM sleep during administration/
administration (Evans and Lewis, unpublished observations) and would be acting in a manner analogous to chlorpromazine in this situation. However, its clearance from tissues is much more rapid than that of chlorpromazine and so a rebound was observed on withdrawal. On the other hand, in clinical practice, it is usual to reduce the dose over days rather than stopping its administration suddenly as was done here. This would control the rebound so that the sleep disturbance would be minimal.

All the hypnotics investigated using the sleep E.E.G. techniques have been shown to have a REM suppressant effect followed by a return to baseline levels (Oswald et al. 1969). Gross et al. 1968, on giving paraldehyde to a patient found that the resulting sleep lasting six hours contained no REM sleep. Morphine too has shown a REM suppressant effect in rats (Khazan et al. 1967) and in man (Kay et al. 1968). Although the effects of steroids on sleep have been less well investigated, Kawakami and Yoshida (1965) have suggested that ACTH may also have an inhibiting effect on REM sleep. ACTH and other steroids have been advocated for the treatment of delirium (Smith, 1950; Fischbach, 1952). It would therefore appear that despite the plethora of treatments that have been advocated since the concept of delirium tremens was introduced, most appear to have the common property of reducing REM sleep. However, all the drugs advocated - paraldehyde, morphia, opium, chloral, and of/
/of course alcohol and barbiturates themselves - have at some time been shown to be capable of resulting in D.T.s. This would appear paradoxical unless it is remembered that to promote delirium the drug should be abruptly withdrawn.

When discussing chlormethiazole, it was indicated that the usual clinical procedure was a gradual reduction in the dose rather than abrupt cessation. This procedure is usual in all substitution regimens. It is possible that by decreasing the daily dose, the "pressure" for REM sleep is released slowly thereby enabling the underlying physiological mechanisms to spread the rebound over several nights or weeks. If the drug is suddenly withdrawn, it may not be possible to prevent REM sleep mentation intruding into waking phantasy. If this occurs the REM rebound is abrupt with a sharp rise in REM times giving rise to drug withdrawal symptoms. Evidence for this hypothesis can be obtained by arranging the data of Greenberg and Pearlman (1967) as shown in Fig. 15. It can be seen from this graph that those patients who developed delirium had high REM times sooner than the non-delirious group.

The hypothesis that for delirium to develop there must be an abrupt release of REM pressure presupposes that REM periods can spill over into waking life. This would be experienced by the patient as the intrusion of dream phantasy into wakefulness which intrusion becomes disturbing. Such a phenomenon can be seen in narcolepsy./
FIGURE 15  REM sleep in patients during alcohol withdrawal. The delirious group have a greater shorter lived rebound than the non-delirious group. (Redrawn from Greenberg & Pearlman, 1967).
One of the outstanding features of the narcoleptic attack is that it is an episode of REM sleep frequently not followed by orthodox sleep (Rechtschaffen et al., 1963; Hishikawa et al., 1968; Evans and Oswald, 1967). The narcoleptic is unique in present experience in his ability to enter REM sleep abruptly without prior orthodox sleep. Thus, it is possible to find consciousness and REM sleep in direct continuity. Narcoleptic patients frequently develop paranoid symptoms; these could be brought about by a consciousness-dream-consciousness experience instead of a consciousness-orthodox sleep-dream-orthodox sleep-consciousness sequence. Similarly, a person waking from a particularly vivid dream often experiences disorientation in time, place and person for several minutes. The dream lives on in wakefulness when he has experienced a consciousness-orthodox sleep-dream-consciousness sequence.

The inability to dissociate phantasy and reality when dreaming and waking are in continuity would indicate that there is a common mechanism underlying both REM sleep and the paranoid delirium of drug withdrawal states. The present experiments would lend further circumstantial evidence to the relationship.

The idea that dreams and hallucinations are closely related is by no means new. Jung (1944) clearly held this view: "Let the dreamer walk about and act like one wakened, and we have the clinical picture of dementia praecox". Hughlings Jackson (1958) though more/
/more cryptic, was of the same opinion: "Find out about dreams and you will find out about insanity". Kant (1952) too expressed similar views in his "Critique of Judgement".

E.E.G. sleep investigations of psychotics do suggest that psychotic hallucinations are associated with excess REM sleep (Gulevich et al. 1967; Caldwell and Domino, 1967). However, the present experiments and in particular the study of chlorpromazine substitution, emphasise one of the problems of investigations of sleep in clinical situations. The prolonged effects of drugs such as chlorpromazine and barbiturates make it essential that in future investigations of the sleep of psychiatric patients, those patients included in the study must not have been in contact with psychotropic drugs. The alternative is that drug therapy must have been stopped a considerable time before the investigations begin, not only to ensure the absence of false negatives due to tolerance or continued action of the drug, but also to minimise the possibility of false positives due to "rebound".

One flaw in this argument is that withdrawal of amphetamine does not lead to delirium. This fact is seen most clearly when amphetamine withdrawal is contrasted with barbiturate withdrawal. Although the withdrawal effects seen in sleep of the two drugs are similar, the clinical picture of the two syndromes is entirely different. On the one hand, barbiturate withdrawal leads to a state of behavioural excitation, while on the other lethargy/
Lethargy and apathy are the sequelae of amphetamine withdrawal. It might be suggested therefore that at the purely behavioural level there is an explanation for the non-appearance of delirium with amphetamine withdrawal. However, if there is any credence in the hypothesis that at least some of the mechanisms of delirium will be revealed in sleep, then a closer examination of sleep data is necessary. Feinberg (1968) has carried out such an examination and has put forward the following hypothesis. "The probability of such a (drug withdrawal) delirium is directly proportional to the ability of addicting drugs to suppress both the phasic aspects of REM sleep and the mechanisms which govern stage 4 sleep. ................. the likelihood of delirium is enhanced if the temporal relations during withdrawal are such that stage 4 mechanisms remain suppressed when the REM sleep rebound occurs."

Barbiturates, during their administration, not only reduce REM sleep, they promote stages 3 and 4. In withdrawal there is a marked rise in REM sleep but relative to the % REM, little stages 3 and 4. In contrast, the orthodox sleep compensation for reduced REM sleep during amphetamine administration is an increase in stages 1 and 2. Indeed there is a decrease in stages 3 and 4. It has been demonstrated that with deprivation of stages 3 and 4 plus REM sleep, in recovery stages 3 and 4 take precedence over REM sleep. Hence, in amphetamine withdrawal, not only is there an increased % REM sleep, there is an associated increase in % 3 and 4. On Feinberg's hypothesis, therefore/
Therefore, delirium would not be expected during amphetamine withdrawal. Furthermore, Feinberg has suggested that the results obtained in the present amytal-chlorpromazine experiment may be only half the story. His suggestion is that the efficacy of chlorpromazine in the treatment of drug withdrawal delirium lies in the drug's ability to promote stage 3 and 4; its REM depressant effect has only secondary value.
III.F. Overdose of tricyclic anti-depressants and deductions concerning their cerebral action.

Introduction

The tricyclic anti-depressant drugs are established therapeutic agents, yet their mode of action has remained obscure. The usual delay of some 10 or more days before they produce beneficial effects has never been satisfactorily explained. Again, the long period of weeks or months necessary for lasting cure, capable of surviving stoppage of drugs, has caused uncertainty as to whether patients should be regarded as temporarily "dependent" upon them. Slow brain processes have to be inferred, of a duration often met in psychiatry (Oswald, 1967). The observations in this report have features in common with many other slow brain recovery processes and may cast light upon the mode of action of anti-depressant drugs, as well as providing further insight into the chemical mechanisms of sleep. The latter are currently believed to be governed in part by cerebral mono-amines, which the tricyclic drugs are thought to affect.

The observations were made on three women who had taken overdoses of tricyclic anti-depressant drugs and whose sleep was studied for several weeks afterwards, especially their REM sleep. Jouvet (1967) reported that imipramine suppressed this kind of sleep in the cat and that no immediate "rebound" increase followed. Hartmann (1968a and b) described suppression of REM sleep lasting three nights in man after a small single dose of amitriptyline and found no rebound/
/rebound in the following three nights. By way of contrast many other drugs which suppress REM sleep cause a withdrawal "rebound" excess of REM sleep. Examples are amphetamine (Oswald and Thacore, 1963) and various hypnotics (Oswald and Priest, 1965; Kales et al. 1968; Evans et al. 1968). The rebound after these drugs persists during many weeks.

The Patients

Among 53 patients who had taken overdoses of tricyclic anti-depressants and who came under the psychiatric surveillance of Dr. I. Oswald during 1968 were three women in whose cases (a) the original prescription of the drug by the general practitioner appeared of doubtful appropriateness because their depression was reactive to circumstances; (b) personal problems warranted hospital admission. While they were in-patients, and, thanks to their co-operativeness, for a time after discharge, their sleep was studied. The drugs were not resumed. The clinical histories were as follows:

**Patient S:** Aged 20, single. First attended psychiatric Outpatients three years before; two years intermittent psychotherapy; "psychopathic traits since age 13". Alcoholic father, separated from the mother, towards whom patient was ambivalent. Unstable sexual unions and work record. Fed up with job, complained to general practitioner of depression in February, 1968. Given amitriptyline which she took rarely. Two days before overdose resigned job and on 19th June broke with boy friend. Had double gin about 22.30hrs., took 157 tablets of amitriptyline 25mg./
/25mg. then told mother. Admitted to Royal Infirmary of Edinburgh 23.30hrs. Stomach wash-out. Two major convulsions. Rousable by powerful stimuli. Dilated pupils, brisk reflexes, flaccid tone, ECG showed bundle branch block for a few hours. After 36hrs. had tachycardia of 160, with brisk reflexes, restless and twitchy movements, delirious, talking as if hallucinated, but replying to questions. "Pressure" of speech (sudden bursts of rapid syllables). 60 hours after admission transferred to psychiatric ward. Oriented and rational the next day.

Soon after admission, blood showed "Tryptizol-like" substances 150 ug per 100ml. After 36 hours "less than" 50 ug per 100ml. None detected in sample taken on 6th day.

A co-operative ward patient but sulky and indifferent about her future. After discharge on 19th day moved into flat away from her mother. Frequent employment and boyfriend difficulties but the frequency of minor crises settled over the next six months.

Admitted to Royal Infirmary of Edinburgh 22.30hrs. Moderately productive stomach wash-out. Responding to painful stimuli. Six major convulsions in first 24hrs. Tachycardia of 112 with occasional dropped beats, temperature 99.8°F, some hypotonia and intermittent limb twitchings. After 96 hours was overactive, paranoid and aggressive to staff. Given 100mg. chlorpromazine and 13ml. paraldehyde and transferred to psychiatric ward where paranoid and overactive features settled within 46 hours.

Remained in hospital 25 days. A vigorous woman with aggressive feelings towards her husband. Would always turn the conversation towards children. Talkative and lewdly joking with other women. Denial mechanisms always operative over cancer. After discharge resumed work and general adjustment improved.

Patient M: A quiet girl of 16. Had never got on well with mother but been very attached to father who died when she was 16. Following an overdose of 12 sleeping tablets, she married largely to escape the home. Continual friction with husband and mother-in-law. One child of four months. Her complaints of depression led her doctor to prescribe imipramine 50mg. b.d. which she took for eight months prior to admission. History of a major convulsion four years earlier.

Following a row with own mother took 40 tablets imipramine 25mg. about 14.00hrs. At 16.30hrs. husband noticed drowsiness. Vomited once. Admitted to Royal/
Showing drug-induced accentuation of EEG sleep spindles. The two representative excerpts from the records of Patient K both illustrate stage 2 sleep with comparable amounts of slow wave activity, but the spindles are still accentuated 9 nights after her overdose whereas they appear normal on the 17th night. (The amplification signal refers to the EEG channels and is greater by a factor of 2 than the eye movement channels).
Royal Infirmary of Edinburgh 22.30hrs. Unproductive stomach wash-out One major convulsion. Tachycardia 140, temperature 99.6°F. Easily roused when spoken to. Hypotonia and twitchings of limbs. Next day still slightly drowsy and sudden "pressure" of speech on intermittent words. Transferred to psychiatric ward, to which her baby was also admitted a week later. Therapy directed to family relationships. Discharged after three weeks. Two months later was happier as a rented house was about to become available.

Results

The drowsiness associated with the overdose disappeared about the time of transfer of the patients and their sleep duration became normal. The sleep EEGs showed an excess of drug-induced fast activity having the appearance of accentuated sleep spindles (Fig. 16). The accentuation was obvious on simple inspection for 6, 12 and 7 days after the overdose in the case of patients S, K and M respectively.

Patient S had no REM sleep on either of the first two recorded nights though there was evidence, in the EEG frequencies themselves, of the usual cyclical pattern within the night. REM sleep returned on the 5th night after the overdose and rose abruptly to the high level of 36.0% on the 6th night (Fig. 17). However it was not until the 11th night that the peak abnormal REM percentage of 44.6% occurred. In the mornings following the 10th to 14th nights she spontaneously complained of having/
OVERDOSE OF TRICYCLIC ANTIDEPRESSANTS:
EFFECTS ON REM SLEEP OF 3 WOMEN
(Lewis and Oswald, 1969)

DELAY TO 1ST REM AMITRIPTYLINE IMIPRAMINE NORTRIPTYLINE
<45 min X X X X X X
REM SLEEP IN 1st 2 h >35 min X X

FIGURE 17

The effects on REM sleep of the overdose. The whole night percentages of REM sleep have been plotted and a curve of the equation shown has been fitted to the common data above the asymptote, below which it has been extrapolated by hand. The asymptote represents a mean for normal young women (Williams et al., 1966). At the top of the illustration are shown the nights when the arbitrary limits of normality indicated were exceeded. N.B. x = Night after overdose containing modal % REM sleep — X.
having had dreams which were exceptionally vivid, frightening and often strongly sexual in theme. On the morning after the 11th night, she said: "A terrible dream just as I was going off to sleep, about 20 minutes after". On that night she had in fact gone straight into REM sleep for 2 minutes, after only one minute of Stage 2 sleep and 10 minutes later did so again for a 20 minute period which ended with a brief awakening. She refused to describe the sexual dreams but they involved the psychiatric registrar on two nights. Return to normal took four weeks with an abnormally early onset of the first REM period as late as the 26th night (Fig. 17).

The other patients were essentially similar. Patient K showed an abnormally early onset of REM sleep (9 min.) and frequent brief REM periods in the early night of recording (8th after overdose). On the 9th night there was actual sleep onset REM sleep and on the 10th night she reached 31.1% REM sleep with only 1 minute of NREM sleep preceding the first REM sleep. Her whole-night REM percentages were lower than for the other two patients and her highest all-night percentage was not till the 20th night. She too complained spontaneously of vivid, frightening, "violent", "obscene" or "not nice" dreams from the 13th to the 17th nights.

Patient M had only 6.5% REM sleep on her third night after overdose but nevertheless had an early onset, with a 3 minute REM period after 6 minutes of NREM sleep. She reached a peak on the 10th night with 38.5% REM sleep.
Again she spontaneously complained after the 9th to 13th nights of vivid and frightening dreams: "On a planet, it was going to blow up. An aeroplane, couldn't get it to go.....frightened.....as if trying on and on to wake myself but couldn't". Again she referred to sexual themes but refused to describe them.

The results of the three women have been combined in Fig. 17 and a best-fitting curve (Elderton, 1938) applied to the recovery period, the equation for the curve being as shown. The curve was fitted to the data above the asymptote (taken as 24%) and extrapolated for the portion below the asymptote. This value of 24% is a mean figure for young women taken from Williams et al. (1966), though may represent a slightly high normal for our patients. If in Fig. 17 one considers the area under the fitted curve, but above the asymptote, it is over 150% of that other area which lies below the asymptote, to the left of the curve and to the right of the arrow indicating the approximate time of the overdose. The second area would represent the "loss" of REM sleep time. The peak of the curve is flattened and lies between the 9th and 12th nights. The asymptote is reached after approximately 28 days.

Discussion

a) The Bad Dreams as Withdrawal Symptoms. REM sleep is the state most regularly accompanied by dreaming. The profusion of eye movements, or number per unit time/
During REM sleep, is related to the dream content. The greater the profusion, the more active or vivid are the dreams (Dement and Wolpert, 1958; Berger and Oswald, 1962). Barbiturates decrease both duration of REM sleep and profusion of eye movements (Oswald et al., 1963; Baekeland, 1967). When barbiturates, nitrazepam, or glutethimide are withdrawn the profusion rises above base-line levels (III.C. Allen et al., 1968; Oswald, 1969) with other evidence of increased intensity of REM sleep, including vivid, frightening dreams (Oswald and Priest, 1965; Kales and Jacobson, 1967; Kales et al., 1968b; Evans et al., 1968). Frightening dreams with increased REM sleep are also found in alcohol-withdrawal (Gross et al., 1966; Greenberg and Pearlman, 1967; Bergamasco et al., 1968) and tranylcypromine-withdrawal (Le Gassick et al., 1965). Increased dream vividness also accompanies REM rebound following REM sleep deprivation by behavioural techniques (Pivik and Foulkes, 1966).

Hence when these 3 patients reported bad dreams during the time of peak REM sleep percentage, their dreams were presumably another example of an intensity factor increase. The bad dreams would represent drug-withdrawal symptoms.

The sexual themes may have been fortuitous, or have been a reaction to the male bed-time environment, but were probably a true withdrawal phenomenon. REM sleep is curiously associated with sexual function, e.g. the erections that are an integral part of the state in the male (Karacan et al., 1966). There seems no reason why this feature/
feature, like others, should not be intensified in rebound periods.

Immediate symptoms upon withdrawal of imipramine have been described, such as coryza (in contrast to the drug-induced dryness), giddiness, headache, nausea, abdominal pains and diarrhoea (Kramer et al. 1961; Anderson and Kristiansen, 1959). They are rarely of clinical importance.

Patient M took a fairly small overdose, amounting to the equivalent of four days' maximum clinical doses, and vomited some of it. Yet her rebound phenomena were comparable with those of the other 2 patients who took large overdoses. If it were confirmed, as would be predicted, that there is REM rebound with intense and unpleasant dreams 10-14 days after cessation of prolonged therapeutic dosage, it might help explain why many patients return with symptoms after this delay. Some common process might be reflected in unpleasant affect both by night and by day.

b) REM "Compensation"

When Dement (1960) published the first account of selective deprivation of REM sleep ("dream deprivation") he proposed that the increase which followed deprivation should be regarded as a compensation for the dreams that had been lost. Those who have done similar experiments have not examined the duration of the recovery period but 3 reports indicate a return to normal in from 5 to 8 days (Dement, 1960 and 1965; Kales et al. 1964), and that/
that the total "compensation" is only a fraction of the "lost" REM sleep time. The largest "compensation" appears to be about 60% in one report (Dement, 1965).

The rebound of REM sleep observed considerably exceeded what was lost, as was true of rebound after amylobarbitone (Oswald and Priest, 1965) and after heroin (III.H.). Although intensity increase is a factor during rebound after behavioural deprivation (Pivik and Foulkes, 1966) as well as following drugs, there is nothing to suggest that it is greater after the former. Consequently it appears that the rebound increase in REM sleep upon withdrawal of a drug which had suppressed REM sleep, represents more than mere "compensation", or elimination of some pent-up autotoxin, such as Dement (1965) later proposed.

The REM sleep rebound of Patient K was to less high levels than seen with the other two patients. She had been given 100mg. chlorpromazine on the 5th day, which may have inhibited REM sleep rebound (III.Ei).

c) The Long Time-Scale of the Withdrawal Rebound

The fitted curve in Fig.17 returned to asymptote after a month. It has previously been pointed out (Oswald et al. 1969) that addictive drugs cause (1) immediate reality-escape (2) REM sleep suppression (3) REM sleep rebound. The tricyclic drugs give no immediate relief and are not subject to abuse, but the withdrawal dreams observed would add justification to the view that patients become dependent on the drugs. The course of recovery was similar to that which follows withdrawal of amphetamine (Oswald/
short-acting barbiturates (Oswald and Priest, 1965; Evans et al. 1968), nitrazepam (Oswald and Priest, 1965) or heroin (III.H.), as are the parameters of their mathematical equations. There is, however, one major difference from amylobarbitone or amphetamine, namely, the delay of some 10 days to the peak of the rebound, instead of it following almost immediately upon fall in blood concentration, and this may be attributed to persistence of anti-depressants within the brain, as will be discussed below.

The slow recovery processes underlying REM sleep after drugs is interpreted as the slow reconstruction, through protein turnover*, of the intra-neuronal machinery which governs REM sleep, machinery currently believed to be linked with cerebral mono-amines. In the case of the tricyclic anti-depressants taken by these patients, their presence in the brain for several days would be a time in which modification of REM sleep-governing machinery would have been brought into being. The modifications would presumably undergo correction in the subsequent weeks.

d) Implications for the mode of action of tricyclic anti-depressants.

It has been suggested (e.g. Schildkraut and Kety, 1967) that the level of mood is regulated by the amount of noradrenaline available to post-synaptic adrenergic receptors of some cerebral neurones. The tricyclic drugs are uniquely/

*For a discussion of this hypothesis, see IV. B.
uniquely potent in blocking the active re-uptake mechanism for removal of noradrenaline from the synaptic cleft (Iverson, 1967), and hence should tend to increase the noradrenaline available to the receptors and so elevate mood. They or their products rapidly enter the human brain - witness the immediate suppression of REM sleep (Hartmann, 1968a). Yet their action on mood, unlike that of amphetamine, is delayed 10 days or more and requires weeks to produce durable change. The theory does not meet the clinical facts. A mechanism for slow and lasting neuronal change is required.

The constant protein turnover within cerebral neurones meets the time-scale requirements that underlie the prolonged REM rebound phenomena. The tricyclic anti-depressants affect adrenergic function and data on reserpine to be mentioned in IV indicate that at least some cerebral catecholaminergic neurone functions are indeed governed by the slowness of protein synthesis. A delayed 10-14 day peak recovery process after tricyclic anti-depressants has been demonstrated. A delayed 10-14 days clinical response is normal. While recovery may not be a mirror-image of response, common mechanisms may be suspected, namely the active formation or active reformation of neuronal equipment induced by the drugs or by their release.

Toyoda (1964) described the accentuation of EEG sleep spindles after 12.5-50mg. of imipramine in man. A few hours after massive overdose of tricyclic anti-depressants only minute traces can be found in the blood-stream, from/
from which total disappearance (e.g. Patient 5) is rapid. Yet evidence of the persistence of these drugs or their products in the brain was manifest in the EEG sleep spindles of these patients for 6-12 days, which would suggest that these compounds do not leave the human brain by simple diffusion into a blood-stream where their concentration is low, but only by gradual release from neuronal storage sites as these become reformed. The findings are compatible with the evidence from animal studies that many tissues have high affinity for imipramine, so causing the low plasma levels found in man (Moody et al. 1967).

In conclusion it is suggested that the delayed clinical response to tricyclic anti-depressants, and the weeks required for their beneficial effects to become "fixed", depend upon the slow re-construction of intra-neuronal machinery, and that processes governing sleep, which has been demonstrated, serve as examples of such slow procedures, probably involving both protein synthesis and cerebral mono-amines.
III.G. Comparative Effects of Some Amphetamine Derivatives on Human Sleep.

Oswald et al., (1968) reported a comparative study of the effects of fenfluramine and diethylpropion. The doses used, 40mg. and 50mg. respectively, were considered to be equivalent in their anorectic effect. Silverstone (1968) has criticised this study on the grounds that the dose of diethylpropion was too large. In view of this, the present study, which extends that of Oswald, used 25mg. diethylpropion. The other drugs used were chlorphentermine and amphetamine. As there is evidence, both clinical and neurophysiological, that fenfluramine, in contrast to amphetamine, has "sedative" properties, it was decided to include a tablet containing both amphetamine and fenfluramine.

Method

The subjects were eight young male volunteers of normal weight and of good physical and mental health. In addition to an analysis of sleep stages four other parameters were considered:-

1) Minutes of intervening wakefulness.

2) Number of shifts from any stage of sleep to stage 1 or stage 0 in an upward direction, i.e. from stages 2, 3, 4 or REM, from stage 1 to stage 0 but not from stage 0 to stage 1. Also excluded were sequences of 2,0,1,0,1,2... such a sequence being counted as one shift to stage 0.

3) A measure of subjective quality of sleep was obtained from 5 subjects by having them mark a 10cm. line. One end of this line was labelled "the worst night's sleep you can imagine" and the other "the best night's/
### Table 10

Order of drug administration and doses

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<td>Chlorphenamine</td>
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<td>Placebo</td>
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<td>Fenfluramine</td>
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<td>Amphetamine</td>
<td>Mixture</td>
<td>Diethylpropion</td>
<td>Chlorphenamine</td>
<td>Fenfluramine</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Fenfluramine: 40mg. approx. 0.53 mg/kg.
Diethylpropion: 25mg. approx. 0.35 mg/kg.
Chlorphenamine: 50mg. approx. 0.66 mg/kg.
Amphetamine: 7.5mg. approx. 0.1 mg/kg.
Mixture = Fenfluramine 40mg. + Amphetamine 7.5mg.

*All recordings were made at one week intervals.*
night's sleep you can imagine".

4) Subjective effects of the drugs on sleep were also assessed from the degree of correspondence between the subject's estimate and the EEG estimate of how long he had slept and how long he had taken to go to sleep.

The design of the experiment was based on a Latin square and so the drugs were given in random order. The recordings were made at one week intervals and each subject had two blank tablets at the beginning of the series as adaptation nights. The order of drug administration (Table 10) was not disclosed until after all records had been analysed.

Results

Every effort was made to hold constant the total time available for sleep but some variation was inevitable. However, analysis of variance showed that there were no significant differences in total time in bed either between subjects or between drugs. Nevertheless total sleep time was significantly reduced by the mixture of fenfluramine and amphetamine in comparison with all the other preparations used (Fig. 18 Table 11).

III.6i. Effects on REM sleep.

The delay to the first REM period has an expected bimodal distribution and was therefore analysed by a non-parametric one-way analysis of variance. All the drugs increased this delay over the placebo value (Fig. 19 Table 12). However, fenfluramine had significantly less effect on this measure than chlorphentermine, amphetamine, diethylpropion or the mixture.
### Table 11

Amphetamine derivatives and total sleep time

**A) Analysis of variance †**

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>Degrees of freedom</th>
<th>Mean square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between subjects</td>
<td>33161.73</td>
<td>7</td>
<td>4797.39</td>
<td>1.56</td>
</tr>
<tr>
<td>Within subjects</td>
<td>121275.25</td>
<td>40</td>
<td>3031.05</td>
<td>5.99**</td>
</tr>
<tr>
<td>Drug</td>
<td>51995.96</td>
<td>5</td>
<td>11187.19</td>
<td>5.99**</td>
</tr>
<tr>
<td>Residual</td>
<td>66537.29</td>
<td>35</td>
<td>1888.78</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>134494.28</strong></td>
<td><strong>47</strong></td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**B) Differences between pairs of means ††**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mixture</th>
<th>Diethylpropion</th>
<th>Chlorphenarnine</th>
<th>Placebo</th>
<th>Amphetamine</th>
<th>Fenfluramine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Totals</td>
<td>2704</td>
<td>3539</td>
<td>3569</td>
<td>3441</td>
<td>3457</td>
</tr>
<tr>
<td>Mixture</td>
<td>2704</td>
<td>—</td>
<td>855 *</td>
<td>664 *</td>
<td>757 *</td>
<td>763 *</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>3539</td>
<td>—</td>
<td>27</td>
<td>102</td>
<td>316 *</td>
<td>653 *</td>
</tr>
<tr>
<td>Chlorphenarnine</td>
<td>3569</td>
<td>—</td>
<td>—</td>
<td>75</td>
<td>16</td>
<td>37</td>
</tr>
<tr>
<td>Placebo</td>
<td>3441</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>3457</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>3504</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* p < 0.05  
** p < 0.01
### Table 12

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mixture</th>
<th>Chlorpheniramine</th>
<th>Amphetamine</th>
<th>Diethylpropanol</th>
<th>Fenfluramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rank Sum</td>
<td>190.5</td>
<td>164.0</td>
<td>175.0</td>
<td>164.0</td>
<td>134.5</td>
</tr>
<tr>
<td>Mixture</td>
<td>190.5</td>
<td>-</td>
<td>6.5</td>
<td>14.5</td>
<td>20.0**</td>
<td>26.5**</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>164.0</td>
<td>-</td>
<td>-</td>
<td>8.0</td>
<td>20.0**</td>
<td>49.5**</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>175.0</td>
<td>-</td>
<td>-</td>
<td>12.0</td>
<td>29.5**</td>
<td>110.0**</td>
</tr>
<tr>
<td>Diethylpropanol</td>
<td>164.0</td>
<td>-</td>
<td>-</td>
<td>12.0</td>
<td>31.5**</td>
<td>122.0**</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>134.5</td>
<td>-</td>
<td>-</td>
<td>29.5**</td>
<td>28.5**</td>
<td>85.5**</td>
</tr>
<tr>
<td>Placebo</td>
<td>54.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) Due to the expected bimodal distribution of this parameter, the Kruskal-Wallis non-parametric analysis of variance was used (Wilcoxon and Wilcox, 1964).

* $p < 0.05$  
** $p < 0.01$
**FIGURE 19**

**AMPHETAMINE DERIVATIVES and DELAY REM PERIOD**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Delay to First REM Period (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLANK</td>
<td>XXX X X X</td>
</tr>
<tr>
<td>FENFLURAMINE (40mg)</td>
<td>X X XXX(g) X</td>
</tr>
<tr>
<td>CHLORPHENTERMINE (50mg)</td>
<td>X X X X X X X</td>
</tr>
<tr>
<td>DIETHYLPROPION (25mg)</td>
<td>X X X X X X X</td>
</tr>
<tr>
<td>AMPHETAMINE (7.5mg)</td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td>AMPHETAMINE * + (7.5mg)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>FENFLURAMINE (40mg)</td>
<td></td>
</tr>
</tbody>
</table>

*One subject had no REM sleep when given the mixture.

**FIGURE 18**

**AMPHETAMINE DERIVATIVES and TOTAL SLEEP TIME**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Sleep Time (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLANK</td>
<td></td>
</tr>
<tr>
<td>FENFLURAMINE (40mg)</td>
<td></td>
</tr>
<tr>
<td>CHLORPHENTERMINE (50mg)</td>
<td></td>
</tr>
<tr>
<td>DIETHYLPROPION (25mg)</td>
<td></td>
</tr>
<tr>
<td>AMPHETAMINE (7.5mg)</td>
<td></td>
</tr>
<tr>
<td>AMPHETAMINE * + (7.5mg)</td>
<td></td>
</tr>
<tr>
<td>FENFLURAMINE (40mg)</td>
<td></td>
</tr>
</tbody>
</table>

*FIGURE 18*
Fenfluramine alone did not affect the proportion of REM sleep either over the first three hours of sleep (Fig. 20 Table 13), or over the whole night (Fig. 20 Table 14). Diethylpropion, chlorphentermine, amphetamine and the mixture reduced the amount of REM sleep in the first three hours when compared with placebo and fenfluramine. Over the whole night however, the effects of diethylpropion were not significantly different from either placebo or fenfluramine. The mixture and chlorphentermine, over the whole night, maintained their REM sleep reducing effect compared with fenfluramine and placebo. Chlorphentermine administration resulted in greater REM reduction than diethylpropion or amphetamine. Amphetamine itself reduced REM sleep when compared with placebo.

III.iii. Effects on NREM sleep.

Amphetamine appeared to increase % stage 1 above placebo values over the whole night but this was not significant (Fig. 21 Table 15). The addition of fenfluramine to amphetamine, however, resulted in the increase in stage 1 being significant with respect to all other preparations while chlorphentermine led to a significant increase in stage 1 sleep compared with placebo. In the first three hours of sleep, the only significant effect was with the mixture which resulted in a greater proportion of stage 1 sleep than was found with placebo, diethylpropion or amphetamine.

Despite these changes in the proportions of stage 1 sleep, the number of shifts to stage 1, though greater than the number of shifts with placebo, was not significantly increased/
Table 15

Amphetamine derivatives and percent stage 1 sleep in the whole night

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>Diethylpropion</th>
<th>Amphetamine</th>
<th>Fenfluramine</th>
<th>Chlorphenarnine</th>
<th>Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>115.70</td>
<td>130.10</td>
<td>132.67</td>
<td>133.77</td>
<td>159.06</td>
<td>181.32</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>130.10</td>
<td>14.50</td>
<td>16.97</td>
<td>18.07</td>
<td>28.96</td>
<td>51.22*</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>132.67</td>
<td>2.57</td>
<td>3.67</td>
<td>1.10</td>
<td>25.29</td>
<td>47.65*</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>133.77</td>
<td>-</td>
<td>1.10</td>
<td>18.06</td>
<td>48.65*</td>
<td></td>
</tr>
<tr>
<td>Chlorphenarnine</td>
<td>159.06</td>
<td>-</td>
<td>-</td>
<td>25.29</td>
<td>22.26</td>
<td></td>
</tr>
<tr>
<td>Mixture</td>
<td>181.32</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Source Sums of squares Degrees of freedom Mean square F
Between subjects 371.0035 7 50.1143 2.57
Within subjects 626.5103 40 20.6629 5.22
Drugs 355.1400 5 70.6281
Residual 475.3756 35 13.9250
Total 1196.3198 47

† After arcsin transformation

* p < 0.05  ** p < 0.01
AMPHETAMINE DERIVATIVES and SLEEP DISTURBANCE

(a) NUMBER of SHIFTS to STAGE 1 in FIRST 3 HOURS of SLEEP

(b) AMOUNT of STAGE 1 in FIRST 3 HOURS of SLEEP

(c) NUMBER of SHIFTS to STAGE 1 in WHOLE NIGHT

(d) % STAGE 1 SLEEP in WHOLE NIGHT

AMPHETAMINE DERIVATIVES and REM SLEEP

(a) WHOLE NIGHT

(b) FIRST THREE HOURS OF SLEEP
Amphetamine and the mixture increased the number of shifts to stage 0 compared with placebo in the 1st three hours but the total duration of intervening wakefulness was not significantly increased either in the 1st three hours or over the whole night.

Stage 3 + 4 was not significantly affected in either period of analysis though stage 2 was significantly increased by amphetamine over the whole night.

III.Gi.ii. Subjective Quality.

Administration of the mixture of amphetamine and fenfluramine resulted in the subjects feeling that they had had a "poorer" night's sleep than after any of the other preparations. (Table 16).

III.Giv. Judgement of Sleep Time.

The absolute difference between EEG and subjective estimates of total sleep time was increased by all the drugs but due to very large individual differences, this change in correspondence was not significant. However, the mixture significantly decreased the correspondence between the objective and subjective estimates of the delay to sleep onset even though neither fenfluramine or amphetamine alone had significant effects (Table 17).

III.Gv. Taking all measures into consideration and using Wilcoxon's sign-rank test and repeated comparison with placebo, it was possible to order the drugs. This gave an indication of the global "degree of change" in sleep time for each drug in comparison with the blank. The order for the 1st three/
### Table 16

Amphetamine derivatives and subjective quality of sleep

1) Analysis of variance

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>Degrees of freedom</th>
<th>Mean square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between subjects</td>
<td>226.0471</td>
<td>4</td>
<td>56.51</td>
<td>1.0</td>
</tr>
<tr>
<td>Within subjects</td>
<td>1741.7902</td>
<td>25</td>
<td>109.67</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>1644.1841</td>
<td>5</td>
<td>328.84</td>
<td>5.99</td>
</tr>
<tr>
<td>Residuals</td>
<td>1097.6051</td>
<td>20</td>
<td>54.86</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2967.8375</td>
<td>29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2) Differences between pairs of means

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mixture</th>
<th>Fenfluramine</th>
<th>Chlorpheniramine</th>
<th>Amphetamine</th>
<th>Placebo</th>
<th>Diethylpropion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>122.80</td>
<td>186.16</td>
<td>206.92</td>
<td>221.02</td>
<td>227.99</td>
<td>228.36</td>
</tr>
<tr>
<td>Mixture</td>
<td>-</td>
<td>63.35       *</td>
<td>65.12           **</td>
<td>90.22</td>
<td>105.18</td>
<td>105.56</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>186.16</td>
<td>-</td>
<td>26.77</td>
<td>34.97</td>
<td>41.83</td>
<td>42.21</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>206.92</td>
<td>-</td>
<td>-</td>
<td>14.10</td>
<td>21.05</td>
<td>21.44</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>221.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.96</td>
<td>7.34</td>
</tr>
<tr>
<td>Placebo</td>
<td>227.99</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.36</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>228.36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Only 5 subjects were included in this measure

* * p < 0.05   ** p < 0.01
### Table 17

Amphetamine derivatives and correspondence between subjective and EEG estimates for the delay to sleep onset.

#### 1) Analysis of variance

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>Degrees of freedom</th>
<th>Mean square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between subjects</td>
<td>35007.00</td>
<td>7</td>
<td>501.01</td>
<td>1.65</td>
</tr>
<tr>
<td>Within subjects</td>
<td>109269.07</td>
<td>40</td>
<td>2731.78</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>30518.17</td>
<td>5</td>
<td>6103.63</td>
<td>2.71</td>
</tr>
<tr>
<td>Residual</td>
<td>78751.50</td>
<td>35</td>
<td>2250.04</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>144276.67</td>
<td>47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 2) Differences between pairs of means

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Fenfluramine</th>
<th>Diethylpropion</th>
<th>Amphetamine</th>
<th>Chlorphentermine</th>
<th>Placebo</th>
<th>Mixture</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>99</td>
<td>136</td>
<td>196</td>
<td>225</td>
<td>285</td>
<td>705</td>
<td></td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>-</td>
<td>37</td>
<td>97</td>
<td>126</td>
<td>156</td>
<td>705</td>
<td>*</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>136</td>
<td>-</td>
<td>60</td>
<td>89</td>
<td>119</td>
<td>569</td>
<td>*</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>196</td>
<td>-</td>
<td>-</td>
<td>29</td>
<td>59</td>
<td>509</td>
<td></td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td>225</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>430</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>285</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>450</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixture</td>
<td>705</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* *p < 0.05
/three hours was:

Placebo-Fenfluramine-Diethylpropion-Chlorphentermine-Amphetamine-
Mixture,
and for the whole night:
Placebo-Diethylpropion-fenfluramine-Chlorphentermine-Amphetamine-
Mixture.

Discussion

Several authors have adduced evidence to suggest that fenfluramine and amphetamine are qualitatively and not just quantitatively different. Schmitt and Le Douarec (1965) demonstrated that in rabbits there was a decreased excitability of the reticular activating system and a depression of the recruiting response of the diffuse projection system on administration of fenfluramine. Although these authors could show only a slight modification of the EEG others (Foxwell et al., 1969) have demonstrated marked increase in the amount of cortical slow wave activity as well as confirming and extending Schmitt and Le Douarec's findings. It is pointed out however by Foxwell et al., (1969) that the effects of fenfluramine are not the same at all levels of the CNS. Zianes and Kinnard (1967) have further shown that while amphetamine reduces reserpine depression and increases motor activity in mice, fenfluramine will increase reserpine depression and decrease motor activity. At the clinical level, Brodbin and O'Connor (1967) report sleepiness as a side-effect of fenfluramine though the drug does not appear to affect choice reaction time (Dr. R.M. Barnes, personal communication). In view of these results, the/
The results obtained in the present study and those of Oswald et al., (1969), it would appear that fenfluramine has a dual effect in that it has both excitatory and sedative effects on the CNS.

Oswald et al., (1968) also suggested that a qualitative distinction could be made between fenfluramine and diethylpropion. While the present study would endorse the fenfluramine-amphetamine distinction, the distinction between fenfluramine and diethylpropion is less clear, since the REM suppressing effect of diethylpropion is apparent only in the first 3 hours of sleep and not over the whole night. This was due, presumably, to the small dose of diethylpropion used (0.35mg/kg). For the same reason, it is not surprising that, over the whole night diethylpropion was "nearer" to placebo though in the first three hours more marked effects were detected.

In the present study, no effect was found for fenfluramine on the number of shifts to stage 1 sleep. This is in contrast to the results of Oswald et al., (1969). On re-evaluating Oswald's raw data, it was found that the majority of his subjects were females and that it was these individuals who contributed most to the differences between placebo and fenfluramine. While the dose of fenfluramine in his study and in this one was the same, it is reasonable to assume that the dose/kg body weight would be less in the present study since here the subjects were all males.

If fenfluramine were simply "sedative" and amphetamine "stimulant" a mixture of amphetamine and fenfluramine might be expected to have little or no effect on sleep as each/
Each would cancel the other. In fact the mixture used, 40mg. fenfluramine and 7.5mg. amphetamine, revealed a potentiation of some amphetamine effects, viz. reduced total sleep time, increased % stage 1, decreased stage 2 and changes in subjective effects. This would argue some qualitative similarities between amphetamine and fenfluramine; it also raises the question of the definition of a stimulant.

It would seem that there is no absolute definition of a stimulant for it must depend on the biological system being considered. To a biochemist, a stimulant drug is one which increases turnover or synthesis; to a pharmacologist it is one which increases the rate of firing at either inhibitory or excitatory synapses; to the behaviourist a stimulant elevates mood, increases motor activity and pressure for thought and speech. Fenfluramine is a drug which can exhibit both stimulant and sedative effects. It increases free fatty acids and "ketones" in blood; increases the shifts to arousal in sleep; decreases cerebral responsiveness and can counteract amphetamine induced motor activity in the mouse (Selpharm Laboratories, unpublished observations).
III.H. Heroin and Human Sleep.

Drugs of addiction are taken, initially at least, because they make possible escape from reality into a phantasy, dream-like world. The recent interest in the two kinds of sleep has led to an examination of the effects of drugs which lead to escape from reality and the state of sleep accompanying dreaming. The present evidence (IV.A) suggests that all the common drugs of addiction cause (1) immediate reality escape, (2) initial suppression of paradoxical sleep and (3) after their withdrawal cause a rebound excess of REM sleep.

There has been little study of the effects on sleep of the "hard" drugs of addiction, morphine and heroin. In a study using rats, Khazan et al. (1967) demonstrated that morphine reduces the amount of REM sleep and that continued administration resulted in a gradual return of the proportion of sleep time spent in REM sleep to pre-drug levels. Kay et al. (1968), using human subjects (post addicts), confirmed the REM suppressant effect and in a pilot study of morphine withdrawal found evidence of a delayed REM sleep rebound in 2 subjects.

III.Hi. The subjects used were Drs. I. Oswald, J.I. Evans, M.O. Akindale and the author. Three baseline night sleep records were obtained (excluding the adaptation night record) from each subject, prior to the subcutaneous administration of 7.5mg. heroin; this is equivalent to approximately 20mg. morphine. Sleep recordings were obtained on each of three consecutive nights of heroin administration and the three subsequent withdrawal nights.
boiling water bath for 1 hour.

2) Cation Exchange (Tompsett, 1968).

The column of the cation exchange resin had the following characteristics: Resin - Dowex 50W x 12 (mesh 200/400), Weight - 3 g.
Diameter - 10mm.
Height - 70mm.

The acid hydrolysed urine was applied to the column. The column was then washed with 100ml. of N hydrochloric acid. Morphine was then eluted with 100ml. of 2.5N hydrochloric acid.

3) Solvent Extraction.

An aliquot of the 2.5N hydrochloric acid eluate was neutralised (pH 7) by the addition of solid sodium hydrogen carbonate. The mixture was extracted three times with a chloroform/n-propanol (3/1) mixture.

The combined solvent extracts were dehydrated by the addition of anhydrous sodium sulphate, filtered and then evaporated to dryness in an all glass vacuum still.

4) Colorimetric Determination.

The residue (3) was dissolved in 5ml. of 0.1N hydrochloric acid. 0.5ml. of 20% (w/v) sodium nitrite was added. 2 minutes later, 0.5ml. of 20% (w/v) sodium hydroxide was added and the absorbance measured at 495 millimicrons without delay against an appropriate blank.

5) Thin Layer Chromatography.

Residues obtained after solvent extraction (3) were examined by a thin layer chromatographic technique/
technique similar to that described by Haywood and Moss (1968).

The procedure was controlled by the examination of standard solutions of morphine.

Results

III.iii. Subcutaneous injection of 7.5mg. heroin immediately decreased the proportion of REM sleep in the whole night (Fig. 22). Continued administration of heroin resulted in a gradual restoration of % REM sleep to pre-drug levels though over the period of 3 nights restoration was incomplete. On withdrawal, there was a small but immediate rise in the proportion of REM sleep. However, this rise was not significantly different from the pre-drug proportion ($t = 2.26, p = 0.06$).

III.Hii. Detailed results for these two subjects (I.O. and S.L) are shown in Fig. 23 where REM suppression is obvious in both subjects. Subject S.L. had not returned to base-line two months after the first series of heroin injections. However, again reduced % REM and the gradual return to base-line was observed. This was also true of subject I.O. who had, by the time of this second series of injections, returned to within normal limits. On stopping heroin, one subject (S.L.) showed a marked and immediate REM sleep rebound which declines over about 3 months. The other subject showed little evidence of REM sleep rebound, the only indications of rebound being on the nights of September, 28th and October, 9th when the delay to 1st REM was 42 mins and 33 mins respectively. On October, 10th this subject had a heavy head cold which may have reduced % REM sleep.
EFFECT OF HEROIN ON REM SLEEP OF 4 MEN

FIGURE 22
Figure 23

Upper histogram: subject I.0.

Lower histogram: S.L.

Both sets of results include the results for these two subjects from Figure 22 and show also the nights on which the arbitrary limits of normality indicated were exceeded. Marked individual differences are seen in the magnitude of response to the drug and to its withdrawal.
A best-fitting curve was obtained for the withdrawal period of the subject showing rebound (S.L.). This was found to be a Pearson type I curve (Elderton, 1938) with the equation:

\[
\begin{align*}
y &= 7.7211 \left(1 + \frac{x}{10.4144}\right)^{0.4354} \left(1 - \frac{x}{23.1322}\right)^{0.9671}
\end{align*}
\]

where \(y\) is the \% REM sleep and \(x\) the number of days since the last injection minus the mode. Fig. 24 shows this curve and it can be seen that there is a return to the base-line on night 34 (October, 29th). Nevertheless, as mentioned, Fig. 23 shows evidence of subtle abnormalities of REM sleep for a longer period.

Total morphine output during the initial withdrawal period for the two subjects is shown in Fig. 25. Both subjects had significant amounts of free and conjugated morphine in their urine for 216 hours and 264 hours respectively after the last dose of heroin. It is interesting to note that in Fig. 24 the peak REM percentage was on night 9 which was the first night after heroin excretion had ceased in subject S.L.

**Subjective Feelings**

The subjective experiences resulting from heroin administration have been described by others, but these descriptions were obtained under special circumstances (Lee, 1942; Martin and Fraser, 1961). The immediate post-injection effects experienced by the four subjects here were noticed about 5-10 minutes after the injection. The first/
The curve has been fitted to the data of subject S.L. from Figure 23. N.B. $x$ is as in Fig. 17.
The first symptom to be experienced was described as a "warm, glowing flush in the abdominal region". This was quickly followed by an intense itching particularly around the nose and mouth. If, at this point, the subject stood up, there was ataxia and a "feeling of being drunk without the euphoria of alcohol". There was also a sense of restriction of breathing due to a "lump in the throat". When lying in bed in the dark there was an intense desire to remain still and "pressure to carry on an hypnogogic conversation with yourself", the so-called 'soap-boxing' effect. These two phenomena were associated with a feeling of disembodiment and depersonalisation as demonstrated in the following hypnogogic hallucination experienced by S.L.

"I was lying in bed when the room suddenly seemed as though the light had been put on. Several people, unknown to me came into the room and looked at me in bed. I was one of those people. It was not frightening because I was objectively standing by looking at myself looking at myself. I was orientated enough to appreciate that I had to remember these events. Suddenly I did panic and opened my eyes. After a second or two I realised what had happened and that I must remember it. After getting settled down again to go to sleep several more people came in with flame torches. This was slightly alarming. I seemed to sit up with a start but was prevented by someone bending over me. Again I was standing watching this/
/this objectively. The overall effect was unpleasant and there were several moments of panic."

The other subjects also commented on these attacks of panic which lasted only a few seconds and would come on even though the mind was a "complete blank", which may have been related to respiratory effects. The frequency and intensity of all these phenomena never diminished over the period of heroin administration. The mornings were characterized by headache, dryness of the mouth, physical and mental inertia and loss of libido.

The withdrawal symptoms, which were apparent in I.O. and S.L. in the late afternoon prior to the last three injections of heroin, included weariness, headache, yawning, shivering, coryza, hand tremor, poor grip and a mild depression. Apart from the weariness and coryza, these symptoms had disappeared by the end of the first week of withdrawal.

During the second period of heroin administration and the initial withdrawal period, diurnal measurements of heart rate, respiratory rate, ventilation volume and forearm blood flow were obtained and have been reported elsewhere (Rosenthal et al., 1969). The only immediate effect of the heroin was a reduction in ventilation volume. No withdrawal effects were observed. A diurnal two-fold increase in forearm blood flow was observed but this did not appear to be related to the heroin or its withdrawal.

Discussion/
Discussion

It has been commented (e.g. Beneau, 1969) that in experimental self-addiction using rats or monkeys some animals will not become addicted, a situation analogous to man and alcohol. The results from the two subjects in the second study may indicate individual differences in response. Neither subject has ever been addicted to any drug, though S.L. is an inveterate smoker, and neither experienced withdrawal "craving" for the drug. However, one may speculate that the marked and prolonged recovery process demonstrated in S.L. could indicate a constitutional difference rendering him more "at risk".

A prolonged recovery time from opiate addiction has been described by Himmelsbach (1942) for several physiological indices. However as his subjects were physically dependent on opiates and had been for some time, many of these variables (e.g. basal metabolic rate, erythrocyte sedimentation rate, haemocrit and caloric intake) would have been confounded by the prior nutritional state. Nevertheless, sleep disturbance based on nurses' observations, was apparent for approximately two months after the last dose of opiate.

Fraser et al., (1961) and Martin and Fraser (1961) have similarly described withdrawal from heroin in patients serving sentences for contravention of narcotic laws. Using subject and observer rating, the Addiction Research Center Inventory (Haertzen, 1965a,b)showed that after 10 days withdrawal, the intensity of the abstinence symptoms was still 10 points above base-line. Examination of the curve of "abstinence intensity" shows it to be exponential and that it is unlikely/
unlikely that base-line would have been reached for about another 2 weeks.

The hypothesis that drugs of addiction have a characteristic sequence of events on sleep is supported in part of this study. There can be an immediate rebound of REM sleep on withdrawal from heroin though there would seem to be considerable individual differences.
III.I. Subjective estimates of sleep: an EEG evaluation.

Introduction

McGhie and Russel (1962) have demonstrated differences in the amount of sleep taken by different age groups and between the sexes. These have been confirmed by Tune (1968). Again Masterton (1965) has suggested differences in the amount of sleep obtained by the various grades of hospital medical staff. These surveys utilised subjective assessment and presupposed that subjects can estimate how long they are awake in the night. The same assumptions apply to the study by McGhie (1966), which, while confirming that there is a sleep disturbance in many psychiatric patients, was unable to differentiate the affective disorders by this means.

The importance of these assumptions becomes more critical when evaluating hypnotic and other drugs such as slimming pills, suspected of disturbing sleep. Using subjective methods Parsons (1963) suggests that there is little justification in classifying the barbiturates in terms of their length of action, and Silverstone et al. (1968) using interview techniques, indicated that diethylpropion (Tenuate, an amphetamine derivative) caused difficulty in falling asleep. Oswald et al. (1968) using sleep EEG techniques has confirmed that diethylpropion disturbs sleep significantly. While there has been in recent years a considerable increase in the amount of research into sleep, occasioned by the finding of a physiological concomitant of dreaming (Aserinsky and/
The objective EEG study of sleep mitigates against the use of large numbers of subjects. If the object is to study the sleep of large numbers of normal or psychiatrically ill subjects, it is more practical to use the interview (Clement and Bourliere, 1961), questionnaire (McGhie and Russell, 1962) or sleep chart (Hasterton, 1965; Tune, 1968) methods. Despite the well known problems of subjective assessments little attempt has been made to validate such estimates of sleep. This paper attempts such a validation and considers changes in estimates brought about by the administration and withdrawal of drugs.

Method

6 physically and mentally healthy young males acted as subjects. There was no evidence that these volunteers were unusually concerned about their sleep. They were not selected on the basis of personality or whether they considered themselves "good" or "poor" sleepers (Monroe, 1967).

On reporting to the laboratory on recording evenings electrodes were attached at the standard EEG and EOG sleep recording positions (Oswald and Priest, 1965). They then retired to quiet air-conditioned bedrooms, separated from the recording room. EEG recording was continuous from approximately 23.30 hours to 08.00 hours.

116 subject-nights were recorded: 29 control (pre-drug), 43 drug and 44 withdrawal. The control recordings were obtained for each subject followed by the drug night/
This investigation was an adjunct to studies on the effects of drugs on sleep. There was therefore no control over the drugs or the doses included. They were: Largactil (chlorpromazine) 25mg. and 100mg.; Heminevirin (chlormethiazole) 2G; and a hypnotic, Tuinal (quinalbarbitone sodium and amylobarbitone sodium) 600mg.

Drug administration was continuous over 5-14 nights although recordings were not taken every night. On stopping the drug, recording was continued though again not necessarily on successive nights throughout the withdrawal period.

In this study three parameters measurable from the EEG were of interest since these are the ones most commonly considered in surveys and most usually asked about by a doctor. They were, (i) delay to sleep onset, (ii) total sleep time and (iii) number of awakenings. With regard to this last parameter it was considered unreasonable to expect subjects to be aware of awakenings of less than 1 minute. Therefore, only these periods of 1 minute or more were noted although shorter periods were taken into consideration when calculating total sleep time. It is possible that some subjects register very brief periods of arousal. For example, after a body movement it is not uncommon to find that the α-rhythm is present for a few seconds. If the α-rhythm is present for 10 seconds or more, then this is counted as an awakening when calculating total sleep time but not the number of awakenings. Indeed it is possible that some individuals may on some occasions be able to register arousals of the order of one or two seconds.
Mean Judgement - Tendency (over-estimation or under-estimation) of subjects during the control, drug, and withdrawal phase.

Figure 26

Mean Judgement - Error (absolute error) of Subjects during the control, drug, and withdrawal phase.

Figure 27
On waking in the morning, the subjects were asked to estimate the same three variables. On no occasion were they told how close to the EEG measures their estimates were.

**Results**

Two measures of accuracy of estimate were derived from the objective EEG data and the subjective estimates. The first, "judgement-error", was the absolute difference between objective and subjective estimates. The second measure took account of whether there was subjective over- or under-estimation. This was the "judgement-tendency" (Smith and Beecher, 1960). For example, a subject may estimate his total sleep time as 420 minutes (7 hours) and his delay to sleep onset as 40 minutes whereas they might be 450 minutes ($7\frac{1}{2}$ hours) and 20 minutes respectively on EEG criteria. In this case the judgement-error would be 30 minutes for total sleep time and 20 minutes for the delay to sleep onset while the judgement-tendency would be $+30$ minutes and $-20$ minutes respectively. The means for the two measures on each phase of the study and for each variable are shown in Figs. 26 & 27. As can be seen subjects under-estimated their total sleep time but over-estimated the delay to sleep onset and the number of awakenings.

Non-parametric analysis of variance for related samples demonstrated that there was no difference between subjects or drugs on any of the variables (Siegel, 1956).

While there were differences between the control,
<table>
<thead>
<tr>
<th></th>
<th>Total Sleep Time</th>
<th>Delay to Sleep Onset</th>
<th>Number of Awakenings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 29)</td>
<td>0.18</td>
<td>-0.06</td>
<td>-0.09</td>
</tr>
<tr>
<td>Drug (n = 43)</td>
<td>0.60**</td>
<td>0.38**</td>
<td>0.22</td>
</tr>
<tr>
<td>Withdrawal (n = 44)</td>
<td>0.58**</td>
<td>0.47</td>
<td>0.09</td>
</tr>
<tr>
<td>Overall for three phases (n = 116)</td>
<td>0.60**</td>
<td>0.42**</td>
<td>0.09</td>
</tr>
</tbody>
</table>

1. Spearman rank correlation (Siegel, 1956)
2. The overall correlation was calculated separately and not averaged from the individual correlations.

* p < 0.05
** p < 0.01
control, drug and withdrawal phases on the variables (Fig. 26), Table 18 shows that there is a relationship between the subjective and objective estimates during the drug and withdrawal periods for total sleep time and delay to sleep onset. However, there was a significant difference between the objective and subjective estimates as shown in Table 19. In other words, although subjects are not accurate in their estimates, their estimates do shift in the same direction as the objective measures.

Discussion

The assessment of the effectiveness of hypnotic drugs is important and the only practical way in terms of labour and the number of subjects that can be used, is some form of subjective estimate of sleep. An overall evaluation of the night's sleep has been shown to have a poor correlation with nurses' ratings and motility scores (Hinton and Marley, 1959; Cox and Marley, 1959). This study would confirm the unreliability of subjective estimates when compared to objective EEG measures. That a subject is unreliable in judging his sleep is unfortunate since "subjective evaluation (of sleep) is important, if for no other reason than that the clinical use of hypnotic agents is most frequently concerned with alleviation of patients' complaints," (Lasagne, 1954). However, this study would suggest that provided evaluation of the drug if not based on absolute time estimation but on relative measures the subjects would be reasonably accurate since the correlations are positive and significant.
Table 19

Analysis of differences between objective and subjective (absolute) estimates.

<table>
<thead>
<tr>
<th></th>
<th>Total Sleep Time</th>
<th>Delay to Sleep Onset</th>
<th>No. of Awakenings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-3.146</td>
<td>+3.329</td>
<td>-0.569</td>
</tr>
<tr>
<td>Drug</td>
<td>-2.021*</td>
<td>+1.017</td>
<td>+3.89***</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>-1.715</td>
<td>+1.864</td>
<td>+2.372**</td>
</tr>
</tbody>
</table>

1. Wilcoxon's matched-pairs sign-rank test (Siegel, 1956)

* p < 0.05
** p < 0.01
*** p < 0.001
In the present study, however, there is a striking withdrawal effect seen in all parameters. It is well known that patients, when their sleeping tablets are stopped will complain of their sleep. The present study demonstrates that they exaggerate the extent of this "poorness" of sleep.

Overall assessment of sleep by the subject must depend partly on his estimate of the duration of the sleep, which in turn depends on how long he takes to fall asleep, and how often, and for how long he wakens. If he is inaccurate in his assessment of these factors then he will, ipso facto exaggerate the poorness of his sleep. For example, one subject, on the first night of stopping 600mg. Tuinal adamantly maintained that at most he had slept for 30 minutes in the whole night. He had in fact slept nearly three hours.

In the design of clinical trials of hypnotic drugs the withdrawal effect is important. It is not uncommon, e.g. Parsone (1963) to find that placebo is administered immediately after the drug. The withdrawal effect makes it inevitable that placebo will appear worse than the drug. It is therefore essential either to separate the placebo from the drug by many nights or to have the placebo preceding the drug on all occasions. The same considerations apply to the comparison of hypnotics; their administration must be contiguous otherwise the subjects will tend to compare the second drug with the nights intervening between the first and second drugs. These intervening nights are/
/are withdrawal nights.

Our knowledge about norms for the sleep of healthy subjects under different conditions depends on subjective estimates (Gesell and Amatruda, 1945; Lewis and Masterton, 1957; Williams, 1959; McGhie and Russell, 1962; Murray, 1967; Tune, 1968) as does information about the patterns of sleep disturbance in psychiatric patients (Hinton, 1963; McGhie, 1966). This study would suggest that the values for total sleep time etc. quoted in several of these studies are if anything under-estimations but in view of the poor correlations obtained in the control period in this study they are more likely to be unreliable.

Monroe (1967) has demonstrated personality differences between people considering themselves to be "good" or "poor" sleepers. It is also known that personality is a factor in accuracy of estimation of short time intervals (Orme, 1962). A study is currently being carried out to investigate this in relation to accuracy of sleep estimation.

It is of course possible that the drug and withdrawal effects observed are related to altered time perception and not to altered sleep. While this hypothesis may be true, it does not alter the implications of the study for the design of trials of hypnotics or of the practical considerations for the doctor trying to stop a patient taking hypnotics.
IV. GENERAL DISCUSSION
A) **Addictive Drugs cause Suppression of Paradoxical Withdrawal Rebound.**

Drugs of addiction are taken, initially at least, because they make possible an escape from reality. Those most vulnerable are people who, through their personalities, are beset by conflicts and anxieties. They obtain but little solace from contact with the real world. Access to certain drugs enables them to escape to a less harsh world, a world removed from reality and nearer to the world of dreams. It is less harsh too in that those with whom they associate are of kindred spirit and the result is a therapeutic group. However much the cult of transcendentalism is abhorred or condoned it is undoubtedly less harmful since its tenets deny its adherents escape through drugs.

There was until recently a distinction made between drugs of addiction and drugs of habituation. Only the former were supposed to provoke "physiological" abnormalities on withdrawal. The Interdepartmental Committee on Drug Addiction of the Ministry of Health (1961) accepted this line of thinking and so did not consider amphetamine as an addictive substance. The distinction between "physiological" and "psychological" dependence was a relic of a past in which the medical profession regarded the body and soul as dichotamous. Today, it is believed that mental events are determined by brain (physiological) events. Craving is the most characteristic feature/
/feature of any abstinence syndrome. As this was merely psychological it was accorded little importance. Is it not ludicrous not to recognise that the craving for a drug has its basis in brain function, that function being as yet unascertainable, just as all drugs that are said to produce "psychological dependence" do so because they affect brain physiology and change the person's feelings and thoughts? Given sophisticated techniques for measuring brain function, techniques sensitive to as little as a single capsule of barbiturate, "physiological" features of dependence and abstinence will inevitably become more and more frequently reported. The amphetamine and phenmetrazine evidence (Oswald and Thacore, 1963) was but an early example and as has since been demonstrated, it is unwise to condemn a drug because of its parentage, e.g. fenfluramine.

Emphasis has been placed on the long-lasting increase in the amount of REM sleep subsequent to drug withdrawal. It has been pointed out that not only is there an increased pressure for REM sleep but that there is also an intra-REM pressure as demonstrated by the increased profusion of the eye movements. That these phenomena are not due solely to a restoration of what has been lost during drug administration is shown by comparing the recovery periods following behavioural and pharmacological REM deprivation. In behavioural deprivation, the rebound accounts for about 30% of what has been lost, whereas after pharmacological deprivation of REM sleep (which/
(which is not total deprivation) the rebound is of the order of 120-150% of that lost. Despite the relatively small compensation after behavioural deprivation, Pivik and Foulkes (1966) have shown that in this period there was an increase in profusion of eye movements and increased vividness and bizarreness of dreams. The commonly encountered patient who has been taking barbiturates for years, when studied in the laboratory, reveals a big rebound into high levels of paradoxical sleep with nightmares. Restoration of the drug restores sleep to normal while re-withdrawal causes a return of the abstinence syndrome.

In patients who have just had their hypnotics withdrawn, a noticeable feature of their behaviour is high anxiety level. The anxiety is manifest by day, as well as in their nightmares. This anxiety is literally caused by the medication they had been given for possibly brief periods only, but it must be seen as a potent factor in the aetiology of prolonged dependence upon hypnotic drugs. To suppose that hypnotics have effects limited to a few hours or, at most, the 48 hours of detectable blood levels is a common error. Rebound sequelae may last for weeks.

One must further conclude that the vast and increasing consumption of hypnotics is iatrogenic. Consumption of barbiturates doubled in Britain between 1969 and 1964; it doubled in Czechoslovakia between 1958 and 1965 (Vondracek et al. 1968); the absolute expenditure/
Expenditure on hypnotics in Australia doubled between 1961 and 1965 (Commonwealth Director General of Health, 1962, 1966) while in the U.S.A. "from 1952 to 1963, the retail sales of sedatives and tranquillizers increased 535 percent" (Dept. of Health, Education and Welfare, 1967). A major corollary of this world-wide increase, and one which throws an increasing burden on medical services, is the rise in the use of drugs for deliberate self-poisoning, admissions for which have increased about tenfold in as many years in both Edinburgh (Matthew, 1966) and Western Australia (Oswald, 1966) even though completed suicide rates have varied little. The increases in self-poisoning with hypnotics and the increasing realisation that brain physiology is disturbed for many weeks after clinical recovery will inevitably bring about a demand for longer follow-up of the patient by the psychiatric services attached to poison treatment centres. This will strain existing resources to their limit.

As has been discussed throughout this dissertation, drugs other than hypnotics cause a suppression of paradoxical sleep with rebound increase on withdrawal. It should be noted that there is representation from a vast diversity of chemical groups showing this sequence of events. Emphasis has been laid on the rebound increase of paradoxical sleep as a nocturnal correlate of that unpleasant day-time mood which makes the patient crave his drug. Other psychoactive drugs have different/
Different actions and one, reserpine, is notable for the unpleasant mood it induces at a time when its administration, not its withdrawal, is promoting paradoxical sleep at night (Hartmann, 1966). It would be wrong to assume that increased paradoxical sleep was invariably associated with intensification of mood in the direction of negative hedonistic tone. There could be circumstances where it was associated with intensification of other emotions such as sexual emotion (Oswald et al., 1966). There are potent psychoactive drugs which do not induce dependence. Though there is reduced paradoxical sleep with administration of these drugs, they have been said not to provoke a rebound in withdrawal e.g. amitriptyline (Hartmann, 1968) and nielamid (Jouvet, 1967). However, the evidence for the non-occurrence of withdrawal rebound is now not so convincing at least for very high doses of the tricyclic anti-depressants and for the hydrazine MAOIs (Akindele, 1969). Interestingly ECT, also used to treat depression, suppresses paradoxical sleep but causes neither rebound (Zarcone et al., 1967) nor addiction. Diphenylhydantoin (Epanutin), like ECT causes suppression but no tolerance and no rebound of paradoxical sleep (Cohen, et al., 1968). This drug could, in a sense, be thought to be addicting but within the generally accepted ambit of addiction it can be excluded. Phenothiazines again are different and whether or not there is observed REM sleep enhancement and no withdrawal rebound or REM sleep depression and slow rebound is dose dependant.
dependent. Although drugs like amitriptyline and chlorpromazine are potent and valuable drugs clinically, they do not give the patient an immediate escape from reality and do not invite abuse. Equally, administration of Nardil must be continued for at least 10 days before any clinical improvement is observed and the same time for the appearance of changes in REM sleep. Again, there is no possibility of immediate escape.

At present then it is possible to say that the study of sleep, and especially the phase associated with divorce from reality, has provided a tool for the study of addictive drugs and has made it possible to demonstrate neurophysiological consequences of their administration which extend far into the post-withdrawal period. The drug LSD, while liable to abuse, is generally not regarded as addictive in a manner comparable to amphetamine but as belonging to a different category of mind influencing drugs, perhaps like cannabis. Muzio et al. (1965) showed that LSD is unusual in that it enhances paradoxical sleep and that the rebound on withdrawal was a rebound decrease of paradoxical sleep.

Among the slimming pills known to cause dependence,
dependence, amphetamine, phenmetrazine and diethylpropion share the usual effects on paradoxical sleep as does chlorphentermine though there are no cases of dependence to this last drug in the literature. In contrast, fenfluramine, though chemically related, has no effect on paradoxical sleep (Oswald et al. 1968). It will be a matter of interest to see whether or not time will prove fenfluramine to cause dependence for this would provide one test of the proposition that drugs capable of causing dependence are drugs which suppress paradoxical sleep and provoke a rebound enhancement of paradoxical sleep when withdrawn.

This alone can clarify the link between addictive properties and effects on paradoxical sleep. The link may be direct, it may be chance, or it might be connected with the phenomenon of the rebound and the rapidity of onset of the rebound. An abrupt rebound, manifest in paradoxical sleep, could simply reflect the abrupt rebound distortion of numerous other, less easily measurable, features of central nervous activity.
Table 12

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mixture</th>
<th>Chlorphentermine</th>
<th>Amphetamine</th>
<th>Diethylpropion</th>
<th>Fenfluramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rank Sum</td>
<td>190.5</td>
<td>184.0</td>
<td>176.0</td>
<td>164.0</td>
<td>134.5</td>
</tr>
<tr>
<td>Mixture</td>
<td>190.5</td>
<td>-</td>
<td>6.5</td>
<td>14.5</td>
<td>26.5**</td>
<td>56.0**</td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td>184.0</td>
<td>-</td>
<td>-</td>
<td>8.0</td>
<td>20.0</td>
<td>49.5**</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>176.0</td>
<td>-</td>
<td>-</td>
<td>12.0</td>
<td>-</td>
<td>31.5**</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>164.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>29.5**</td>
<td>110.0**</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>134.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>85.5**</td>
</tr>
<tr>
<td>Placebo</td>
<td>54.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) Due to the expected bimodal distribution of this parameter, the Kruskal-Wallis non-parametric analysis of variance was used (Wilcoxon and Wilcoxon, 1964).

* p < 0.05  ** p < 0.01
IV.B. The Possible Mechanisms Involved in the Effects of Drugs on REM Sleep.

Several workers have indicated that there is a "need" to dream. It was thought that the increase in the amount of REM sleep following deprivation was a compensation for the dreams that had been lost (Dement, 1960). However, as Dement (1965) later appreciated, this "psychic" hypothesis is unlikely. Doubt had been shed on the proposition that REM sleep was the only time that mental life was present (Kamiya, 1961; Foulkes, 1962; Rechtschaffen et al., 1963). This, taken in association with animal studies (Jouvet et al., 1964; Jouvet, 1965), led Dement to state that "It is likely therefore that loss of the psychological experience of dreaming has little to do with the increased tendency for REM sleep to occur (after deprivation)". He replaced this "loss of psychological experience" hypothesis with a biochemical one. In this it was suggested that whatever it was that controlled REM sleep built up during deprivation and at some critical level began to act like an "autotoxin". These deductions were made on the basis of behavioural deprivation studies and the extrapolation to drug studies would suggest that rather than there being a passive build-up of a hypothetical substance, there is some active feed-back mechanism operating.

The nature of the graphs obtained by plotting percent REM sleep on each night with continued drug administration demonstrates that "tolerance" develops. If Dement's "autotoxin" hypothesis were correct, then a rebound would be expected/
/expected during continued drug administration. This does not occur. The amount of REM sleep in the night can remain at base-line levels for some time in the continuing presence of the drug. It is more likely therefore that some feed-back mechanism operates to control the amount of REM sleep in the night. The constancy of the REM sleep within a species suggests that it may be genetically determined.

The most obvious conception of the result of a demand for more of that which induces REM sleep is that a secondary mechanism is brought in to play, which, after a few nights, is capable of fulfilling the role of the primary mechanisms. On stopping drug administration, the primary mechanism is again able to function fully provided the drug is immediately cleared from tissues. The secondary mechanism is not abandoned immediately however; it continues to operate for some time at a decreasing rate. Thersby giving rise to the progressive return to "normal" values of REM sleep. A delay to the peak of the rebound may indicate the rate of clearance of a drug from brain tissue as was suggested in the discussion of the results obtained with the tricyclic anti-depressants and heroin. Postulating a secondary mechanism leads to complications and for the drug administration period, if taken in isolation, such a postulate is unnecessary. There is no reason why the results from this period of the experiments should not be explained on the basis of an increasingly efficient detoxication mechanism. This would mean that the drug would become progressively less effective/
effective and more rapidly made inactive. That this is possible is evidenced by the tendency of patients taking hypnotics or addicts taking heroin to increase the dose and in the case of the latter to increase the frequency of drug ingestion. It is of course equally possible in terms of Dement's hypothesis that some of the receptors for the substance controlling REM sleep are blocked and that there is a build up of this substance sufficient to occupy unblocked receptor sites, or indeed to induce receptors. However, neither a detoxication mechanism nor accumulation of an autotoxin could account for the rebound and the slow return to normal. It is unlikely that a detoxicating mechanism would have a facilitatory effect on REM mechanisms nor is it likely that the autotoxin would be dissipated as slowly as to result in the REM times remaining elevated for some weeks.

In view of these arguments it would seem reasonable to postulate a secondary mechanism to account for the sequence of events observed. Schematically the sequence of events would be as in Fig. 28.

It is well known that the rate of production of enzymes can be adjusted to cope with the body's 'demand' for them. A blockage in any enzyme system results in a gradual increase in the rate of production. The increased production rate and the increased amount of "free" enzyme that would be present when the block is removed would not halt immediately or dissipate immediately. Such enzyme induction has been demonstrated in studies with the bacterium Escherichia coli involving the organism's production of isoleucine which/
FIGURE 28  Schematic representation of the activity of the mechanisms involved in REM sleep during drug administration and withdrawal and the resultant variations in REM sleep amount.

--- REM sleep.
----- Primary mechanism.
......... Secondary mechanism.
FIGURE 23

Upper histogram: subject 1.0.

Lower histogram: S.L.

Both sets of results include the results for these two subjects from Figure 22 and show marked individual differences in the magnitude of response to the drug and to its withdrawal. Differences are seen in the magnitude of the arbitrary limits of normality indicated on the graphs on which these two subjects for these two subjects include the results of both sets of results.

HEROIN 15 19 21 29 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60

BASE-LINE MEAN

HEROIN 15 19 21 29 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60

BASE-LINE MEAN

REM SLEEP IN 1st 2h > 35min

% REM SLEEP IN WHOLE NIGHT

REM SLEEP IN 1st 2h > 35min

% REM SLEEP IN WHOLE NIGHT

DELAY TO 1st REM < 15min

( Doseage - 7.5 mg Nightly )

EFFECT OF HEROIN ON REM SLEEP OF 2 MEN

JULY

AUG.

SEP.

OCT.

NOV.

DEC.

JAN.

FIGURE 23
which is needed for protein synthesis. Using radio-active tracer techniques, it has been shown that a deficiency of isoleucine leads to an increase in production while an excess in decreased production rate.

However, any postulated mechanism involving enzyme induction or receptor induction results in an unwarranted assumption. The review of the literature and the present experiments demonstrate that drugs of diverse chemical structure all result in the same sequence of events in REM sleep and so hypotheses such as those above would have inherent in them the premise of non-specificity of the enzymes or receptors. This is highly improbable. The effect of the drugs is much more likely to be a non-specific one such as an inhibition of the rephosphorylation of AMP to ATP or a similar but indirect effect at the cytochrome level of the respiratory chain. These have been suggested as the mode of action of the barbiturates (Aldridge, 1964; McIlwain, 1964). At the same time, a search of the literature has not revealed any evidence which would suggest that the time course for alterations in rephosphorylation would be that predicted from the sleep studies. On the other hand there is no reason why effects on rephosphorylation should be no more than an intermediate step.

The time course of the recovery period extending, as does, over a period of 4 to 8 weeks, may betray some active repair process in intraneuronal machinery. The most likely fundamental mechanism would involve protein synthesis. The synthesis is seen as the creation of new neuronal machinery/
/machinery either to replace what has been damaged by external insult or to replace what has been created to counter-act (or make possible tolerance to) a drug.

Induction of protein synthesis appears to be related to the development of morphine tolerance as witnessed by two facts. First there is an increase in the protein content of microsomal-soluble fraction of the brain of tolerant animals. Secondly, 6-azaguanine, which inhibits protein synthesis, is effective in blocking tolerance to the lethal and analgesic effects of morphine (Spoerlein and Scrafani, 1967; Cox et al., 1968). Collier (1965a and b) has discussed the possibility of induction of so-called "silent" receptors, which are themselves proteins. The results obtained by Spoerlein and Scrafani would be consistent with this hypothesis as would the results of Cohen et al. (1965) who demonstrated that actinomycin-D, another inhibitor of protein synthesis, also blocks tolerance to morphine. However, Cohen et al. interpreted their results as indicating an induction of synthesis of polypeptides by morphine.

Haynert and Klingman (1962), using very large doses of morphine, found an increase in brain norepinephrine and suggest that tolerance develops as a result of this increase in norepinephrine synthesis brought about by induced synthesis of an enzyme in the biosynthetic pathway for the catecholamines. On the other hand, Way et al. (1968) have implicated 5-HT mechanisms in the development of tolerance to morphine. In this study, not only did they confirm that protein inhibition stopped the development of tolerance, they found that in the tolerant animals there was an increased 5-HT turnover. The study/
/study was extended to examine the effects of para-
chlorophenylalanine (PCPA), a 5-HT synthesis inhibitor, on
the development of tolerance. As predicted, PCPA
administration resulted in there being no tolerance and it
was concluded that the protein involved in morphine
tolerance was tryptophane hydroxylase since hydroxylation
is the rate-limiting step in 5-HT synthesis. It is
interesting to note that PCPA suppresses REM sleep
(Weitzman et al., 1968; Dement et al., 1969).

However, the report by Clouet and Ratner (1966) that
the incorporation of C\textsuperscript{14} leucine into total brain protein is
reduced in morphine tolerance raises additional questions.
They interpret their data as indicative of depression of
protein synthesis in tolerance. The data, however, might
equally well indicate decrease in protein turnover or
alteration in protein composition in the tolerant animal.

Finally, it is worth noting that in a discussion,
Dement (1968) comments that streptomycin produced a "strange"
effect on REM sleep: it decreases the amount. Perhaps
in the context of the present hypothesis it is not such a
"strange" effect.

It was suggested that an intermediate step in the
effects of drugs on sleep might be a blockage in rephosphoryl-
ation. Protein synthesis is inhibited by oxygen lack and
the presence of 2,4-DNP. It is therefore thought that the
incorporation of amino-acids into proteins requires ATP,
the system being as follows:\/-
follows:

\[
\begin{align*}
R-CH-CO_2H & \rightarrow \text{R-CH-CO}_2 \text{E} & \text{AMP} & \rightarrow \text{R-CH-CO}_2 \text{eRNA} \\
\text{NH}_2 & + \text{ATP} & \rightarrow & \text{NH}_2 & + \text{P2P} & \rightarrow & \text{NH}_2 & + \text{AMP} + \text{E} \\
\hline
\end{align*}
\]

(After McIlwain, 1966).

\((E = \text{amino-acid activating enzyme}).\)

If drug effects on sleep were mediated indirectly through inhibition of rephosphorylation, then the predicted result would be a decrease, not an increase, in protein synthesis. In view of the findings of protein synthesis induction during tolerance and the non-development of tolerance with blockade of protein synthesis, any possible effects on rephosphorylation can probably be discounted.

A rebound is not a phenomenon unique to REM sleep. No matter which biological system is disturbed, renewal of the disturbance will result in an overshwing. Although many diverse drugs result in the appearance of the same phenomenon, it does not imply a common mechanism. Furthermore, all the evidence so far mentioned relates to the phenomenon of tolerance, not withdrawal, and there is no good reason why it should be assumed that withdrawal is the mirror image of tolerance.

Administration of centrally acting drugs, even in clinical doses, is an insult to cerebral neurones. Curves of similar duration to those found with REM sleep after drug administration are found with other forms of insult/
/insult to cerebral neurones. After 28 ECTs in one week (an overdose of anti-depressant treatment) there are EEG abnormalities which take three weeks to disappear (Callaway, 1950). The technique used, estimating the delta index, i.e. the "amount" of EEG waves less than 8 c.p.s., with a map measurer, was crude but more refined techniques including evocative procedures, revealed abnormalities 5-7 weeks after the last ECT of a normal course of treatment (Roth, 1951).

Insult to rat cerebral neurones by means of hypoglossal axon injury (Watson, 1968) results in a recovery process extending over some 4-10 weeks in which nucleolar nucleic acid, and, by inference, ribosomal protein synthesis, follows a curve very similar to that found in recovery from anti-depressant overdose and from heroin.

An example of drug effects apparent long after the drug has been cleared from brain tissue is found with reserpine, notable for causing depression on a long time scale. This drug depletes brain cells of catecholamines very rapidly and itself disappears from brain tissue in a matter of hours. Yet the catecholamine restoration process follows a course of 4-8 weeks (Carlsson et al., 1957). The slowness in the reformation of storage particles for catecholamines in the cell bodies is believed to depend on protein synthesis (Iverson, 1967).

There are many examples of slow recovery processes in the behavioural sciences but the most apposite example is the finding by Flexner et al. (1967) that puromycin can inhibit maze learning in the rat for up to 3 months.

Puromycin is/
is a drug inhibiting RNA induced protein synthesis. This is what might be called a "blanket" hypothesis. The phenomenon of the rebound of REM sleep may indeed be akin to rats falling off poles when given many different drugs. The reason for their falling off the pole can have many causes.

Nevertheless, the slow recovery processes underlying REM sleep after drugs would be interpreted as the slow reconstruction, through protein turnover, of the intraneuronal machinery which governs REM sleep. One obvious way to test the hypothesis is to take animals, all of whom receive the same afferent stimulation, and examine changes in the base ratios and the rate of protein turnover after REM deprivation.
His bed's reply.

That I maie be a rest of cares,
an end of toyling paine:
See stomacke thine be not surcharge,
when slepe thou wouldest gaine.
If sugred slepe (devoide of dreames)
thou likest to enjoye:
Then live with little: and beware
no cares thy hedde anoye.
And lastly deme thy feathered bedde
alwaies they graspyng grave;
So rest by me thou shalt obtains,
and eke much comfort have.

Translated from the Latin
of Dr. Haddon by Timothy Kendall
1577.
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Drug Withdrawal State
An EEG Sleep Study
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It has been shown in many publications1,2 that there are two types of sleep: orthodox or nondreaming sleep and rapid eye movement (REM) or dreaming sleep. The description of these two separate physiological states and the finding that barbiturates have a profound and long-lasting effect on REM sleep3 gave impetus to many recent studies of the effects of drugs on sleep. It has been found that hypnotics,3-5 meprobamate,6 and alcohol7 cause an immediate decrease in REM sleep. With continued administration, tolerance develops so that REM sleep values return to normal. On withdrawal, there is an immediate overshwing or "rebound" in REM sleep taking several weeks,3 even from small doses4 of the drug, to return to predrug levels.

During some drug withdrawal syndromes, there is an excess of REM sleep. This is true of both alcohol withdrawal8,9 and barbiturate withdrawal.10 In the initial withdrawal period a frequent clinical complaint is what the alcoholic calls "night terrors" and the studies by Greenberg and Pearlman8 and by Gross9 would suggest that REM sleep mechanisms are intimately involved in the production of "night terrors" which appear to be severe nightmares.

Phenothiazines, in particular chlorpromazine, are commonly used in the treatment of drug withdrawal delirium. It has been shown11 that 100 mg chlorpromazine will depress REM sleep with no immediate "rebound" in withdrawal. It is therefore of interest to study the effect of chlorpromazine on REM sleep during withdrawal.

Assuming the excess of REM sleep in drug withdrawal, chlorpromazine administered immediately after stopping, for example, a barbiturate could have one of three possible effects: (1) The chlorpromazine could have no effect on REM sleep and the rebound could continue. (2) The chlorpromazine could have a delaying effect on the rebound such that it would appear after the chlorpromazine had been withdrawn. (3) Chlorpromazine could block the rebound completely.

The results of a previous study11 makes the first hypothesis unlikely and the slow clearance of chlorpromazine from body tissues12 coupled with clinical evidence suggests that the last hypothesis (3) is the most likely.

The present study was designed to test these hypotheses using barbiturate withdrawal as the model.

Method

The EEG and EOG recording of sleep was as previously reported from this laboratory.11 Six baseline night records were obtained from each of two healthy young male subjects over a period of weeks prior to the administration of the drugs. There was another baseline night record, an earlier one, which was discarded as it was an adaptation night.13 Four
hundred milligrams amobarbital (Amytal) was administered for 14 consecutive nights, recordings being taken on nine of these as shown in Table 1. On nonrecording nights, the subjects took the drug at approximately the same time, 30 minutes before retiring. They were instructed to keep to the same bedtime and to refrain from taking all drugs, other than the experimental ones, throughout the experiment.

Following the last “amobarbital” night there were two nondrug nights. These two nights were followed by five nights on which the subjects received 100 mg chlorpromazine orally, approximately 30 minutes before retiring. Four recordings were obtained, though the fourth night was omitted; as before, the subjects still received the chlorpromazine. On stopping the chlorpromazine, their sleep was monitored on 15 of the first 45 “withdrawal” nights. The nights on which recordings were obtained are indicated in Table 1.

Results

The initial stage of this experiment, the administration of 400 mg amobarbital, was to enable the later induction of a drug withdrawal state. Although records of the subjects’ sleep were obtained, little comment on the results of this stage is necessary since they followed exactly those obtained by Oswald and Priest. There was the expected depression of the percentage of REM sleep and tolerance with continued administration (Figure). On withdrawing the amobarbital the initial stages of the expected rebound were seen.

The Figure shows that during five successive nights of chlorpromazine (100 mg) there was a gradual decrease in the percentage of REM sleep. On stopping chlorpromazine no rebound was seen despite the sampling over 45 subsequent withdrawal nights.

Using the technique of analysis outlined in a previous report,11 it was found that chlorpromazine, after 14 nights of amobarbital, does not result in REM sleep time (in minutes) being significantly different from the control values. Further, despite the significant (t = 2.5714, P < 0.01) decrease in total sleep time (Table 2), the mean REM time during chlorpromazine administration was not significantly different from that to be expected for the observed total sleep time (obtained from a regression equation11).

It was noticed in the process of this analysis that on the first two nights on which the subjects received chlorpromazine, the observed REM time was greater than expected, while the reverse was true for the third and fifth nights. Neither of these pairs of nights, however, was significantly different from control or from each other.

The significant decrease in total sleep time during chlorpromazine administration can be accounted for in terms of the increased delay to sleep onset (Table 2; t = 3.3069, P < 0.01). In withdrawal this parameter was not significantly different from either the control or chlorpromazine stages. This was also true of total sleep time.

During the administration of chlorproma-

---

**Table 1. Distribution of Recording Nights**

<table>
<thead>
<tr>
<th>No. Subjects</th>
<th>Sex</th>
<th>No. Baseline*</th>
<th>Drug</th>
<th>Drug† Recording Nights</th>
<th>Withdrawal Recording Nights</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>M</td>
<td>6</td>
<td>Amobarbital</td>
<td>1,2,4,7,8,9,10</td>
<td>15,15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorpromazine</td>
<td>17,18,19,21</td>
<td>22,23,25,28,30, 32,35,37,39,42, 46,51,53,59,62</td>
</tr>
</tbody>
</table>

*This excludes the first adaptation night record.
†Drugs were administered on successive nights even though a record was not obtained each night.
The first withdrawal night was the night immediately succeeding the last drug night.

**Table 2. Effect on Sleep**

<table>
<thead>
<tr>
<th></th>
<th>Total Sleep Time (min)</th>
<th>Delay to Sleep Onset (min)</th>
<th>Delay to 1st REM Period (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Control</td>
<td>446.7 ± 5.8</td>
<td>21.0 ± 7.6</td>
<td>76.5 ± 13.0</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>445.4 ± 5.0</td>
<td>46.0 ± 15.9</td>
<td>65.9 ± 13.0</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>455.0 ± 4.5</td>
<td>31.4 ± 22.8</td>
<td>86.9 ± 22.9</td>
</tr>
</tbody>
</table>

Arch Gen Psychiatr—Vol 19, Nov 1968
Effect of chlorpromazine on sodium amytal withdrawal.

zine, the delay to the onset of the first REM period of the night decreased (Table 2) with respect to the control values \( (t = 1.3955, P < 0.05) \) while in withdrawal it was significantly increased when compared to drug values \( (t = 2.4266, P < 0.05) \).

**Comment**

It was predicted that chlorpromazine would block the rebound of REM sleep seen in drug withdrawal. The results of this experiment show that this prediction was correct. Further, no delay in the rebound was observed despite following the course of the withdrawal for 45 nights. The only observable withdrawal effect was a slight decrease in total sleep time associated with an increase in the time taken to fall asleep.

Drug withdrawal delirium is only seen after tolerance has developed and the drug is abruptly removed. In sleep this abrupt stopping of a drug is manifest as an *immediate* rebound in REM sleep. In other words, there is a sudden release of REM “pressure.”

Circumstantial evidence from the clinical field is found in the study by Greenberg and Pearlman\(^8\) where it is seen that those patients who developed delirium had high REM times sooner than the nondelirious group.

Since the middle of the 19th century, the treatment of drug withdrawal delirium has emphasised the importance of sleep. With little exception, treatment has been effected by the use of opiates, paraldehyde, and, later, hypnotics. The recent trend has been to use phenothiazines. It has been shown that morphine\(^{14,15}\) will depress REM sleep, as will hypnotics\(^3,5,16\) and phenothiazines,\(^11\) and that all these drugs will produce delirium when stopped abruptly from high dosage. The fact that the drugs used to treat withdrawal delirium depress REM sleep, and so presumably block the withdrawal rebound, makes it an attractive hypothesis that to treat this delirium the mental life associated with REM sleep must not be allowed to intrude into wakefulness but must be contained wholly within sleep.

An underlying assumption of the hypothesis is that the mental life of REM sleep can spill over into waking life. This would be experienced by the patient as the intrusion of dream fantasy into wakefulness which is disturbing. Such a phenomenon is seen in narcolepsy.

The sleep attack of the narcoleptic is an attack of REM sleep frequently not followed by orthodox sleep.\(^{17-19}\) The narcoleptic is unique in present experience in the ability to enter REM sleep *without* prior orthodox sleep. Thus it is possible to find conscious¬ness and REM (dreaming) sleep in direct continuity.

A similar phenomenon is observed in a person waking from a particularly vivid dream who may often experience disorienta-
tion in time and place for several minutes; he has experienced a consciousness:orthodox sleep:dream:consciousness sequence.

The inability to dissociate fantasy from reality when dreaming and waking are in continuity would indicate that there is a common mechanism underlying both REM sleep and the paranoid delirium of drug withdrawal states. The present experiment would lend further circumstantial evidence to the relationship.

Summary

It has been shown that in drug withdrawal delirium there is an excess of rapid eye movement (REM or dreaming) sleep. Such delirium is commonly treated with chlorpromazine. In the present study, two male subjects received amobarbital (Amytal) for 14 consecutive nights. After two withdrawal nights, in which an excess of REM sleep was observed, they received 100 mg chlorpromazine for five consecutive nights. The prediction that the chlorpromazine would block the withdrawal REM sleep excess was borne out by monitoring the subjects’ sleep for 45 nights after stopping chlorpromazine. This experiment gives further evidence for the hypothesis that there is a common mechanism underlying both REM sleep and the paranoid delirium of drug withdrawal states.

Professor Carstairs and the Board of Management of the Royal Edinburgh Hospital made available the facilities for the study; Mr. J. Henderson helped with the recordings; and May and Baker, Ltd. provided advice and financial assistance.

Generic and Trade Names of Drugs

Chlorpromazine—Thorazine.
Amobarbital—Amytal.

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Sleep and Barbiturates: some Experiments and Observations*

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Summary: To determine the effect of barbiturates on sleep two subjects, after a control period, received 200 mg. of sodium amylobarbitone for 26 nights. All night sleep records taken during this period showed that the barbiturate shortened the delay to sleep, increased the total sleep period, lengthened the delay to rapid eye movement (R.E.M.) sleep, and depressed R.E.M. sleep. After five nights R.E.M. sleep returned to baseline values—that is, showed tolerance. On stopping the drug withdrawal phenomena were seen, even to this small dose of the drug.

In a second experiment a subject dependent on 600 mg. of Tuinal was found to have low normal R.E.M. sleep while on drugs. On withdrawal, delay to sleep increased and total sleep time fell. R.E.M. sleep was doubled and the delay to R.E.M. became abnormally short.

These findings suggest that hypnotics allow sleep to be "borrowed," and that patients should be supported while they are being withdrawn.

Introduction

In the past decade drugs have become the focus of attention of many groups in society. Doctors have become more aware of their side-effects, prolonged actions, effects on foetal development, and the possibility of addiction and overdose. Society has become anxious over the questions of abuse and addiction, and these anxieties have produced a number of standing committees in an effort to control this complex problem.

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The need for such control is apparent even when the quantity of drugs consumed for therapeutic reasons is appreciated. Ministry of Health (1964) statistics show that hypnotics, analgesics, and tranquillisers constitute 22.6% of all prescriptions. Of this group barbiturates are the largest contributors, making up 8.1% of all prescriptions, and the amount increases annually. Other indices confirm the increasing use and abuse of these drugs. Overdosage by hypnotics has increased steadily as a means of attempting suicide (Kessel, 1965), and delirium due to abrupt withdrawal is a frequent hazard (James, 1963).

Many doctors were taught that whatever else they could not do for their patients they could at least provide sleep. This expectation seems to have passed on to the patients, as doctors often complain that they feel under pressure to prescribe hypnotics.

In the past decade knowledge about sleep has also greatly increased. It has been found to consist of two regularly alternating states (Aserinsky and Kleitman, 1953, 1955), which differ drastically in many physiological criteria.

At the beginning of the night the normal subject enters a cycle of sleep which is characterized by slow waves and spindling activity in the E.E.G., slow rolling/absent eye movements, the presence of muscle activity, and regularity of pulse rate, blood pressure, and respiration. After about an hour of this slow wave or "orthodox sleep" there is an abrupt change. Spindles disappear from the E.E.G., muscle tone drops precipitately in the submental region (Berger, 1961), the E.E.G. becomes low-voltage, and runs of sharp waves appear—the "saw tooth" frontal activity which is followed by bursts of jerking synchronous eye movements (Dement and Kleitman, 1957). Respiration and pulse rate become irregular and blood pressure is variable (Snyder et al., 1963, 1964). After 10 to 20 minutes the eye movements disappear, often after a body movement, and spindles reappear as another cycle of slow wave sleep begins. This second type of sleep has been called "paradoxical" or rapid eye movement (R.E.M.) sleep.

In the normal night five or six cycles of orthodox sleep with an equivalent number of periods of paradoxical sleep occur. Paradoxical (R.E.M.) sleep usually occupies about 24% of the total sleep. Normally, orthodox sleep takes precedence over R.E.M. sleep, and the first R.E.M. period of the night does not occur until after at least 45 minutes of orthodox sleep (Rechtschaffen and Verdone, 1964; Oswald and Priest, 1965).

Mental activity differs in these two types of sleep. In orthodox sleep mental activity is variable, often fragmentary, and more reality-orientated. During R.E.M. sleep disorientation in time and place is common and dreams are reported (Aserinsky and Kleitman, 1953; Goodenough et al., 1959; Monroe et al., 1965). To determine the effect of drugs on
sleep we have conducted a number of electroencephalographic studies in volunteers.

**Method**

During these investigations subjects reported to the laboratory at 22.00 hours, and electrodes were attached with adhesives to Fz Cz Pz positions of the 10/20 system to collect the E.E.G.; to frontal and outer canthi positions to monitor eye movements; and over the belly of the submental muscles to record muscle tone. Bipolar montages were employed and the electroencephalograph was run continuously from 23.30 to 8.00 hours.

Subjects were instructed to keep regular hours of sleep throughout the total experimental period and refrain from alcohol or drugs other than those prescribed in the experiment.

The record—almost a quarter of a mile (400 m.) of paper—was analysed according to the types of sleep. Normal indices were (i) the total sleep time (T.S.T.) from first spindle to final arousal minus any intervening period of wakefulness; (ii) total R.E.M. sleep and percentage R.E.M. sleep—the sum of all R.E.M. activity from first eye movements to last R.E.M. minus any intervening period of spindling activity which can intrude into R.E.M. sleep; (iii) the delay to sleep (iv)—the interval in minutes from the start of recording from "lights out" to first spindles; and (iv) delay to R.E.M. (D)—the interval from first spindles to first R.E.M.

**Experiment 1**

Two female subjects were used as their own controls. Over a period of six weeks seven baseline recordings were made at irregular intervals. The first record was discarded, as is accepted practice, since the results are often low owing to a "first night" effect (Mendels and Hawkins, 1967). Subjects then received 200 mg. of sodium amylobarbitone at 23.00 hours each night for 26 nights. Recordings were taken at intervals over the next two weeks until all variables were within the normal range. Altogether 27 nights were recorded over a period of almost three months (see Fig. 2).

**Results**

The immediate effect of the drug was to decrease the delay to sleep and prolong the T.S.T. (Fig. 1). R.E.M. sleep was depressed (Fig. 2) and orthodox sleep was enhanced. R.E.M. sleep continued below the baseline for five nights; then tolerance occurred and R.E.M. values rose to baseline or a little above it. During this period of tolerance the drug still promoted and enhanced orthodox sleep so that T.S.T. remained raised.
The delay to the first R.E.M. period was increased by the drug. However, at nights 12–14 T.S.T. fell, the delay to sleep increased slightly, and the amount of R.E.M. activity rose: at night 12 the delay to R.E.M. period was below the baseline value.

Fig. 1.—Effects of sodium amylobarbitone 200 mg. nocte on sleep of two female subjects.

When the barbiturate was stopped, T.S.T. fell abruptly for the first two nights and the delay to sleep was much prolonged. Delay to R.E.M. became abnormally short (less than 45 minutes) during this period, and R.E.M. sleep was increased—up to

Fig. 2.—Effect of sodium amylobarbitone 200 mg. on the paradoxical sleep of two subjects.
31% of the night. R.E.M. sleep subsided towards baseline in a fluctuant manner over the next fortnight.

Experiment 2

This subject had been taking 600 mg. of Tuinal nocte (quinalbarbitone sodium 300 mg. and amylobarbitone sodium 300 mg.). Over a period of three years after a hospital admission for treatment of a post-gastrectomy anaemia he had built up his consumption from 200 to 600 mg. of this drug. He reported that after several months at each dose level the drug "lost effect" and he had to increase the dose. When he tried to stop the drug he claimed that he did not sleep at all.

The recording procedure was as in experiment 1, though no drug-free baseline nights were possible.

During the experiment the subject was asked to estimate his delay to sleep and total sleep time.

Results

While taking drugs this subject slept between 90 and 100% of the time available (Fig. 3). He regularly underestimated his total sleep and similarly overestimated his delay to sleep by a regular amount (Figs. 3 and 4). R.E.M. sleep was consistently at low normal levels (Fig. 5). At night 12 the drugs were stopped. R.E.M. sleep doubled in value and the first R.E.M. period was abnormally early. Total sleep time fell to 76% of that available and the number of awakenings increased. The delay to sleep was over 90 minutes. This disturbed night caused the subject to complain that he had not slept at all. Over the next three nights of withdrawal R.E.M. time remained increased, and the delay to sleep continued to be increased and total sleep time remained shortened. The subject continued to seriously underestimate the extent of his sleep and complained of fatigue and restlessness. His R.E.M. sleep was very active; not only were the periods of R.E.M. sleep longer but the movements themselves were more intense. The increase in "activity" has been shown to occur in withdrawal from other hypnotics (Evans and Lewis, 1968). Under these circumstances nightmares have been shown to occur (Oswald and Priest, 1965; Evans and Oswald, 1966).

At the subject's request the hypnotics were restarted at night 16. R.E.M. activity fell to its former level, and T.S.T. and delay to sleep returned to previous drug night values. The subject's estimates returned to their previous reasonably accurate level.

Hypnotics were stopped again at night 20. The effects were similar to the previous withdrawal period and the irregularity of the onset of delay to sleep and total sleep time continued while the R.E.M. time remained raised in a fluctuant way.
Fig. 3.—Percentage of sleep in time available.

Fig. 4.—Delay to sleep.

Fig. 5.—R.E.M. activity.
Discussion

These experiments demonstrate the effects of barbiturates as well as some of the problems which accompany their use. A single tablet of sodium amylobarbitone promotes the early onset of sleep and enhances orthodox sleep while depressing R.E.M. sleep. The body responds immediately and attempts to restore the amount of R.E.M. sleep to normal values. After a week on the drugs the principal effects are in shortening the delay to sleep and promoting continuous sleep. However, even while the drug continues there are times when the delay to sleep increases; total sleep time falls and R.E.M. time is raised above the baseline. Though in experiment 1 this tendency was not severe, an "escape" phenomenon of this type may be the reason why patients increase the dose of hypnotics. Greenberg and Pearlman (1967) in their work on alcohol, which is very similar to barbiturates in its effect on sleep, also found that R.E.M. time could increase after a period of depression though the alcohol continued in full doses. It is possible that over a longer period total sleep time would fall and delay increase, as patients report.

Stopping the drug allows the overswing of R.E.M. sleep. This is experienced as an increase in activity by the patient, who may suffer from frightening dreams but frequently wakes up during R.E.M. periods. The R.E.M. activity, increase in the delay to sleep, and number of awakenings lead to a serious underestimate of the quality of sleep, and the sort of situation where the patient complains of total insomnia, while relatives or nurses differ in their opinion.

The temptation is to restart the tablets at the same or higher dose, and this, as seen in experiment 2, puts the patient back to previous drug values. However, while the withdrawal effect of 200 mg. of sodium amylobarbitone takes almost two weeks to clear (Fig. 2), Oswald and Priest (1965) found that 600 mg. of sodium amylobarbitone took five weeks to subside. Thus by increasing the dose of hypnotics the patient is enhancing the duration of the withdrawal state. Although there is an end to these withdrawal effects the need to return to the drug is understandable.

If tolerance and withdrawal are the hallmarks of addiction, then only one tablet taken for a week could be seen to be addicting. However, the withdrawal is not severe. Serious withdrawal problems are not likely to occur until 800 mg. to 1 g. of barbiturate is being regularly consumed. Although there is insufficient experimental evidence to suggest that all hypnotics act in this way, nitrazepam (Mogadon) depressed R.E.M. activity initially and produced a similar withdrawal state (Oswald and Priest, 1965). Kales et al. (1968) has shown that methyprylon (Noludar), glutethimide (Doriden), and methaqualone (Melsedin) also depress R.E.M. sleep initially and show a R.E.M. "overswing" withdrawal state. The literature con-
firms that almost all hypnotics, if taken in sufficient dose and for long enough, when stopped abruptly bring on a severe insomnia and a paranoid hallucinating state identical with delirium tremens (de Clerambault, 1910; Hudson and Walker, 1962; James, 1963; Ewart and Priest, 1967). Recent work has shown that R.E.M. sleep is grossly increased in delirium owing to alcohol and barbiturate withdrawal (Gross et al., 1966; Greenberg and Pearlman, 1967; Evans and Lewis, 1968). Thus it seems likely that experiments will show that all hypnotics have these effects on R.E.M. sleep in some measure.

These experiments demonstrate that with barbiturates it is possible to promote sleep. However, there is some cost. In many ways hypnotics allow sleep to be "borrowed," and this must be paid back during withdrawal. It seems advisable to tail off hypnotics slowly, even from small doses, to minimize the withdrawal state, but it is also necessary to support the patient through the period of withdrawal, which is after all a limited event. It would perhaps be better to consider hypnotics as a course of treatment, with a beginning and a definite end, as soon as circumstances permit. It may also be more logical to prescribe intermittent courses of hypnotics so that withdrawal effects may be dissipated periodically and excessive build up of drugs prevented. It is an old criticism that doctors are good at starting and continuing treatment but not so good at stopping.

**References**


Printed in Great Britain by Fisher, Knight and Co., Ltd., St. Albans.
SLEEP PATTERNS DURING AFTERNOON NAPS IN THE YOUNG AND ELDERLY

BY

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Reprinted from
THE BRITISH JOURNAL OF PSYCHIATRY
Vol. 115, No. 518, January 1969
Sleep Patterns During Afternoon Naps in the Young and Elderly

By S. A. LEWIS

Recently there has been interest in the nocturnal sleep of the elderly. The studies by McGhie and Russel (1962), Weiss et al. (1962), Kales et al. (1967) demonstrated that, compared with young adults, elderly people have a reduced total sleep time, more awakenings following sleep onset and a moderate reduction in REM (rapid eye movement) sleep. In other words, elderly people have a more disturbed sleep. While this group have a shortened night’s sleep, they are given to taking afternoon naps, and it may be that through these they can compensate for their insomnia at night.

In a study of afternoon napping in young adults, Maron et al. (1964) demonstrated that their sleep cycle was similar to the nocturnal pattern for this age group. The present study considers whether patterns of sleep during afternoon naps differ between age groups.

**Method**

Two groups of paid volunteers were used as subjects. Group I consisted of 10 undergraduates (5 female, 5 male) while Group II was composed of seven individuals in the age range 71–84 years (6 male, 1 female). No person was included in the study who was taking medication of any kind, in particular hypnotics or tranquillizing drugs. Analgesics of the salicylate family were permitted. All subjects were asked to retire at about 23:00 hours on the night before the recording afternoon or at their usual time if this was earlier. They were asked to refrain from taking alcohol for at least 24 hours prior to the recording session.

Subjects reported to the sleep laboratory at 13:30 hours, when the experimental procedure was explained to them. In an attempt to reduce any anxiety which might arise from delay in getting to sleep it was emphasized to the subjects that the result would be just as valid if they did not sleep at all. All were told to prepare themselves as they would for a nap at home. This meant that a few changed to night attire, while others merely loosened tight clothing and sat in a lounge chair. Electrodes were attached in the standard EEG and EOG sleep recording positions, and the subjects were left in a warm, quiet bedroom separated from the recording area. The recording lasted approximately 120 minutes, and was frequently terminated by the subjects themselves. The sleep EEG records were scored according to the criteria of Williams et al. (1964, 1966).

On awakening, subjects were asked for an account of any dreams or other mentation they might have had, whether or not REM patterns were observed during recording.

**Results**

As in nocturnal sleep, the elderly subjects after falling asleep had fewer period of wakefulness than the young subjects, but were awake for a greater mean time at each period. There was no difference between the groups in the delay to sleep onset. Also, it should be noted that the delay to the onset of REM sleep, if any, was always greater than 45 minutes, which is the lower limit of the nocturnal range. Although the elderly group spent significantly longer in bed than the young group on the first recording, their total sleep time was significantly shorter. No significant differences were obtained between first and second recordings (Mann-Whitney U-test; one-tailed criteria). (Detailed results may be obtained on request.)

Reports of mentation which the subjects called “dreaming” were obtained from four subjects, all of whom were in the young group. The records of three of these subjects showed REM patterns.
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(Received 25 April, 1968)
LEARNING WHILE ASLEEP

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Recently commercial interest in the sale of ‘sleep-learning’ equipment has increased. This would appear to have arisen from the present fervour to extend the notion of increased productivity to as much of our life as possible. It would seem that, despite the recognized need for rest in the form of sleep, we should put this apparently ‘wasted’ third of our life to good use. After all Huxley, in his Brave New World, used the periods of sleep to condition the attitudes of his people! On the face of it, the suggestion that people could learn while asleep does not appear unreasonable. A mother, as is well known, will waken to the cry of her child but not to the rumble of a passing train. This phenomenon is assumed to be the result of a selective perception mechanism which would entail the operation of some form of Bruner’s ‘gating’ (Bruner, 1957). This in turn, and at the superficial level, implies that the cortex is not ‘asleep’ but is in a state in which it can receive and interpret incoming sensory information. Hence, why should we not be able to increase our knowledge while asleep?

The experimental study of learning while asleep can be conveniently divided into three groups: (a) Studies in which the criteria of sleep were time after retiring and behavioural indications of arousal such as restlessness, i.e. there is no indication that EEG criteria were used; (b) Studies using EEG-monitoring of the subject’s stage of sleep; and (c) Russian literature.

(a) Studies using behavioural criteria

An early attempt to reduce the time taken to train military forces was carried out by Thurstone (1955). He succeeded in reducing the time taken to train 16 U.S. Navy men in a Morse code course by three weeks. However, his criteria of sleep are not known and Le Shan (1942) maintains that the experiments were abandoned before results were obtained due to the breakdown of the apparatus.

This early attempt to utilize the sleeping hours was not followed up, at least in the English-speaking world, until the experiment by Le Shan (1942). His experimental group of nail-biters at a summer camp outside New York heard in all 16,200 repetitions of the sentence ‘My finger nails taste terribly bitter’. His criterion that the children (median age = 9 10/12) were asleep was whether or not they responded to questions 20–30 minutes after lights out. The record of the ‘conditioning’ sentence was started 2-3 hours later, if there was still no response to the enquiry as to whether anyone was awake. A serious flaw in the experimental method was that the volume was merely lowered if there was any sign of restlessness; it was not turned off. Since 40 per cent of the experimental group stopped their nail-biting, it was felt that this indicated the ‘possible therapeutic use of suggestion during sleep’.

Le Shan (1955) followed this with an unpublished experiment in which he had a single subject learn a different nonsense-syllable list each morning for 12 mornings. Although there is a lack of information about the criteria of sleep—and it is reasonable to assume that these would be similar to those of his earlier study—he claims that there was a 50 per cent reduction in trials to the learning criterion on the two mornings on which the list to be learned had been played over 50 times to the subject during the preceding night. The lack of physiological monitoring of the subject’s sleep in this and other similar studies leaves them open to the criticism that the subject was at most in a drowsy state while the auditory stimuli were being consolidated in the long-term memory store. This criticism can of course be levelled at any experiment dealing with this topic in which EEG monitoring is not used. For example, Hedge’s (1950) attempt to speed the learning of consonants in mentally retarded and aphasic children, allowed no conclusions about the therapeutic value of the procedure since the tape-recorder was not turned off even if the child was awake on behavioural criteria. On the other hand, Elliott (1947) in a study three years earlier was intermediate between EEG monitoring and behavioural criteria. No material to be learned by the subjects was played while ‘clear alpha patterns’ were observed. However, the EEG was not continuous in that it was switched off once the experiment felt that his subject was sure to remain asleep.

At this point it is interesting to note that, of the studies reviewed by Simon & Emmons (1955), 70 per cent are Master’s theses and have not appeared in the general literature.
(Le Shan, 1955; Hedges, 1950; Elliott, 1947; Hoyt, 1953; Stampfli, 1953; Coyne, 1953). This seems to imply that either the experimental design was so poor as not to warrant publication or that the results were equivocal.

(b) Studies using EEG sleep recording

An interesting study in this group is that of Fox & Robbin (1952). Unlike nearly all studies involving the recording of an EEG, they had the subject sleep at home and the machine was taken to them. The machine had to be moved from the bedside since subjects complained that it woke them. However, from Fox & Robbin's comments it is likely that they suspected that the voice giving the Chinese-English pairs was the culprit. Despite setting up what must have been an elaborate EEG recording procedure, they say: 'The experimental situation did not allow verification by E of the condition of actual sleep . . . (but) . . . the subjects were questioned about this, and those who reported hearing the machine on waking up were eliminated.' One is left to wonder why an EEG was taken. Unlike many other studies, however, a matched control was incorporated in such a way as to allow them to eliminate the possibility of learning while awake in the night, and their conclusion was 'that learning can occur during sleep and can be detected by the saving method'. Without doubt, the most carefully controlled studies, both in terms of sleep levels and procedure, have been those of Simon & Emmons (1956) and Emmons & Simon (1956). Although they considered the learning during the various stages of sleep, they did not recognize the presence of the rapid eye movement (REM) stage. Like so many studies using EEG techniques in psychology, they selected their subjects not only on the basis of psychological variables likely to influence learning but also on the basis of a well-defined alpha rhythm. It is always difficult to understand why this should be a criterion of selection in such psychological experiments.

Their procedure was to pretest subjects on a questionnaire of general but unusual knowledge, the subjects having been scaled as average or above in the Otis Self-Administering Test (Form D) as well as the EEG criterion mentioned above. From this questionnaire the items answered correctly were eliminated and the remainder used as the sleep-learning material. After having the questions and answers played over during the night, the subjects were then given a multiple-choice post-test. The results showed conclusively that below stage II (sleep spindle or sleep onset stage) no learning took place. In the preceding EEG stages there was a decreasing amount of retention from 80% in relaxed wakefulness (stage O) to 30% in drowsiness (stage I).*

In their other study Emmons & Simon (1956) presented the learning material (nonsense syllables) only during the non-alpha stages of sleep and concluded that there was no acquisition during these stages. A review by Simon (1961) indicates that, despite the lapse of seven years, his belief that learning during true sleep is not a viable proposition has not changed.

(c) Russian studies

It is a curious phenomenon of Russian psychology that there is in many areas of study a profound belief in latent, innate abilities. This belief is seen in their work on extra-sensory perception and it is seen in the area of sleep-learning. In the studies so far found in the literature (Kulikov, 1964, 1965; Zavalova et al., 1964; Balanescu, 1964; Zukhar et al., 1965; Khilk'chenko et al., 1964), it is evident that the Russians feel that the hours of sleep can be put to profitable use and they have set out to demonstrate this. Furthermore, they indicate that learning while asleep is in some way bound up with the suggestibility of the learner. Another point about the Russian work is that, with the exception of the study of Zavalova et al. (1964), the translations available give no indication that EEG monitoring is used; the criteria of sleep onset are not mentioned.

One of the latest six studies available, that of Balanescu (1964), deals with the elicitation of conditioned motor reactions (CMR) by verbal stimuli during sleep. The motor reactions are conditioned during the waking state and the CSs are artificial words. It is said that, compared with the waking state, the CMRs are modified with sleep in terms of latency, duration and structure but retain their relationships. The modification is determined by signal strength although there are large individual differences. This last relationship implies a fairly high degree of perceptual discrimination which is difficult to reconcile with many of the Western studies on sleep.

Unlike many of the American studies, the Russians do not present their material to the sleeper at the onset of sleep. Instead, they

*The sleep stages O, I, II, III, and IV relate to EEG changes and do not necessarily correspond to behavioural 'depth' of sleep.
prefer to have a delay to the start of presentation. For example, Kulikov (1964), started the tape-recorder only after the subject was asleep for two hours. The results of this study led him to conclude that there is little difference in the quantity of material retained during sleep and during wakefulness if the subject has prior suggestion that he is going to have perfect retention of the material.

This study highlights a further difference between American and Russian work. The former prefer to attempt to disguise the purpose of the experiment (e.g. Fox & Robbin, 1952) while the latter make it quite plain that their intention is to study the ability to learn while asleep. Indeed the Americans go so far as to eliminate from the data for statistical treatment results from subjects who indicate that they appreciate the nature of the experiment.

In another study, Kulikov (1965) discusses the 'theory and practice of learning during sleep'. He maintains that the ability to learn while asleep is natural to everyone and that the ability merely has to be 'awakened'. The knowledge gained during sleep must be transferred to consciousness and it is claimed that, for this transfer to be most effective, it should be postponed for a short period after waking. As in all human activities, there are individual differences and Kulikov feels that the relevant variable giving rise to these differences is the subject's degree of suggestibility.

It is pertinent after this brief review of the experimental work of sleep-learning to ask whether there is any evidence to suggest that sleep-learning would be possible. The optimal conditions under which waking learning takes place are that there must be discrimination of the stimuli, general alertness and a degree of motivation.

No one would doubt that in sleep there is an alteration in consciousness and from this it follows that our awareness of our surroundings is decreased. It would therefore seem to be reasonable to expect that we could not recall anything which happens during states of decreased consciousness or without our consciously knowing what was going on, yet so-called unconscious conditioning is a well-documented and accepted phenomenon. Greenspoon (1955) found that he could increase the number of plural nouns used by a person by saying 'mm hmm' every time one was used. Similarly, Lacey et al. (1955) found that, by giving subliminal electric shocks to subjects who were chain associating to 40 stimulus words, they could raise the autonomic response to the word. The response was not confined to the stimulus word itself; there was considerable generalization.

On a deeper plane of decreased consciousness, Levinson (1965) reports a study of hypnotic regression to events taking place during dental anaesthesia. He shows that while subjects did not have a 'conscious' memory of the acted crisis during the anaesthesia, they could recall it accurately under hypnotic regression. Again, Sterling & Miller (1941) suggest that conditioning is possible during anaesthesia.

Continuing on the line of perceptual discrimination there is the study of Oswald et al. (1960) who have shown that the GSR provoked by auditory stimuli were never present at the moment of falling asleep. On the other hand, they also showed that 'discrimination' returned as cortical vigilance fell even lower. Perhaps more convincing is the experiment by Berger (1963). In this he demonstrated, inter alia, that subjects were able to incorporate emotionally meaningful auditory stimuli in their dreams. The stimulus name was presented during REM sleep. In the experiment by Oswald et al. (1960) there is no indication of the discrimination during REM sleep but unlike the GSR response, the subjects did appear to be able to recognize at least their own name up to stage IV.

The relevant part of the acquisition phase of learning has been dealt with under the heading of discrimination. The retention phase involves the transfer of the material to be recalled at a later date being put into the memory store. Without considering the physiology of how this is possibly achieved in the waking state and whether the same or similar processes could operate in sleep, there are a few experiments which are pertinent.

In a recent study by Portnoff et al. (1966) subjects were awakened during the night and shown verbal learning material. They were then allowed to return to sleep or had to perform a motor task. Retention of material which was immediately followed by a return to sleep was very much poorer than that which was followed by the motor task (enforced wakefulness). These workers conclude that it is probable that non-REM sleep is detrimental to the transfer of material to the memory store. However, this result is in contradiction with the classical finding of Jenkins & Dallenbach (1924). They demonstrated, as have many others since, that an interpolated task between acquisition and recall results is an interference with recall. At the same time it should be pointed out that for retroactive interference to have
its full effect, the interpolated task should be of the same type as the critical task (e.g. the learning of paired associates would have as its interpolated task a second list of paired associates). It may therefore be argued that since in this instance there was little similarity between the material to be learned and the interspersed motor task, this would have little influence on the retention of the critical material. This being so, then the relevant variable is indeed sleep. If material presented during wakefulness is poorly remembered it would seem that material presented during sleep, when discrimination is poor, would have little chance of being put into the store.

On the physiological side, the reviews by Galambos & Morgan (1960) and Smythies (1966) suggest that the areas of the brain in which learning takes place are the limbic and reticular areas. These areas, as is well known, exhibit different patterns of electrical activity in wakefulness and sleep. It is difficult to see how two different electrical patterns can be performing or reflecting the same process when all the literature is strongly in favour of certain rhythms being the physiological concomitant of learning.

Returning to perceptual discrimination but at the physiological level, this does not take place without the dual functioning of the specific and unspecific projection systems. From work on evoked potentials (e.g. Huttenlocher, 1960, 1961), the specific pathways remain open while the unspecific routes shut down.

Conclusions

Direct experiments of sleep-learning suggest that it is not possible for us to put this third of our life to the acquisition of more knowledge. On the other hand, relevant experiments dealing with discrimination during sleep would suggest that at this level of consciousness at least one of the processes necessary for learning is available to us. One area which has not yet been explored is the effect of REM sleep on the learning of material and Jouvet (1965) has propounded the hypothesis that the function of this phase of sleep is the consolidation of day-time material in the stores.

On balance then it seems that 'one cannot prejudge or preclude the possibility of learning during sleep. However, the burden of proof would seem to reside in those who maintain that it can' (Lindsley, 1960, p. 1579).

This research was done while the author held a scholarship from the Medical Research Council.

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