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DRUGS AND SLEEP

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The consumption of drugs that promote or prevent sleep is extremely heavy. The amount of prescribed barbiturates doubled in England and Wales between 1953 and 1959 to about 1.5 g per head per annum (97), since which time the rate of increase has slowed (98). In the U. S. A. a production of 2.4 g of barbiturates per head was quoted for 1948 (58). That the consumption rate has increased steadily is suggested by the fact that whereas the average American family increased its spending on all classes of prescribed drugs by 39% between 1959 and

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1965, "from 1952 to 1963 the retail sales of sedatives and tranquilizers increased by 535 percent" (24)—or about eight times as fast an increase.

In Czechoslovakia the prescription of barbiturates doubled between 1958 and 1965, while prescriptions of drugs of the amphetamine class, having remained approximately constant for about 10 years, increased by 18 times during the period 1959 to 1964 (125). In Australia hypnotic drugs constituted 13.2% of all prescriptions in 1966 (17) against 8.8% in 1962; this represents an absolute rise of about 110% (16). In Britain in 1962 hypnotics represented about 10% of all prescriptions, while amphetamine derivatives contributed about 3% (98).

Many drugs affect sleep, but a few outweigh all others in importance. The present review is written from the point of view of a clinician who has a special interest in the physiology and pharmacology of sleep. It will deal particularly with the assessment of merit in hypnotic drugs and with modern EEG studies of sleep and drugs, and will show a bias towards studies with the principal consumers—human beings.

I. HYPNOTICS: CLINICAL ASSESSMENT AND ITS CURRENT LIMITATIONS

Drugs which are used as hypnotics are also commonly used in smaller doses to allay daytime anxiety. Their use is subject to fashion. Methylpentynol (methylparafynol, Dormison), for example, no longer enjoys the vogue of 15 years ago; thalidomide made a hurried exit. Chloral derivatives in solid form have gained some popularity but the barbiturates retain pride of place. Glutethimide (Doriden), methyprylon (Noludar), ethchlorvinol (Placidyl, Arvynol), methaqualone (Melsedin, Quaalude), and nitrazepam (Mogadon, 1,2-dihydro-7-nitro-2-oxo-5-phenyl-3H-1,4-benzodiazepine) are nonbarbiturates now in common use.

A. The clinical assessment

After the development and testing of hypnotic properties and toxicity in animals (which will not be reviewed here) small doses are usually tried out on hospital patients in "clinical impression" trials. Next comes the controlled double-blind trial in which neither the patient nor the immediately attending staff are supposed to known whether, on any given night, the patient has received blank or drug. In practice the ideal of a completely "blind" study is not always achieved for a variety of reasons, *e.g.*, patients may be able to tell the difference between the tastes of the blank and the drug tablets. As examples of well-designed trials, upon which comment will subsequently be made, we may take the studies of Exton-Smith *et al.* (32) and of Parsons (111), and in commenting upon their failings it is not intended to single out these trials for criticism that could not be applied to many other trials.

In the first of these trials, sodium amylobarbitone (amobarbital sodium, Amytal, sodium 5-ethyl-5-isopentylbarbiturate) 200 mg, dichloralphenazone, 1.3 g (Welldorm), promazine resinate, 50 mg [Sparine Latab, 10-(3-dimethylaminopropyl)-phenothiazine] and meprobamate 800 mg (Miltown, Equanil, 2-methyl-2-n-propyl-1,3-propanediol dicarbamate) were compared with each other and with blank. The most important measure used was the patient's own sub-

jective evaluation of his night's sleep, on the grounds that hypnotics are for symptomatic treatment only. Day nurses administered the tablets at 9.15 P.M. and night staff made hourly assessments of the presence of sleep from 10.30 P.M. to 5.30 A.M. The five medications were administered to each patient on five consecutive nights, in random order according to a Latin square design. The 65 patients were in a female geriatric unit, intelligent and co-operative enough at 8 A.M. to answer questions put by the day nurses about their sleep of the previous night. None were receiving daytime sedatives.

Patients' reports and nurses' reports were each scored as: very good, 3; good, 2; bad, 1; and very bad, 0. Data were missing in six cases and four patients had to be excluded. The method of sequential analysis (3) was used to evaluate the significance of the observations, and with this method it appeared that the patients showed a significant preference for the dichloralphenazone and for the meprobamate, but did not discriminate between the other two drugs and the blank. On the other hand the nurses' scores showed similarity between all four drugs compared with blank, although only promazine and meprobamate were significantly different from blank. An additional finding was that both patients' and nurses' assessments indicated improvement of sleep as the five nights of the trial progressed. Analysis of co-variance showed that patients who slept longer according to the nurses tended to report good nights themselves. The conclusion of the authors was that, for elderly patients, the barbiturate was not satisfactory because, although it induced sleep, the morning hangover caused patients to give an adverse report.

Parsons (111) used a different method. Six successive clinical trials were carried out with two "identical white tablets," A or B on the first night, the reverse on the second night. In the morning after the second hypnotic, each patient was asked two questions. "In which of the last two nights did you have the better sleep?" and, "Have you had any hangover or drowsiness on waking after either of these drugs?". Sequential analysis was again used to evaluate the preferences. The first trial found quinalbarbitone [secobarbital, 5-allyl-5-(1-methylbutyl) barbituric acid] 100 mg was preferred to blank. The second trial indicated no important difference between 100 mg of quinalbarbitone and 100 mg of phenobarbitone (phenobarbital). The subsequent trials allowed the conclusions that, with doses of 100 mg there were no differences between phenobarbitone, butobarbitone (butobarbital, Soneryl) and quinalbarbitone, that butobarbitone gave rise to least hangover, and that phenobarbitone caused less hangover than quinalbarbitone. Parsons concluded that the barbiturates used were essentially similar, and that there was little justification for accepting the suggestion from animal studies that they should be clinically grouped into short-, intermediate-, and long-acting groups. Similar expressed doubts about this grouping have followed studies of hypnotics, including phenobarbitone, by other authors, *e.g.*, Lasagna (79) and Hinton (54).

B. Limitations

Such studies as these are taken as guides to clinical practice. Yet one must have major reservations.

1. Hospitalized patients. Hospitals are noisy and often frightening places, where reasons for the use of a hypnotic may not apply to the patient living at home.

2. The hour of evaluation. To assess the hospitalized patient at 8 A.M. is too limited. Few demands are made upon his skills or initiative at this hour. Kornetsky *et al.* (78) using nurses' assessments found that chlorpromazine 100 mg (Largactil, Thorazine) or 200 mg, and quinalbarbitone 200 mg significantly increased sleep time compared with blank. At 14 to 15 hr after the administration of the drug, performance on the digit-symbol substitution test, the symbol-copying test, and tapping, were all still significantly impaired after the three hypnotic doses mentioned.

In other words, an adequate assessment of a hypnotic drug should answer the question, "What will be the effect of this drug not merely on the patient's subjective feelings about his sleep when he awakens, but on his skill in driving his automobile the subsequent afternoon (particularly if he has consumed alcohol in the lunch-hour)?".

The failure to consider this by Parsons (111) is illustrated by his statement, "The resumption of sleep after breakfast has not been included as hangover because the patients did not usually consider it unpleasant." The tendency of such authors to encourage the prescription of phenobarbitone as a hypnotic appears unjustified in view of its slow elimination and cumulative properties. Butler *et al.* (13) using human subjects reported that the phenobarbitone eliminated from their plasma in the course of 24 hr represented only 11 to 23%.

3. Coma potential. Self-administered nonfatal overdose of sleeping pills is a common emergency. In Edinburgh its frequency has risen about seven times in as many years (95) and is still rising, while an even larger recent rise was described in a report from Australia (102). Since coma caused by phenobarbitone has a much greater duration than coma after an equivalent overdose of intermediate-acting barbituates the rate of elimination must remain an important criterion for an acceptable hypnotic.

4. Nonindependence of successive nights. Another assumption of the usual clinical trial is that successive nights and successive drugs are independent one of the other. In neither the trial of Exton-Smith *et al.* (32), nor that of Parsons (111), for example, was there a statement concerning how many patients had been receiving hypnotics on previous nights. That cross-tolerance arises among all classes of hypnotics is probable, and that tolerance arises is undoubted. Belleville and Fraser (9), using nurses' assessment of the presence of sleep, found some tolerance apparent to quinalbarbitone and pentobarbitone (pentobarbital, Nembutal) within 10 days and no statistically significant increase in sleep above control beyond the 30th day of administration. When electroencephalographic (EEG) and eye-movement studies of sleep are made (see section II), there is suppression of REM (paradoxical) sleep with evidence of decline of this effect within a week on regular nightly amylobarbitone sodium 400 mg or nitrazepam 15 mg (109).

In studies of this nature with these last two drugs (109) or pentobarbitone, glutethimide, or methyprylon (69), a "rebound" increase in paradoxical sleep occurs on subsequent nights when the drug has been stopped, after as little as

three nights on the drug (69). During the rebound, more than merely the duration of paradoxical sleep is increased, for so also is the profusion of rapid eye movements during the periods of paradoxical sleep (66, 81a, 104). The profusion is known to be positively related to the degree of "activity" of the dream content, and in keeping with this nightmares are more frequent and sleep duration is shortened when hypnotics are stopped (68, 104). There is reason to suppose that to some degree all these "rebound" abnormalities tend to occur after a single, isolated night on a hypnotic. As a consequence, in the standard clinical trial of hypnotics, the night on which blank is given is liable to be reported by the patient as "bad," *as a direct result of drugs on preceding nights*, especially if, as must often be the case, the patient has been on some sort of hypnotic for many weeks. Lewis (82) has conducted a study comprising 116 nights on which the EEG was used as a criterion of sleep. He compared the EEG data with subjects' own reports concerning delay to the onset of sleep, duration of sleep, and number of awakenings. Subjects underestimated their sleep on control nights, drug nights, and withdrawal nights but were at their most inaccurate on drug-withdrawal nights.

5. The patient's report. As long as we continue ignorant of the nature of the restitution that sleep bestows upon us, it must remain legitimate to choose the patient's introspection as a guide to merit in hypnotics. Yet it may not be ideal. Tolerance of and dependence (or "addiction") upon barbiturates is common. A report of "good" sleep after heroin would not be regarded as a recommendation for its widespread nightly employment.

The patient's report of "good" sleep after a hypnotic, and "bad" sleep as soon as she tries to give it up must be held responsible for most of the out-of-hospital prescribing. Dependence upon hypnotic drugs is well documented, for example, with barbiturates (38, 131), glutethimide (8, 28), methyprylon (28), ethchlorvinol (86, 130) bromureide hypnotics (59), methaqualone (30, 85), and meprobamate (31); and it occurs also with drugs more commonly used only for daytime sedation, such as chlordiazepoxide (28, 31). Simultaneous abuse of more than one such drug and of amphetamine and alcohol is common (31).

Drugs with hypnotic and dependence-inducing properties are characterized by anxiety-reducing effects, and it could be on this basis, rather than sleep-induction, that the patient experienced a sense of satisfaction with a drug. Smith and Beecher (122) reported that quinalbarbitone 100 mg distorted the judgment of college athletes; they believed their impaired performance was unusually good. One must presume that patients could also unrealistically attribute merit to their sleep while barbiturate was still present in the nervous system in significant quantities.

Although it has been variously stated that clinically observable withdrawal signs follow only fairly heavy dosage of barbiturates (38), and that, for example, 0.2 g daily of pentobarbitone for a year results in no signs of an abstinence syndrome, it may be predicted that subjective unpleasantness would be detected if sensitive psychological rating scales were used; and, indeed, when the EEG is used to study sleep, measurable abnormalities of paradoxical sleep do follow withdrawal of small doses (66). Future advances in techniques for the study of sleep

may be expected to reveal additional physiological indices concomitant with the patient's frequent desire to resume hypnotics whenever an attempt is made to withdraw them, and may be expected to employ more sophisticated psychological assessments than have been customary among clinical observers.

6. Observer judgment. Nurses' observations at intervals of, for example, 1 hr, have frequently been used as a criterion of the presence or absence of sleep. Provided the nurses genuinely have no knowledge of whether a hypnotic drug was administered these must be accepted as valid even if crude. Unfortunately it is not easy to ensure that nurses are "blind." In the Exton-Smith *et al.* study (32) tablets of different sizes were used: patients are liable to remark on the appearance and taste of their tablets. A study of accuracy of nurses' assessments in the light of all-night EEG recording is needed.

7. Other limitations. Exton-Smith *et al.* (32) rightly pointed out that their findings applied to elderly patients. Poor response of elderly patients to barbiturates is frequently quoted in clinical reports and less nocturnal confusion may follow the use of chlorpromazine or thioridazine. There appears no evidence of dependence on the latter drugs, and they have been shown to be effective hypnotics (78, 118).

In the response to hypnotic drugs individual differences other than age may be important, notably personality. Costello and Smith (18) reported, on the basis of nurses' scores, that equal doses of "sedatives" were more effective in prolonging the sleep of introverts than of extroverts (who slept longer without drugs in any case).

C. Some other techniques of assessment

More objective measures than nurses' or patients' reports require apparatus. Though more sensitive, this can be more laborious, and therefore less applicable to large numbers. A popular method has relied upon the fact that body motility is usually less in a person who lies in bed asleep than in one who lies in bed awake. Brazier and Beecher (11) found a significant reduction in overnight body motility after pentobarbitone. Hinton (54) used the technique to compare six barbiturates and a blank. He used 24 psychiatric patients, each being his own control. Hinton emphasized the very large inter-subject differences in nocturnal motility, which generally exceeded inter-drug differences. Body motility cannot be said to have proved itself a sensitive method for studying sleep. Samuel (118) found that patients' judgments discriminated between blank and thioridazine but their motility scores did not do so. Oswald *et al.* (106) found that motility scores discriminated only feebly between heptabarbitone [heptabarbital, Medomin, 5-(1-cyclohepten-1-yl)-5-ethybarbituric acid] 400 mg and blank, whereas when the EEG was used on the same nights the presence of sleep or wakefulness and the stages of sleep were distinguished much more sensitively.

II. ELECTRICAL POTENTIALS AND DRUGS WHICH AFFECT SLEEP

The EEG provides a sensitive tool for the intimate study of sleep and is being used increasingly to elucidate drug effects. It is tedious in application to large

numbers of subjects. Many published EEG studies of the action of drugs on the animal brain must make us ask what we mean by the term "sleep." The term is properly used to indicate a recurrent, healthy state of inertia and unresponsiveness and one which, in contrast to coma or anesthesia, is readily terminable by external stimuli. Drugs given to promote sleep tend to make arousal and its EEG signs more difficult to elicit, so that the term "sleep" can legitimately be used only where comparatively small doses are employed to facilitate the natural onset of sleep, and not when the drugs are the principal cause of inertia and unresponsiveness.

The barbiturates are noted for causing fast (*beta*) activity in the 12 to 20 c/sec range to appear prominently in human EEG from frontal and temporal leads over normal but not abnormal cortex (72), and similar fast activity is seen with chlorpromazine (81) and nitrazepam (109). The drug-induced fast activity is present in wakefulness and accentuated in drowsiness but disappears once the person is fully asleep (stage 2, see below).

In the 1950s there was formulated the concept of the ascending activating reticular formation of the brain stem, with sleep being seen as a negative state brought about by lessened excitement of the reticular formation. The action of drugs on the reticular formation was reviewed by Killam (75a). In animal studies it was observed that thiopentone [thiopental, Pentothal, 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid] and pentobarbitone administration to the cat caused a rise in arousal thresholds, both EEG and behavioural, and a diminution of evoked potential responses in the reticular formation after discrete sensory stimuli (2, 10a, 40). It was therefore postulated that the barbiturates induced sleep and anesthesia by a special effect on polysynaptic mechanisms in the reticular formation, and reduction of nonspecific ascending activating impulses to the cortex.

The simple elegance of such concepts has been shattered. Italian workers have adduced evidence for the existence of tonically-acting, sleep-promoting mechanisms in the lower brain stem. Magni *et al.* (87), with the encéphale isolé preparation, ligated the communicating vessels between the internal carotid and vertebral arteries at the base of the brain. When they made intracarotid injections of thiopentone, the "wakeful" preparation showed the EEG signs of sleep, but when they injected thiopentone into the vertebral arteries of the already "sleeping" preparations it showed EEG signs of arousal, presumably because the drug in this case inactivated tonic sleep-promoting mechanisms in the lower brain stem. Again, the notion of sleep as a negative state arising from diminished reticular formation excitement had always been difficult to reconcile with the earlier work of Hess (51a) who produced apparently natural sleep by electrical stimulation of the brain stem, and equally difficult to reconcile with the appearance of a state resembling sleep as a provoked response (100a) following overwhelmingly intense stimuli ("transmarginal stimuli" of Pavlov). In more recent times sleep has come to be seen not simply as a negative state but also as one which may arise in a positive way through the increased influence of a hypnogenic brain stem system (14), which, if destroyed experimentally, can lead to

total insomnia and death (95a). I know of no evidence relating hypnotic drug action to such a hypnogenic system.

Even greater cause for abandoning the simple reticular formation-suppression hypothesis for the action of hypnotic drugs arises from the current knowledge of two different kinds of sleep, one of which appears to be suppressed by barbiturates.

A. Two kinds of sleep

The realization that there are two different kinds of sleep (101) arose from the pioneering observations of Aserinsky, Kleitman, Dement (4, 21, 23) and others. There are available many reviews of the physiology and psychology of the states of sleep (*e.g.*, 47, 62, 103).

The two states are commonly known as NREM (non-rapid eye movement), orthodox, forebrain, or slow-wave sleep on the one hand and as REM (rapid eye movement), paradoxical, hindbrain, activated, desynchronized or "fast" sleep on the other. Other terms have been used, notably "deep" and "light," each of which was unfortunately used for each kind of sleep, but owing to their inappropriateness these adjectives have now been largely dropped.

NREM or orthodox sleep is characterized by EEG slow waves and spindles and in man is customarily divided into stages 1, 2, 3, and 4 (23). The respiration, heart rate, and blood pressure are regular, skeletal musculature is greatly but not fully relaxed, the eyeballs are motionless, and if subjects are awakened thereform and asked what had just been going through their minds they describe it as "thinking" (rather than "dreaming") and give reports of a mundane nature.

If subjects are wakened from REM or paradoxical sleep they more often categorise their immediately preceding mental life as "dreaming" and the descriptions are much lengthier, more vivid, and detailed (37b). The EEG during REM sleep is of low voltage, in the cat resembling that of wakefulness, but in man containing much slower frequencies than in wakefulness, being made up chiefly of 4 to 10 c/sec waves. The rapid eye movements occur in intermittent bursts and are often preceded by a second or two of EEG waves of characteristic appearance, the "saw-tooth" waves of 2 to 3 c/sec. Each period of REM sleep in man lasts about 20 min and the two states of sleep alternate about five times nightly.

The distinct physiology of the two kinds of sleep has now been repeatedly demonstrated, only a few illustrative examples being necessary here. Although in REM sleep brief major body movements are more frequent (106) the loss of muscle tone is otherwise much more profound (9a, 58a). It represents, indeed, a paralysis caused by inhibitory impulses acting on the spinal anterior horn cells (112), causing loss of electrically-induced reflexes (57a) in man, in whom the inhibitory impulses descend by the anterior columns (121a). Whereas in NREM sleep brain temperature tends to fall below waking levels, the onset of REM sleep brings a sharper rise than does awakening (70b). The same is true of cerebral blood flow, which is very much greater during REM sleep than in wakefulness (117), especially in the rhombencephalon (7a). Whereas in NREM sleep the

penis is flaccid it is erect throughout each period of REM sleep except in a small percentage of instances associated with concurrent dream anxiety (37a, 70a). In contrast to NREM sleep the heart rate, respiration, and blood pressure are each subject to sharp and frequent fluctuations during REM sleep (122a).

1. The need for each. The differences between the two states might lead to the supposition that each served a different, even though unknown restitutive function, and experimental evidence indicates a need for each. Dement (21a) conducted a classic experiment, though first interpreting his work as indicating a "need to dream." Since NREM always precedes REM sleep, when Dement repeatedly woke subjects each time they entered REM sleep, and kept them awake for a couple of minutes before allowing resumption of sleep, they became progressively and selectively deprived of REM sleep. As a consequence REM sleep began to appear at shorter and shorter intervals, as if a "pressure" for it was building up. When on a subsequent night undisturbed sleep was permitted, a higher-than-base line percentage of REM sleep occurred as if in compensation. Repeated awakening from NREM sleep had no such effect. Dement's principal finding has been repeatedly confirmed in animal and human studies, though it may be noted here that the compensatory increase has never been found to be more than a moderate fraction of the lost REM sleep as far as duration is concerned, whereas in the "rebound" after withdrawal of various drugs, to be described below, the increase of REM sleep has, in some studies, more than exceeded in duration the REM sleep lost during drug administration.

Selective deprivation of REM sleep in cats causes abnormalities in cerebral sensory processing (25) and in sexuality and feeding behavior (22). There is evidence from man of subtle emotional disorder (14a, 1b).

There is, too, evidence of specific need for NREM sleep. The latter is commonly divided into stages 1, 2, 3, and 4 on the basis of the human EEG appearance, stage 4 having the largest and slowest waves. The normal occurrence of the latter stage chiefly at the beginning of the night suggests some urgent priority. When volunteers are deprived of all sleep for several successive days and nights and then allowed to sleep, they take a significant excess of stage 4 on their first recovery night (9b, 127a) and only on the second night does the REM sleep percent exceed normal. These findings suggest that NREM sleep stage 4 has priority as a restorative. It may be noted here that while this response is seen in very sleepy people, another group of people who feel very sleepy owing to withdrawal of amphetamine derivatives take an immediate excess of REM sleep (110). If normal subjects are deliberately disturbed whenever they enter stage 4, so that they become deprived of that stage, they subsequently take more of it, as if in compensation (1a). Dement and Greenberg (21b) argued that if the stages 1, 2, 3, and 4 were merely stages along a continuum of depth or worthwhileness of NREM sleep, then loss of stages 2 and 3 might result in increase of stage 4 by way of nonspecific compensation. They therefore restricted the sleep of subjects over a period to about 5 hr nightly (normally after 5 hr NREM sleep consists almost exclusively of stages 1, 2, and 3). The procedure had the 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 (125a). Physical exercise also promotes stage 4 sleep (7).

There is thus evidence that we need both kinds of sleep. Williams and Williams (128a) have proposed that "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 only in their infancy, but it is plain 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 effect. Examples of both such kinds of distortion will be detailed below. Hypnotics are among the drugs which suppress REM sleep, while fenfluramine specifically diminishes NREM sleep stages 3 and 4.

2. Measures of the two kinds of sleep. At this point some reference should be made to the techniques currently used for assessing the effects of drugs on the two kinds of sleep. It has become generally accepted that the results of at least the first night in the laboratory should be discarded owing to a "first-night effect" which, among other things, is associated with more wakefulness and less REM sleep during the night (1, 115a). Commonly a series of base-line nights have been recorded before a series of drug nights. It is desirable that not merely the "on" effect, but also the "off" effect of giving the drug should be assessed by an additional series of postdrug nights, though so far only a minority of investigators have done this. As "off" effects may persist for weeks, the demands on time and labour are high. Since there may be nonspecific effects of adaptation to the experimental environment, a late series of base-line nights, well after "off" effects have finsihed, would also be desirable. As subjects should abstain from alcohol and from late nights throughout any period of study, there are in practice difficulties in achieving the ideal. Most laboratory studies have been carried out on volunteers. It is desirable that more studies of the effects of drugs on sleep should utilise patients: anxiety might, for example, interact with a drug to modify conclusions about its effects.

There are now internationally recommended schemes for recording and scoring all-night EEG and eye-movement records (114a). A concomitant recording of muscle tonus can assist discrimination of REM and NREM periods. The simultaneous recording of other variables such as heart rate and body temperature, which normally fall during sleep, and of skin electrical resistance, which normally rises during sleep, would also be worthwhile in the assessment of an hypnotic, for there is evidence that what is subjectively regarded as "poor sleep" can be associated with a lesser fall of heart rate and body temperature and, paradoxically, with a greater rise of skin resistance (98a).

While it is preferable to give subjects blank medications on base-line nights there has been widespread agreement among research workers that suggestion can have little effect on the NREM-REM sleep distribution. Deliberate attempts, for reward, to try and affect the distribution cause a positive but very small effect (115a). While maximum information will be obtained from whole-night sleep recordings, the most essential information may be in some instances obtainable by recording only the first 2 or 3 hr of sleep. The effects of barbiturate with-

drawal, for example, are seen most markedly in the altered distribution of REM sleep during the night, from low values in the early night while on the drug, to very high values in the early night when it is withdrawn.

When subjects are used as their own controls, few problems arise concerning interpretation of the scores of, for example, percent REM sleep. In clinical studies advantage must sometimes be taken of briefly available patients, in whom a set experimental design is impossible. In this connexion certain arbitrary limits of normality may be useful.

There has been a remarkable uniformity among published studies giving the mean REM sleep in the whole night as a figure close to 23%. There is, however, a lack of collated data from different centres to indicate the range of normal. Many earlier studies are unreliable because it was not realized that drugs or alcohol taken in the preceding days or weeks can later cause high percentages. Low all-night percentages may merely result from brevity of sleep owing to REM sleep being least in the first part of the night. Knowledge of experience in this and other laboratories would cause me to regard as abnormal a figure exceeding 35% for the whole night, and of under 12% for a total night's sleep of 7 hr or more. In 1963 we suggested limits unlikely to be surpassed more than once or twice per hundred instances and among these was an arbitrary lower limit of normal of 45 min from first onset of the spindles of stage 2 sleep at the beginning of the night to first onset of REM sleep (110). Since this delay period or latency is probably the most sensitive single index of altered "pressure" for REM sleep, and recordable with only modest expenditure of energy, some further consideration is worthwhile. It is a measure which is lengthened by first administration of hypnotics and shortened by their withdrawal or by prior selective deprivation of REM sleep. It has also been reported as shortened in occasional cases of severe depression or chronic insomnia and occasional cases of schizophrenia, of severe anxiety, and or organic dementia (see especially 36a).

In 1963 we stated (110) that we had encountered no instances where the delay or latency to first REM was under 45 min among 70 normal recordings in this laboratory. In reviewing 185 more recent normal recordings from this laboratory where we were confident that the subjects had not taken sleeping pills in the preceding weeks. S. Lewis and I have noted three instances, of 36, 38, and 42 min respectively. Half of all the values lay between 59 and 91 min and the distribution was heavily and positively skewed. A number of authors, without stating the range, have stated the mean and standard deviation for their own findings, but, owing to the heavy skew, to calculate the latter would appear an invalid and misleading procedure. Rechtschaffen and his colleagues reported on a series of 80 normal nights in which the shortest delay to first REM sleep was 46 min (115a) and elsewhere stated "according to our knowledge of nocturnal sleep, subjects do not have REM periods before 45 min of NREM sleep has elapsed" (91). Dement and Kleitman (23) in their original study of 126 normal nights gave the shortest delay as 45 min from sleep onset (*i.e.*, stage 1). While the initial stage 1 is usually only a couple of minutes it can be much longer. Here again there is a heavily skewed distribution. Consequently the latency from stage 2 onset to first REM

sleep is to be preferred and has been used also by Feinberg, who reported that some normal elderly patients had short REM latency, and especially, to an even greater degree, patients with chronic brain syndrome (36b). The figure of 45 min may thus only be valid as an indication of the extreme 1 to 2% of normal for the young adults who predominate in most series. On the other hand Feinberg did not say anything about the use of sleeping pills by his group of aged normals, and indicated in his paper that some patients at least had received such drugs up to 3 weeks before, which could be a sufficient cause of short latencies as will be noted below (109). The sensitivity to drug administration of the REM latency is such as perhaps to limit its value in some clinical studies.

B. Amphetamine and its derivatives

Amphetamine was long regarded as having effects opposite to barbiturates so that the clinical use of mixtures of the two appeared nonsensical. Studies of REM sleep, however, provide evidence of some similarities of action.

Many reports have testified to the subjective wakefulness-inducing properties of amphetamine, but the clearest demonstration of its sleep-preventing action was provided by Kornetsky *et al.* (77). Williams *et al.* (128) had just shown that sleep loss causes measurable impairment in tasks requiring sustained attention, and that when the rate of working is imposed on a subject ("paced" tasks), errors of omission are frequent. They proposed that these errors arise from brief falls of vigilance, or "microsleeps." Kornetsky *et al.* (77) then showed that the degree of impairment in paced tasks caused by 68 hr without sleep could be halved by oral dextroamphetamine (Dexedrine, *d*-α-methylphenethylamine) 15 mg, and that the smaller impairment detectable on "unpaced" tasks could be abolished.

Rechtschaffen and Maron (115) gave 10 or 15 mg oral dextroamphetamine to 10 volunteers. The authors found a significantly increased delay to the first onset of REM sleep, a reduction in the proportion of REM sleep, and increased frequency of body movements during sleep. They gave other subjects a mixture of dextroamphetamine 15 mg with pentobarbitone 100 mg. On control nights these same subjects received only the pentobarbitone 100 mg. On pentobarbitone alone REM sleep averaged 18.4%, but it averaged only 9.0% when the amphetamine was added ($P < 0.01$). The suppression could not be attributed to any different frequency of movements or awakenings after the mixture. It has since been confirmed that the addition of amphetamine causes a greater suppression of paradoxical sleep than does pentobarbitone alone (6).

Patients with long-standing addiction to amphetamine, to a mixture of amphetamine and amylobarbitone (Drinamyl, Dexamyl), or to phenmetrazine hydrochloride (Preludin, 3-methyl-2-phenylmorpholine hydrochloride) were found by Oswald and Thacore (110) to have approximately normal proportions of REM sleep, but, when the drug was withdrawn, total sleep was increased, REM sleep was increased above normal limits especially early in the night, and it began abnormally quickly after the beginning of sleep, namely less than 45 min, and often less than 20 min, after first onset of EEG sleep spindles. Restoration of drugs abolished the abnormalities, but they returned when drugs were withdrawn again.

Over a period of 2 months sleep gradually returned to normal. The excess of REM sleep on withdrawal of such drugs has been referred to as a "rebound" phenomenon.

A related drug is diethylpropion hydrochloride (Tenuate, 2-diethylaminopropiophenone hydrochloride). Oswald *et al.* (108) found this to delay and suppress REM sleep, to cause frequent awakenings and frequent shifts to NREM sleep stage 1 (drowsiness) from all other stages, when compared with blank. In a withdrawal study with two subjects on each drug, both phenmetrazine and diethylpropion caused signs of rebound, with abnormally early onset of REM sleep, namely after 0 and 25 min latency respectively. On the other hand fenfluramine (see below) did not do so in any of four subjects, all subjects having received the drugs regularly for a week.

Tranylcypromine (Parnate, trans-(±)-2-phenylcyclopropylamine), another amphetamine derivative, can suppress paradoxical sleep (116). It is also a monoamine oxidase inhibitor (see section II K). There are two reports of patients addicted to the drug who sometimes had no REM sleep at all after taking the drug, but showed a rebound increase after it was withdrawn, as much as 75% of their sleep being REM sleep. After withdrawal their REM sleep occurred repeatedly at the onset of sleep and there were associated nightmares (19, 80).

Methylphenidate hydrochloride (Ritalin, methyl-α-phenyl-α-piperid-2-ylacetate hydrochloride) suppresses REM sleep (5). Information about its withdrawal is not available.

Another derivative of amphetamine is fenfluramine (Ponderax, *N*-ethyl-α-methyl-3-trifluoromethylphenethylamine) which has been in use in Europe for several years as an anorexiant (99). A number of clinical reports suggested that drowsiness was a side-effect of its continued use. Oswald *et al.* (108) observed the effect of 40 mg oral doses on young adults during the first 3 hr of sleep. In contrast to other amphetamine derivatives, fenfluramine had no effect on REM sleep, nor, with reference to blank, did it increase the frequency of brief awakenings, nor time awake. It did, however, disturb sleep in that it caused frequent shifts from other sleep stages to stage 1 sleep (drowsiness), and more total sleep time in stage 1 sleep.

C. Other "stimulant drugs"

Caffeine citrate 5 mg/kg body weight (about 3 cups of coffee) was administered on single nights to 7 subjects by Gresham *et al.* (42) without significant effect on REM sleep duration compared with blank. Schwertz and Marbach (121) gave their subjects caffeine alkaloid 200 mg in capsules at four set times, three being in the day before the experimental night. The EEG was not used and time of falling asleep was based on body movement frequency. By this criterion caffeine significantly delayed the onset of sleep, while, through the night, rectal temperature and the rate of small movements were significantly higher after caffeine than after lactose capsules. Since rectal temperature normally falls by over a degree during a night's sleep but subjective "poor" sleep is associated with a lesser fall (98a) it would seem likely that caffeine not only delayed

sleep onset but caused frequent breaks in sleep with associated movement together with some deficiency in the quality of sleep itself.

Lysergic acid diethylamide (LSD) in doses ranging from 0.08 to 73 μg/kg was administered to 12 human subjects by Muzio *et al.* (100) on a total of 36 nights, which were compared with 69 control nights on the same subjects. The drug was administered orally just before sleep or after 1 hr of sleep. LSD increased the duration of the first or second REM period. Durations of, for example, 52 min for the first REM period, and 141 min for the second REM period, occurring after LSD far exceed normal limits: Dement and Kleitman (23) for example, in their series of 126 cases reported upper limits of 36 and 54 min, respectively. Muzio *et al.* also observed that when an abnormal excess of REM sleep had been induced early in the night there was a below-normal amount of REM sleep during the second half of the night (a type of reverse "rebound" within the one night) and that there appeared to be an increased liability to awakenings after LSD.

In the rat, Hartmann (48) found doses of 2.5 to 10 μg/kg of LSD significantly to increase REM sleep. Contrary observations were made with cats given either 20 μg/kg or 2 μg/kg (57), there being a statistically significant reduction of REM sleep. Hobson (57) suggested that the latter effect could arise from the increased frequency of brief awakenings, which did not allow the sustained periods of NREM sleep that normally precede REM periods. Clearly the effect may also be species- and dose-dependent.

Nicotine tartrate 15 μg/kg was administered by injection to 8 human subjects before sleep by Domino (26) but REM sleep averaged 24.7% against 25.7% after saline injection. Both these figures were significantly higher than earlier nights without medication, but clearly do not differ significantly from one another and one must suppose other factors operated on the earlier control nights, such as a lingering "first-night effect" (though they had had an adaptation night). However, 10 μg of nicotine per kg injected intravenously into sleeping cats caused first wakefulness for a few minutes, then, after 15 to 25 min, a period of REM sleep for a significantly longer time than followed injections of saline or epinephrine (27). The effect could be prevented by mecamylamine, a ganglion-blocking agent capable of passing the blood-brain barrier, but not by trimethidinium, a ganglion-blocking agent not capable of crossing the blood-brain barrier.

Jewett and Norton (60), in two cats given nicotine bitartrate 100 μg/kg subcutaneously, described a significant rise of REM sleep with the drug, but its abolition in one cat when the dose was doubled. The question of rebound after the drug was not considered.

D. Barbiturates

Oswald *et al.* (106) found that heptabarbitone 400 mg orally at bedtime significantly reduced not only the proportion of REM sleep but, compared with blank, also the frequency of rapid eye movements per minute during periods of REM sleep of human subjects. Baekeland (6), using pentobarbitone 100 mg,

confirmed both of these effects, and emphasised that although the drug delayed the first appearance of REM sleep and reduced its total, the underlying periodicity in the cyclical alternation of the two kinds of sleep appeared unaffected. Hartmann (50) made similar observations with pentobarbitone. Fisher (37) stated that the penile erections of REM sleep may appear at the expected times when pentobarbitone or dexamphetamine have suppressed the rapid eye movements and the usual EEG signs.

In two adult subjects whose sleep was studied during a 4-month period, Oswald and Priest (109) described return of REM sleep percentages to normal within 3 weeks when amylobarbitone, up to 600 mg, was given each night. After withdrawal of the drug there appeared abnormally short delays between onset of NREM sleep and the first REM period, and also abnormally high percentages of REM, especially in the early part of each night. These abnormalities took 5 weeks to disappear.

Kales *et al.* (69) have briefly reported a similar withdrawal "rebound" after three consecutive nights on pentobarbitone 100 mg. The reduction in number of rapid eye movements per minute during REM periods caused by barbiturates is succeeded by a significant increase above base line (predrug levels) when the drug is withdrawn (66, 104), consistent with the more vivid dreams and frequent nightmares that occur (68, 109)—in other words the withdrawal causes a change in the intensity of REM sleep.

E. Alcohol

Gresham *et al.* (42) found that ethyl alcohol (1 g/kg body weight) reduced the adult REM sleep percentage. Yules *et al.* (133) gave three men a similar dose of alcohol on 5 successive nights and reported a reduction of REM sleep on the first night and a rise on subsequent nights. Statistical tests were not applied to this rise but one man, on the fifth alcohol night, had as much as 50% of REM sleep, which is well outside the range of normal. On the sixth night no alcohol was given and all the men had high REM sleep percentages. This is consistent with a "rebound" effect, but the rise on prior nights indicates some complexity. Two reports of alcohol withdrawal from heavy drinkers (41, 43) both described very high REM sleep percentages (up to 100% of sleep) associated with withdrawal and the onset of delirium tremens. One of these reports (41) described REM suppression on most nights while alcohol was being taken by day, but mentioned occasional nights with a high REM sleep percentage.

F. Other hypnotics

Meprobamate to a total of 1.2 g before sleep significantly reduced REM sleep in eight young male adults (39). Withdrawal after repeated nights on the drug can provoke a rebound increase in percent REM sleep, comparable to that seen after withdrawal of barbiturates (107).

Suppression of the signs of REM sleep has also been reported to occur after nitrazepam 15 mg (109); also after glutethimide 500 mg and after methyprylon 300 mg (69). Chloral hydrate was stated to have little effect on REM sleep (69).

Withdrawal of nitrazepam, glutethimide, and methyprylon after 14, 3, and 3 consecutive nights, respectively, caused rebound increase of REM sleep time, which in the nitrazepam study was mentioned as occurring especially in the early part of each night, with also abnormally early onset of first REM periods and persistence of abnormal features into the fourth week after withdrawal. Nightmares were a feature of nitrazepam (109) and methyprylon (68) withdrawal. Lob *et al.* (84) reported that nitrazepam delayed the first REM period of the night in 12 psychoneurotic patients. They apparently did not observe any obvious reduction over the whole nights, but as the single nitrazepam night followed a single first night on blank (average sleep duration 4 hr 23 min) an abnormally low REM percent for the blank night would be expected (a) because sleep duration was so short, REM sleep being less in the early night, and (b) because of the "first night effect" (1).

At this point it is convenient to refer to two drugs related to nitrazepam, namely chlordiazepoxide and the diazepine derivative known as RO 5-6901 (Dalmane). Hartmann (50), in 10 normal adult volunteer subjects given doses of 100 mg chlordiazepoxide or 30 mg of RO 5-6901, found no statistically significant effect on REM sleep when comparing 1 night on the former drug and two on the latter with 5 nights on blanks. One may note from his data that the mean delay between first sleep onset and first REM was increased by half an hour after both drugs, and that there were lower mean whole-night REM percentages, so it is possible that a larger series, or bigger doses, could have revealed a significant effect qualitatively similar to that of the barbiturates. Kales (70) observed no significant effect of RO 5-6901 with doses of 30 mg but a suppression of REM sleep with twice the dose.

G. Reserpine

Reserpine (Serpasil) in doses of about 1.5 mg per 70 kg body weight, given to six adults by Hartmann (46), significantly increased the proportion of REM sleep with early onset of the first REM period (*e.g.*, a mean delay from first NREM sleep of only 37 min in 4 nights from one subject). Hartmann also presented, in graphical form, REM percentages for subsequent nights, which appear to indicate that the observed action on sleep of a single dose of reserpine could persist for more than a single night. A different picture was reported by Matsumoto and Jouvet (92) in a cat or cats (not stated). In comparison with Hartmann's study the dose of reserpine was extremely large, 0.5 mg/kg (half of this dose was said to have no effect). Severe diarrhoea, agitation, and restlessness were followed by increasing sleep after 18 to 24 hr. Slow wave (NREM) sleep predominated and REM sleep was reduced for at least a week. On the other hand Khazan and Sawyer (73) stated that, in the rabbit, reserpine "appeared" to lengthen REM sleep episodes and to increase their frequency of occurrence.

H. Diphenylhydantoin

Observing that their epileptic patients under treatment with diphenylhydantoin (phenytoin, Epanutin, Dilantin) had very small proportions of the night in

REM sleep, Cohen *et al.* (15) studied the effects of its chronic administration (9 mg/kg daily) in cats. A sharp reduction of REM sleep was caused, without signs of tolerance within 3 weeks and without any evidence of rebound on withdrawal.

I. Phenothiazines

Sleepiness is the commonest side-effect in clinical practice with chlorpromazine and thioridazine and both are employed as hypnotics in elderly patients. The evidence concerning their more intimate effects on human sleep is sparse and, possibly because effects may be dose-related, such reports as exist are conflicting. If we exclude reports of isolated clinical cases, consideration is confined to chlorpromazine. Toyoda (124) gave it in doses of 12.5 to 50 mg to eight subjects and reported an increase in paradoxical sleep, especially in two neurotic patients. Their recent history in regard to hypnotics (and hence possible rebound) was not stated; their REM sleep time on chlorpromazine was compared only with a single night on blank medication, which in six of the cases had been the first laboratory night, and hence probably with abnormally low REM sleep time (the "first night effect"). Toyoda's conclusions are consistent with the finding of Lester and Guerrero-Figueroa (81), in a carefully designed study, that chlorpromazine 100 mg orally in adult volunteers significantly reduced the delay between first falling asleep and the first REM period of the night, and significantly increased the duration of the first REM period. These last two phenomena are commonly associated with high REM sleep percent in the whole night; so it would appear that, at the beginning of the night at least, chlorpromazine 100 mg was enhancing REM sleep. There is also evidence from studies in the cat (56) that chlorpromazine 2 mg/kg can shorten the latency to REM sleep. On the other hand large doses given to cats can have the opposite effect and reduce REM sleep over a longer period (56, 60, 63). There is also evidence from human laboratory experiments that while 25 mg doses can increase REM sleep, 100 mg doses may decrease it if the overall night percentages are considered (83). Presumably the observations of Lester and Guerrero-Figueroa with 100 mg doses may have indicated an enhancement of REM sleep by small doses, before full absorption had taken place.

J. Imipramine and derivatives

In five cats studied in a total of 35 recording periods of up to 10 hr, Hishikawa *et al.* (56) reported that imipramine (Tofranil, 5-(3-[dimethylamino]propyl)-10, 11-dihydro-*5H*; dibenz(b,f)-azepine) 4 mg/kg, imipramine 2 mg/kg and desmethylimipramine (Pertofran, Pertofrane) 4 mg/kg significantly increased total sleep time, delayed the first REM period, and greatly reduced REM sleep percent, while desmethylimipramine 2 mg/kg had the last two effects only. Khazan and Sawyer (73) reported reduction of REM sleep in adult rats, and its equivalent in newborn rabbits, by imipramine. Toyoda (124) too stated that imipramine suppressed REM sleep in man and described enhancement of the EEG sleep spindles in NREM sleep. Ritvo *et al.* (117a) studied seven boys aged 9 to 11 years on a total of 62 nights. At least 4 base-line nights were recorded on each boy and compared with 4 consecutive nights on 25 mg imipramine. They

found that the delay between sleep onset and the first REM period was significantly lengthened by imipramine and that the percentage of sleep spent as REM sleep was halved from 24.8 to 12.3%, with concomitant increased duration of stage 2 NREM sleep. Withdrawal effects were not studied. Jouvet (63) mentioned suppression of REM sleep by imipramine 5 to 10 mg/kg, not followed by any withdrawal rebound, in cats.

Hartmann (50) described a detailed study of amitriptyline [Tryptizol, Elavil, 5-(3-dimethylaminopropylidene) dibenzo (a, d) (1, 4) cycloheptadiene], which, in doses of 75 mg at night, reduced REM sleep very markedly and delayed its first appearance. Hartmann mentioned also preliminary observations which suggested there was no rebound on withdrawal nights. Zung (134) gave desmethylimipramine 25 mg thrice daily to 17 adult volunteers and recorded their sleep on 4 consecutive nights, which were compared with 4 previous control nights. Stage 4 NREM sleep was significantly increased in percentage on drug nights, REM sleep was reduced, and shifts from sleep to wakefulness also reduced. In addition mention should be made of the clinical improvement of sleep that may accompany recovery from depressive illness under treatment by imipramine and its derivatives (*e.g.*, 12). The patients cease to complain of waking early or of lying awake in the small hours.

One of the physiological characteristics of REM sleep is the paralysis of most skeletal muscles already described. The patient with idiopathic narcolepsy is peculiarly liable to fall asleep directly into REM sleep. He is also peculiarly liable to attacks of cataplexy, namely sudden brief paralysis while awake, usually provoked by emotion. The suggestion that these attacks represent a sort of partial REM sleep state has been made by several writers. Imipramine and desmethylimipramine reduce the cataplectic attacks in patients, though not the full sleep attacks (55).

K. Monoamine oxidase inhibitors

Mention has already been made of tranylcypromine (section II B). Toyoda (124) stated that Nialamide [Niamid, 1-(2-[benzylcarbamyl]ethyl)-2-isonicotinoylhydrazine] reduces REM sleep in man. In cats, harmaline (3,4-dihydroharmine) 20 mg/kg was like tranylcypromine in causing wakefulness but iproniazid (Marsalid, *N*-isonicotinoyl-*N*-isopropylhydrazine) 80 mg/kg and nialamide 5 to 10 mg/kg were stated to have a selective effect in strongly suppressing REM sleep in cats (65). The action of a single dose of nialamide on REM sleep persisted for a week and there was *no immediate rebound* (63, author's italics).

L. Morphine

Opium alkaloids have been employed for centuries in order to induce sleep. Even in the absence of pain, morphine with hyoscine as a sedative has not entirely disappeared from the present-day clinical scene. There is yet little information from EEG studies concerning the effects of morphine on sleep. Khazan *et al.* (75) in a study of self-maintained morphine addiction in rats described an initial reduction of all sleep, and virtual elimination of REM

sleep, but apparent tolerance or return to control values after 3 days of increasing dosage. They did not refer to any withdrawal rebound. Kay (71) stated that in experimental studies at Lexington, Kentucky, evidence has been found that in man morphine suppresses REM sleep on initial administration, with a rebound on withdrawal. My colleagues and I, using ourselves as subjects and doses of 5 to 10 mg of diamorphine hydrochloride (heroin) nightly for from 3 to 7 consecutive nights, have found the drug considerably to disturb sleep, with frequent shifts to stage 1 sleep, frequent awakenings and suppression of REM sleep, and rebound after withdrawal (83a).

III. STUDIES WITH "EXPERIMENTAL" DRUGS

Drugs discussed above have been in clinical use for their action on the central nervous system. However, the persistence of extreme lethargy in many people when they are wakened from sleep has for long caused a search for "hypnotoxins" or for some chemical basis of sleep. A number of experimental reports has appeared in recent years which consider sleep mechanisms in relation to a variety of compounds.

A. Steroid hormones

Progesterone in sesame oil injected intraperitoneally into cats induces anesthesia in large doses, but in smaller doses of 150 mg/kg was considered by Heuser (52) to induce natural sleep during which REM sleep appeared to be provoked abnormally early. Heuser and his colleagues (53) have also applied progesterone suspension directly to the preoptic area of the hypothalamus of freely-moving, alert cats. Compared with control substances it quickly induced a state of behavioral and EEG sleep. On control runs sleep never occurred in the experimental cage in less than 15 min with 10 cats, but it occurred as soon as 3 min after progesterone. Furthermore REM sleep in the experimental sessions occurred earlier than in control sessions. Gyermek (44) reported that pregnanolone, a metabolite of progesterone, when given intravenously to mice and cats, is a potent short-acting hypnotic which blocks evoked potentials in the reticular formation much as thiopentone does, and that "in comparison with thiopental showed that in the equipotent hypnotic dose the latter exhibited higher degree of respiratory, cardiovascular and ganglionic depression."

Hartmann (45) recorded the all-night sleep of seven women on 127 nights and found higher REM sleep percentages late in the menstrual cycle, especially when there was premenstrual tension, further linking REM sleep and progesterone. Malven and Sawyer (88) reported reduced REM sleep in guinea pigs on the day of estrus, associated with increased wakefulness, also found during proestrus in rats (132). In 1959 Sawyer and Kawakami (119) described a strange immediate sequel to coitus in the female rabbit, including a sleep state with flaccidity, high amplitude *theta* EEG waves from the hippocampus, and a desynchronized frontal cortical EEG, broken by periods of ravenous eating or coprophagy. The sleep state has since been recognized as REM sleep. A number of studies complexly linking the reaction with the hormonal balance have since been described

by Sawyer *et al.* (120) and by Faure and his associates (33, 34, 36), including a report by the latter group of provocation of REM sleep by antidiuretic hormone (35).

Kales *et al.* (67) compared the sleep of seven hypothyroid patients on 3 consecutive nights with that of control subjects. The patients had significantly less of NREM sleep stages 3 and 4 (high voltage EEG slow waves). After treatment with desiccated thyroid the sleep EEGs returned to normal. As the authors pointed out, stages 3 and 4 are characterized by higher awakening thresholds on auditory stimulation, and there is other evidence that suggests they have greater restitutive value than stages 1 and 2, so that therapy may indeed have "improved" their sleep.

B. Cholinergic and anticholinergic drugs

Hyoscine and atropine have long been noted for inducing drowsiness. Bradley and Elkes (10) found that while EEG slow waves resembling those of sleep were caused by intraperitoneal atropine 3 mg/kg in cats, they could continue to be behaviourally active. Jouvet (61) stated that atropine suppressed and eserine (physostigmine) enhanced REM sleep in cats. Subsequently, in rats, Weiss *et. al.* (126) found no statistically significant effect of atropine on REM sleep duration, nor its cyclical recurrence, with either small or large doses. Hernández-Peón (51) applied acetylcholine, physostigmine, atropine, and other drugs locally to delineate a postulated hypnogenic pathway extending through the brain stem to the spinal cord. There must be reservations about the relation between normal physiology and states produced by the large, local concentrations of substances introduced into the brain, and the weight that can be attached to conclusions based on an uncertain small number of observations. It is not possible to see grounds for supposing any specificity of relationship between acetylcholine and the states of sleep.

C. Sodium butyrate and related compounds

Jouvet *et al.* (64) reported that doses of 200 to 500 mg/kg of 4-butyrolactone or sodium 4-hydroxybutyrate injected intraperitoneally into cats induced rapid "narcosis," a state of unresponsiveness in which the eyes remained open and the nictitating membrane was not relaxed, and that, in the normal cat, the decorticate cat, and the cat in which the nucleus pontis reticularis caudalis had been coagulated some weeks before, injection of 50 mg/kg of 4-butyrolactone would cause the rapid onset of REM sleep lasting over 15 min. This last report was supported by Matsuzaki *et al.* (94) (in neither paper are control data specified). Winters and Spooner (129) using cats and varying doses of *gamma* aminobutyric acid, at intervals of 10 days or more, and observing both behavioural and EEG responses, concluded that the drug did not induce sleep, that the periodicity and duration of any signs of REM sleep that appeared after small doses did not differ from normal, and that after larger doses the behavioural and EEG picture resembled generalised nonconvulsant epilepsy. Metcalf *et al.* (96) gave 35 to 63 mg/kg of sodium *gamma* hydroxybutyrate to 20 human adults by day and

observed their EEGs and behaviour subsequently. Coma appeared about half an hour after the larger doses, with myotic, unresponsive pupils, generalised hypotonia, unresponsiveness to stimulation, and EEG slow waves. There were instances of low voltage EEG, but with *delta* frequencies present, and the authors did not describe the appearance of REM sleep.

The interest in these substances had arisen from the known presence of *gamma* aminobutyric acid in the brain, but no clear role for this substance in the control of sleep can be suggested from the experiments outlined above.

D. Precursors of serotonin (5-hydroxytryptamine)

Oswald *et al.* (105) found that a proportion of normal adults (5 out of 16), if given 5 to 10 g of L-tryptophan orally in capsules at bedtime would sometimes enter REM sleep abnormally early (less than 45 min from sleep onset) whereas lactose, L-tyrosine, or DL-methionine did not cause the effect. The abnormalities appeared significantly more often after tryptophan alone than if the antiserotonin agent methysergide [Deseril, Sansert, N-(1-[hydroxy-methyl]propyl)-1-methyl-D-lysergamide] 3 mg daily for 3 days preceded tryptophan administration. There are also two reports of persons in whom REM sleep appeared abnormally early, or where it was increased in duration, after intravenous injection of 5-hydroxy-tryptophan (89, 105). In eight normal adults, Hartmann (49) gave oral L-tryptophan 6 to 10 g (120 mg/kg) in applesauce at bedtime, on a total of 36 nights, and found REM sleep duration significantly increased compared with 55 control nights, but did not obtain earlier onset of REM sleep. Total sleep was not significantly increased.

Since patients with idiopathic narcolepsy are abnormal in that they frequently pass into REM sleep at sleep onset, instead of NREM sleep, Evans and Oswald (29) administered 5 g of L-tryptophan orally to seven narcoleptic patients 15 min before they retired to bed. The mean duration of the initial REM period was doubled: on the 25 occasions after tryptophan it was 29.6 min, compared with 13.7 min on the 25 control occasions.

In experiments with rats Hartmann (48) also found REM sleep affected by tryptophan. A diet containing excess tryptophan fed to rats caused the cycle of REM sleep occurrence to be more rapid, whereas a tryptophan-free diet lengthened the cycle period. These experiments differ from those in man in that the special diets were given for a week. The human experiments involved a single dose at widely-spaced intervals at which adaptation factors in total REM sleep could not operate. In the rats total sleep was not increased by either of the diets; indeed each caused some reduction of total sleep and increased frequency of awakenings.

Jouvet (63), on the other hand, proposed that serotonin precursors lead to suppression of REM sleep. DL-5-Hydroxytryptophan in doses of 30 to 50 mg/kg were injected intraperitoneally or intravenously in each of 2 cats on 3 occasions (the dosage/kg was about 50 times that used in the human experiments mentioned above). The cats entered a state "resembling" NREM sleep but differing in that slow waves were recorded from the lateral geniculate (they were stated

not to occur in normal NREM sleep) and with "rarely a real sleeping posture . . . no relaxation of nictitating membranes." This state lasted 5 to 6 hr, after which REM sleep was increased ["more intense and lasts longer than would be expected following an instrumental selective deprivation of PS (REM sleep) of 4 to 5 hours"]. Jouvet, in his discussion, recognized the complexity of the amine mechanisms that might govern sleep and wrote . . . "the augmented 5-HT would also be liberated in a 'free' or unbound form and would account for the secondary rebound of PS which usually follows the administration of 5-HTP." It would seem therefore that his position is not consistently contrary to the evidence that serotonin may promote REM sleep.

The substance *p*-chlorophenylalanine selectively depletes animal tissues of serotonin. It was administered by Weitzman *et al.* (127) intraperitoneally in dosages of 330 to 1000 mg/kg to monkeys, after baseline nights of sleep. On subsequent nights total sleep was reduced, but principally through reduction of NREM sleep, the absolute reduction of REM sleep being small (so that as a percentage of all sleep it was increased). The authors also reported that the procedure was capable of reducing brain serotonin (except in the cerebellum) by over a third. Increased wakefulness caused by *p*-chlorophenylalanine has also been found in rats (123) and cats (20).

Koella and Czicman (76) have reported experiments with serotonin itself. It was injected into the internal carotid artery (0.2 to 5.0 μg/kg) and caused an initial brief EEG desynchronization with mydriasis, followed by up to 15 min of "hypersynchronous EEG" often with miosis. The second phase did not appear after prior midpontine transection, and no response at all followed the serotonin if the area postrema had been cauterized (it being believed that at this site the serotonin gained access to the brain from the blood stream). The cats in all experiments had already been sedated with allobarbital and urethan. The authors interpreted their findings as indicating a role for serotonin in the "organization" of NREM sleep.

E. Precursors of norepinephrine

Jouvet (63) has postulated a role for norepinephrine in the regulation of REM sleep. As mentioned above, when Matsumoto and Jouvet (92) gave a large dose of reserpine to cats, REM sleep was reduced. To be precise the "tonic" signs of REM sleep, in the EEG and in loss of neck muscle tone, did not appear. Another feature of REM sleep in the cat, however, is ponto-geniculo-occipital electrical spike potentials. These occur in NREM sleep but are much more marked in REM sleep. Although reserpine suppressed the "tonic" signs of REM sleep in the cat it caused intense ponto-geniculo-occipital spiking (63). When dopa (dihydroxyphenylalanine) 30 to 50 mg/kg, a precursor of norepinephrine, was injected into the reserpinized cat, it caused an even greater increase of the ponto-geniculo-occipital spiking, the agitation of the cat was relieved, and NREM sleep appeared, punctuated at intervals by the full picture of REM sleep during the next 5 to 6 hr, after which the reserpinic syndrome reappeared (63). The fact that dopa allowed the appearance of both NREM and REM sleep, whereas

5-hydroxytryptophan (30 to 50 mg/kg) injections allowed the brief reappearance of broken NREM sleep only, is seen by Jouvet as indicating a releasing of REM sleep by norepinephrine. The interpretation of the data would appear difficult owing to uncertainties in current knowledge concerning the distortion of brain chemistry by the large initial dose of reserpine.

Two recent further reports by Jouvet's associates, involving the injection of norepinephrine and dopa respectively, refer to REM sleep. It should first be mentioned that there is evidence that, in young adult male athletes, afternoon exercise is associated with an increased proportion of NREM sleep of stages 3 and 4 (very slow or *delta* EEG waves) at the expense of stages 1 and 2, with no change in REM sleep (7). Matsumoto *et al.* (93) studied the effect of exercise on sleep in the rat. Eight elderly rats kept awake by observation and shaking for 4 hr were then permitted to sleep; REM sleep first appeared after a mean delay of 104 min. On a subsequent day they were strenuously exercised for 4 hr on a treadmill and then allowed to sleep (one passed into a state of "coma"), whereafter NREM sleep occurred earlier than previously, but REM sleep appeared significantly late, after a mean of 366 min. On a subsequent day five rats were on the treadmill for 4 hr, and dopa 50 mg/kg was then injected intraperitoneally. They passed into REM sleep after a mean delay of only 106 min. It was not stated if these last five rats were drawn from the eight used previously nor, if so, how they were selected, nor whether their new mean delay differed significantly from that after the exercise alone. (Apart from the desirability that they should serve as their own controls, it would also be desirable for the dopa to be associated with a first experience of the stressful treadmill as often as with the second experience of it.) When four younger rats were used there was no difference in the delay to REM sleep with or without exercise. The results pointed to a reversal of the effects of fatigue by dopa and the authors suggested that the inhibition of REM sleep by exercise was a result of a deficiency of norepinephrine in the brain.

The other recent report is that of Pujol *et al.* (113, 114). Rats were selectively deprived of REM sleep for 91 hr by the technique of keeping them on small platforms surrounded by water. Radioactive norepinephrine was then injected intracisternally (a) into rats allowed to sleep for the subsequent 5 hr, and (b) into rats put back on the platforms and again prevented from having REM sleep. After 5 hr both groups of rats were killed. The turnover of norepinephrine was reported to have been significantly higher in group (a) than group (b). The difference was attributed to the "marked rebound" of REM sleep possible in those rats allowed sleep. Another control series of rats was, however, studied electrophysiologically: on the platforms their REM sleep was zero and their NREM sleep was reduced by over 40%: their "rebound" in the final 5 hr actually amounted to REM sleep occupying a mean of 11.7% of the 5 hr, while NREM sleep occupied 44.6% (113) so that the percentage of sleep spent as REM sleep was less than 21%, and was almost identical with that of another group of rats, which had not been selectively deprived of REM sleep. Consequently, in the absence of a control group of rats subjected to some other form of prolonged

stress, involving at least as much NREM sleep deprivation, it is difficult to attribute the findings to a "rebound" of REM sleep, when no such rebound in excess of normal percentage apparently took place under the conditions of the experiment.

Cerebral norepinephrine content can be depleted by the administration of *alpha* methyltyrosine. Marantz and Rechtschaffen (90) depleted the cerebral norepinephrine of a group of rats by this technique to half the normal value, but without any effect on the duration of sleep or the percentages of REM and NREM sleep.

In sum it is now clear from work which emanates from independent centres that serotonin and its precursors can modify sleep and, in particular, promote REM sleep. There is some evidence, but so far less secure, that norepinephrine is concerned in the brain chemistry of sleep. One must suppose that time will prove both to be involved, and that change in the amount of bound or unbound amine, or indeed their rate of change, may prove to be important in affecting a number of controlling systems held more or less in equilibrium. It is not necessary to suppose that any one biogenic amine is alone responsible for one or other kind of sleep. One has only to recall the eclipse of the simple notion of sleep as a negative state arising simply out of lesser stimulation of an ascending activating reticular formation, and the demonstration of a complementary hypnogenic system, to realise that some brain amine of contemporary interest might increase the activity of more than one functional system in the brain, in ways which might be opposed, and yet their eventual combined effect be in no way disadvantageous to the organism.

IV. CONCLUDING REMARKS

In spite of the massive prescribing of hypnotics it is only in the last 7 years that intensive international research into the nature of human sleep can be said to have begun. In section II were summarised the more important recent attempts to uncover a chemistry of sleep. The expectation that some natural "hypnotoxin" may mediate the onset and maintenance of sleep will provide the motive for a further rapid expansion of work in this field during the next decade.

The hope that such a "hypnotoxin" may be discovered is sustained by the research of Monnier and Hösli and their colleagues (57b, 120a) who have induced sleep in rabbits by Hess's method of thalamic electrical stimulation and then subjected the venous blood to dialysis. The dialysate, when injected into waking rabbits appeared to induce natural sleep which was not secondary to any effects upon visceral functions such as blood pressure. The authors based their interpretations upon both the behaviour and electrocorticogram of sleep, but confined their description to NREM sleep only. Pappenheimer *et al.* (110a) found that when the CSF from sleep-deprived goats was infused intraventricularly into the brains of rats, the rats were significantly less active for 24 hr than if the CSF had come from normal goats; and, observing that the rats had appeared to curl up and sleep naturally, they proposed a "humoral factor of general and fundamental importance to the sleep mechanism."

Yet the inconclusive work on cerebral amines outlined in section III gives the impression of a first scratching of the surface of a chemical system so complex that it is impossible to believe a single humoral factor can play an overriding role, particularly when we consider not just that there are two sharply differing kinds of sleep, but also that these two can alternate on a time scale spanned by a few minutes.

While therefore we must hope that fundamental research into the chemistry of sleep, and further pursuit of the promising hypnotic properties of steroid derivatives, as well as efforts to find a humoral hypnotoxin, will continue, they seem unlikely for some years to provide a new type of hypnotic drug for clinical use which could be classed as a "euhypnic" or inducer of natural sleep.

We shall therefore be left with hypnotic drugs comparable to those in current use. In section II it was clear that none of these induced natural sleep. For example, all reduced the proportion of REM sleep, and since evidence could already be found that REM sleep lack may cause abnormal behaviour, the distorting effect of the hypnotics on sleep must be held to be bad. It must be supposed that the distortion, and the abnormalities in REM sleep which persist for weeks after withdrawal of hypnotics, are merely features of human brain function currently accessible to easy measurement, and that further research will reveal many other functions, both of sleep and wakefulness, no less distorted by the administration or the withdrawal of contemporary hypnotic drugs.

The newer information about the intimate effect of hypnotic drugs on sleep, and a knowledge of their dependence-inducing properties, coupled with the steady and heavy increase in their prescribing, should, one hopes, lead to restraint in their promotion by pharmaceutical manufacturers and to new policies in prescribing. It would appear to me that none of the currently fashionable hypnotics can be said to have shown a clear superiority over, or major difference from, the others.

It would appear that their prescription may be fully justified for periods of a few nights or weeks in order to combat sleeplessness caused by anxiety, provided there are firm grounds for expecting the cause of anxiety to be removed either by environmental changes or the successful treatment of, for example, the agitated depressive patient by amitriptyline or electroplexy. Where, however, the complaint is of chronic insomnia, or a long-standing personality disorder is apparent, there would appear no justification for the prescription of hypnotics since 1) tolerance develops, 2) some development of dependence is probable, 3) recent research using EEG techniques has shown that hypnotics do not induce natural sleep, and have made plain how ignorant we formerly were about their effect on sleep, and how much more ignorant we shall appear to have been when new techniques become available in the future.

In section II a number of effects on sleep were shown to be common both to many amphetamine derivatives and to hypnotics. The reduction of REM sleep that they cause is also found with imipramine. The first two classes of drugs have long been recognised not only to affect sleep but to alter mood and bring reality-escape. It is also true that imipramine alters mood when it is used to treat de-

pressive illness, that REM sleep is related to the process of dreaming and that dreaming is the state, *par excellence*, in which we all escape from reality. It is also true that drugs upon which we develop dependence are those which experience has taught us bring quick escape from reality. Nevertheless the effects on mood of the amphetamine derivatives and the hypnotics are immediate, whereas relief of depression by imipramine is usually delayed for 10 days. Imipramine, unlike dexamphetamine or amylobarbitone sodium, does not bring quick reality-escape, nor does comparable dependence upon it seem to occur. Furthermore, LSD and probably nicotine, which also bring a measure of mood-change and reality-escape, have an effect on REM sleep in a direction opposite to that found with the other drugs. It therefore seems to me unlikely that a case can be made for a comprehensive interpretation of these drugs and their effects on the psyche in terms of psychological needs for dreaming (as some authors have been tempted to suggest).

In concluding this review I am left with a sense of restless dissatisfaction. In part, I believe this arises for historical reasons. Everyone sleeps and everyone feels prepared to play the expert when talking of dreams or sleep. Sleeping pills have been in use for many years and, because sleep is a personal thing, all men have felt they understand it and the effects on it of the drugs. The new research the EEG has made possible should bring us to take an entirely new look at common assumptions about sleep, and the clinical use of drugs which affect it. We do not know why we sleep, and we know almost nothing about what constitutes good sleep because we do not know what restitution sleep achieves for us.

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