Review Article

Sleep and Hypnotic Drugs

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Summary

In recent years the effectiveness of hypnotic drugs has had to be assessed in terms of a greatly increased knowledge of the physiology and pathology of sleep. The normal pattern of sleep and wakefulness involves a cyclic alternation between three rather than two basically dissimilar states of the brain and body – alert wakefulness, rapid-eye-movement (REM) sleep and non-rapid-eye-movement (NREM) sleep. The pattern of this alternation in individual people results from the interaction of many influences – biological (including genetic, early developmental and later degenerative influences), psychological, social and environmental factors, various physical and psychiatric disorders, and most drugs which affect the central nervous system. The quality of sleep is not related in any simple or constant manner either to its duration or to the proportions of time spent in each stage of sleep. Among the disorders of sleep, insomnia is a far more common problem of medical management than are enuresis, narcolepsy, somnambulism or nightmares.

With a few exceptions, most hypnotic drugs now in widespread use cease to be effective in treating insomnia after the first few nights. However, the ineffective treatment is often continued because insomnia will be even worse during the initial period of drug withdrawal. These factors and the toxicity

of hypnotic drugs when taken in overdose make the long-term treatment of insomnia more difficult than was previously supposed. Barbiturates should no longer be prescribed. Some of the non-barbiturates, such as glutethimide and methaqualone, have no advantage over the barbiturates. The benzodiazepine hypnotics, nitrazepam and flurazepam, are less toxic in overdose and are relatively effective in treating insomnia. Chloral hydrate and its derivatives are useful alternative drugs for short-term use. Measures to improve sleep without drugs deserve greater emphasis than they have had in the past.

1. Introduction

In most economically advanced countries, hypnosedative drugs appear high on the list of the most frequently prescribed of all drugs (*Commonwealth Director General of Health,* 1969; *Shapiro et al.,* 1969; *Parish,* 1971; *Westerholm,* 1973). Until recent years, the barbiturates formed the mainstay of treatment for insomnia and there was little research into the nature of sleep disorders. The methods for such research had not been well developed and the attitude prevailed that 'no-one ever died of insomnia, anyway'.

Over the past 15 years, this situation has changed. New research methods have been developed, widespread interest aroused and special sleep laboratories established in several countries. Recent research has shown that the treatment of insomnia by means of drugs and the methods by which hypnotic drugs should be evaluated are not as straightforward as we had previously thought. The hypnotic drugs which have been prescribed in huge amounts over the years have proved not only to be a major cause of death when taken in excess but also, in many cases, to produce dependence and to become relatively ineffective in the treatment of insomnia when taken in usual doses for only a few weeks.

This review is concerned with recent developments in sleep research, changes in our understanding of the nature of sleep and insomnia, the evaluation of hypnotic drugs and the overall management of sleep disorders.

2. Physiology of Sleep and Wakefulness

2.1 Periodic Changes in Body Function

All mammals and many other animals lower on the evolutionary scale show a regular alternation of sleep and wakefulness. Ostensibly, sleep follows wakefulness as a passive, secondary phenomenon in which reduced activity of the whole body provides an opportunity for rest in preparation for the next period of activity. This simple explanation has proved to be only partially correct, for in many ways sleep is a highly active state.

2.1.1 Changes in Brain Activity During Sleep

The electroencephalogram (EEG) provided some of the first evidence, in the 1930's, that brain function was not constant during sleep. Another important discovery was made in the 1950's by (*Aserisnky and Kleitman* 1953) who observed that approximately every hour and a half the sleeping subject's eyes flicked from side to side beneath closed eyelids. These rapid eye movements, as they were called, were in marked contrast to the slow, wandering eye movements which occurred at most other times during sleep. Both types of eye movement were recorded electrically throughout the night by means of the electro-oculogram (EOG) (fig. 1). During rapid-eye-movement or REM sleep the EEG resembled that of drowsiness. However, if woken from REM sleep the subject would often recall dreaming (*Dement et al.,* 1967). If woken at other times when the EEG showed mainly high-amplitude, low-frequency waves (delta waves), dreams were less frequently

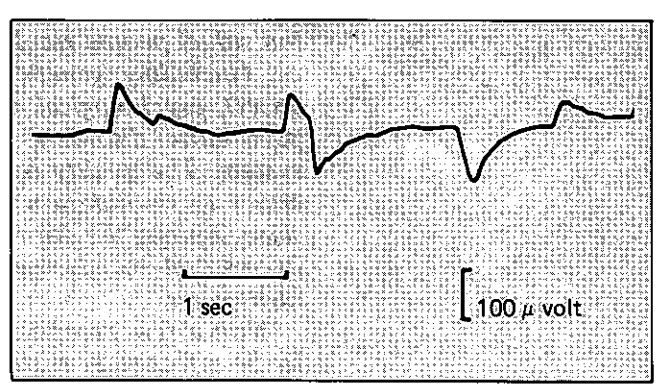

Fig. 1. Rapid eye movements recorded in the electro-oculogram (EOG) from electrodes near the outer canthus of each eye.

ecalled although, as we know now, some form of mental ctivity occurs throughout sleep (*Rechtschaffen et al.*, 963).

With the promise of an understanding of dreaming and erhaps also of the mental aberrations of schizophrenia vhich in some ways resemble those of dreams, the number f people involved in sleep research rapidly increased. The asic methods of sleep research now include all-night recordings of the EEG and EOG, and usually also the electromyogram (EMG) from muscles under the chin, although subjective reports made next day about the quality of the night's sleep are also important (*Johns*, 1971). The various patterns of waves in the EEG were categorised into stages of sleep (1 to 4) according to the presence of spindles and the proportion of delta waves during a given period of 20 to 60 seconds (fig. 2).

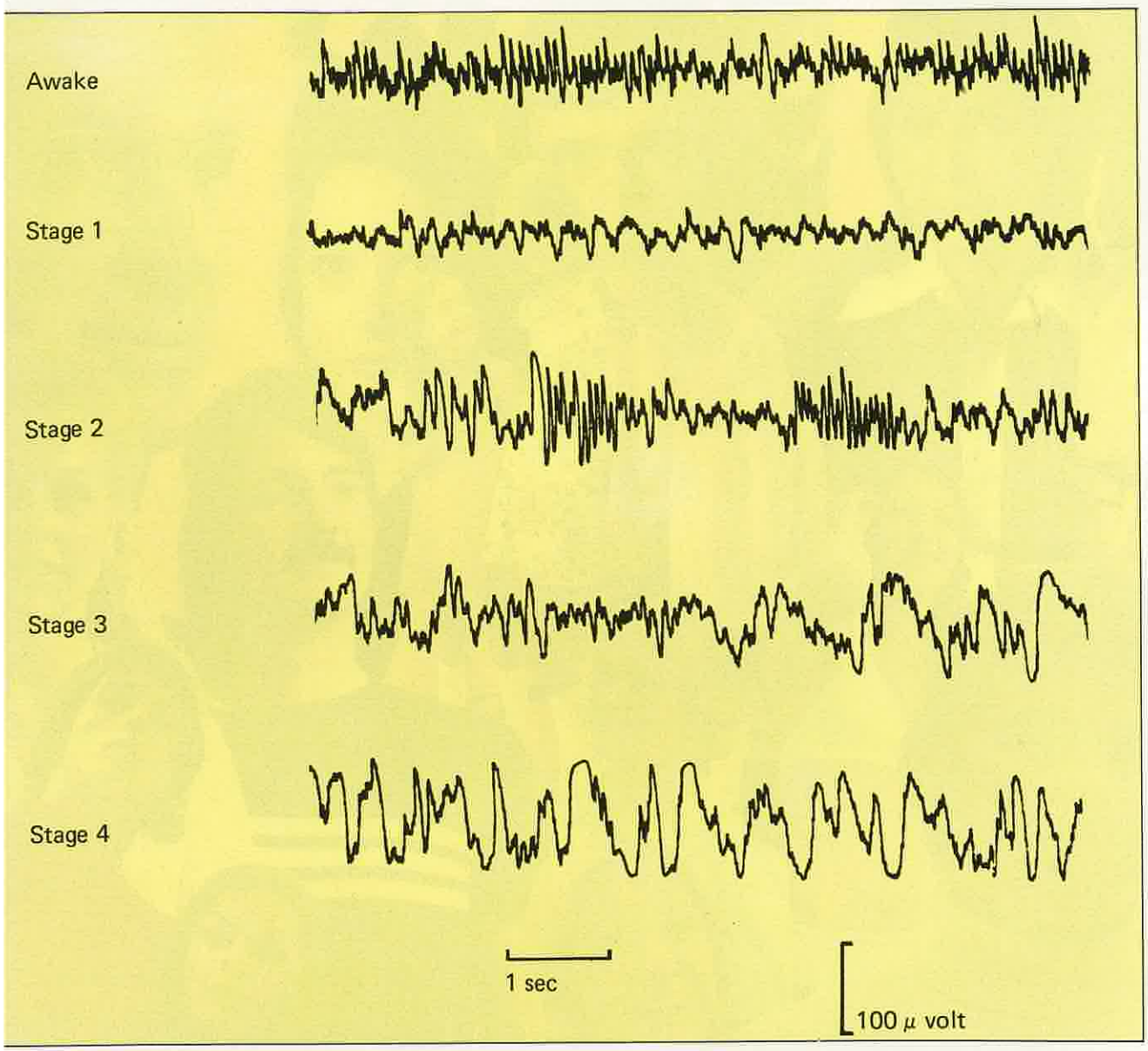

Fig. 2. The electroencephalogram (EEG) recorded during wakefulness and the various stages of sleep. REM sleep occurs when the EEG hows stage 1 and rapid eye movements are recorded in the electro-oculogram. Stage 2 is characterised by spindles, bursts of waves at a requency of 13 to 15 cycles per second which last for about 1 second. Delta-waves are present in stage 2, and these increase in stage 3 and lominate the EEG of stage 4 sleep.

2.1.2 Stages of Sleep

The drowsy state which precedes the onset of definite eep is called stage 1 and usually lasts for a few minutes. his is followed by a longer period of stage 2 sleep (charac-erised by spindles in the EEG) and usually then by stage 3 nd stage 4 with increasing proportions of delta waves ig. 3). An hour or more after first falling asleep rapid eye ıovements appear in the EOG, the level of muscle activity ecorded in the EMG falls and the frequency of the EEG ıcreases as its average amplitude decreases – i.e. the ıaracteristics of REM sleep. There are usually 4 or 5 cycles r recurrence of these stages during the night, although the elative amount of delta-wave sleep (stages 3 and 4) de-reases and that of REM sleep increases as the night rogresses.

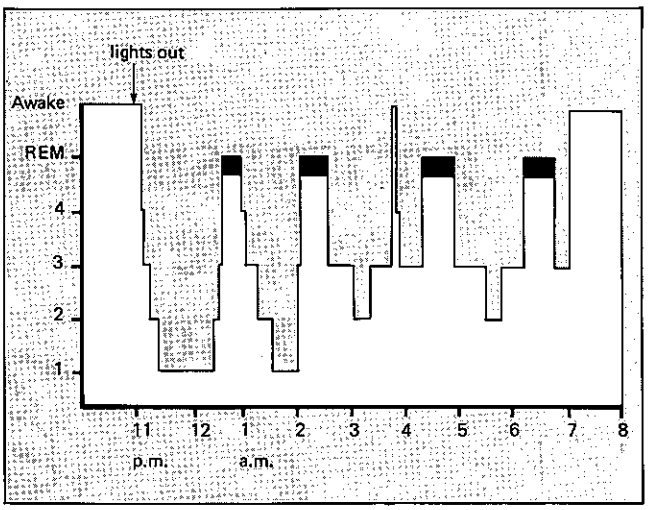

Fig. 3. Cycles of sleep stages in a healthy young adult. Delta-wave sleep (stages 3 and 4) predominates in the first few hours, stage 2 and REM sleep in the last few hours. In the elderly there is less delta-wave sleep overall and awakenings are more frequent.

2.2 Three States of the Brain and Body

Neurophysiological investigations in animals and man ave shown that the pattern of activity in the central ner-ous system is different during REM sleep from, on the one and, that in all the other stages of sleep (which together re called non-REM or NREM sleep) and, on the other and, different from that in wakefulness (*Jouvet,* 1967). leep is not simply the absence of wakefulness. The alter-ation of sleep and wakefulness should be viewed rather as ıanifestations of basic biological rhythms involving three eparate states.

1) Alert wakefulness
2) NREM sleep
3) REM sleep.

The interplay between these three states is represented iagramatically and somewhat hypothetically in fig. 4.

2.2.1 Wakefulness

Wakefulness is maintained by a complex interaction be-ween many different parts of the central nervous system, articularly the mid-brain and thalamic reticular activating ystems and the limbic system (*Jouvet,* 1967). The overall evel of activity in this arousal-promoting system, as we ıall call it, may well vary according to an intrinsic circa-ian rhythm. However, collateral inputs to the reticular ctivating system from sensory nerve tracts (particularly om muscle spindles) as well as mental and emotional acti-ty affecting the limbic system, have a secondary, non-ecific arousal-promoting effect over which there is some oluntary control. To lie down and relax in a warm, dark ıd quiet room leads to a decrease in sensory input. The ıange in psychological functioning which is usually adopted under such conditions may also contribute to the early onset of sleep by way of a reduction of psychic input to the arousal-promoting system.

Falling asleep is associated with a reduction in the level of tonic activity in the sympathetic nervous system, manifested for example by a decrease in the sweat gland activity of the palm of the hand; this can be demonstrated by measuring the electrical resistance of palmar skin (*Johns,* 1971).

2.2.2 Onset of NREM Sleep

Apart from a passive reduction in arousal-promoting activity at sleep onset, another complex neuronal system involving the thalamus, basal fore-brain and the raphé nuclei in the brainstem, actively promotes sleep (*Jouvet,* 1967). There may be an intrinsic circadian rhythm in the level of sleep-promoting activity, but this is augmented by an inhibitory interaction with the arousal-promoting system. It appears that sleep begins when the overall level of arousal-promoting activity falls below that of sleep-promoting activity.

2.2.3 REM Sleep

After sleep onset, a third neuronal system situated in the pons and involved with the manifestations of REM sleep comes into play. This is normally inhibited during wakefulness. There is evidence that serotonergic neurons are involved specifically in the NREM-sleep-promoting system whereas noradrenergic and dopaminergic neurons are invol-

e maintenance both of wakefulness and of REM
ıvet, 1969; *Torda,* 1969; *Hartmann,* 1973). REM
ally comprises between 20 and 25% of the total
›f sleep. This figure is higher in infants but varies
veen adults (*Webb and Agnew,* 1968; *Roffwarg et*
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roportion of stage 4 sleep decreases progressively
n a way which suggests that a degenerative process
ose parts of the central nervous system concerned
production of delta-waves (*Feinberg and Carlson,*
›wever, there is a wide variation in the amounts of
e sleep obtained by different subjects of the same
gnificane of which remains uncertain.

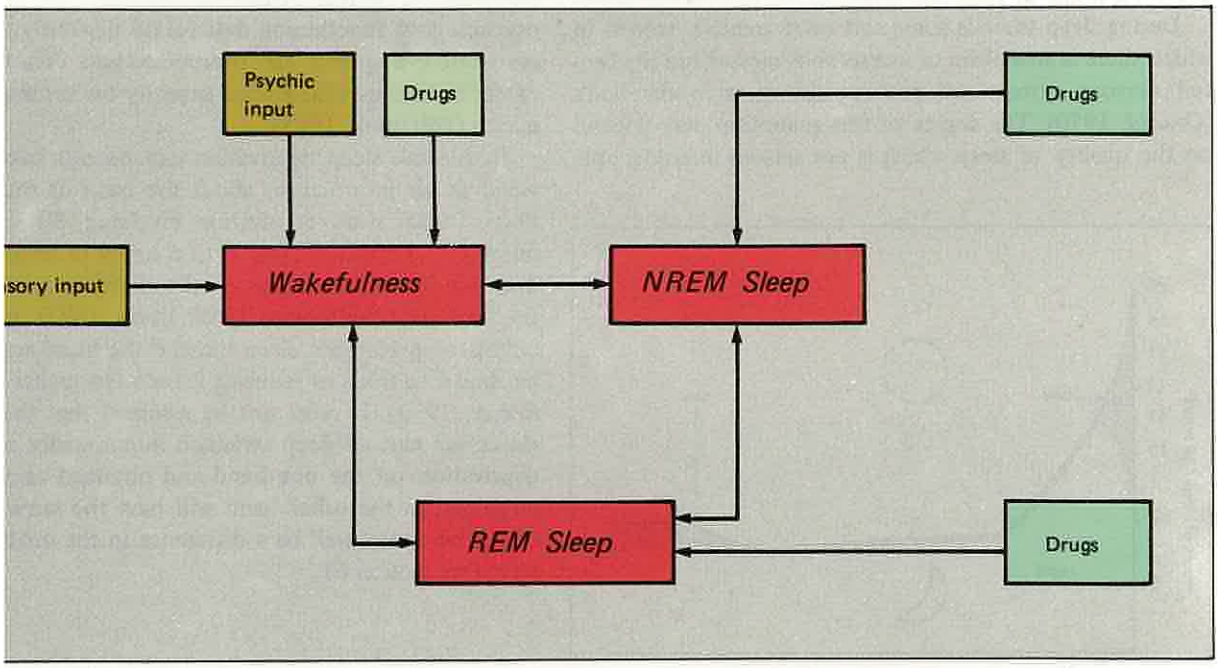
p Habits

animals lower down on the evolutionary scale, it
ıteraction with his social environment, rather than
t effect of sunlight, which determines that he
eep at night rather than during the day, or *vice*
wever, anyone who has flown across several time
hin 24 hours will agree that it takes several days to
make major adjustments to the phase of circadian rhythms such as those of sleep and wakefulness.

Despite differences between weeknights and weekends, most people lead a life which is sufficiently constant over a period of a week for them to describe their sleep habits in a questionnaire (*Johns et al.,* 1970, 1971a). The average amounts of sleep actually obtained per 24 hours by children and adults of various ages are shown in fig. 5. This graph is based on the combined results of several investigations, some of which used subjective reports of sleep habits and others objective measurements in the laboratory (*Kleitman,* 1963; *Kohler et al.,* 1968; *Tune,* 1969; *Webb and Agnew,* 1968; *Johns et al.,* 1970).

3.1 Sleep Habits of Infants and Children

Infants have more than one period of sleep and wakefulness each day. Until the age of about 4 years the amount of sleep at night increases and that during the day decreases. The average duration of sleep at night then decreases until the age of about 20 years, after which there is little change until the 60's.



Interrelations between the three states of the brain and body – wakefulness, non-rapid-eye-movement (NREM) sleep and ıovement (REM) sleep. There are intrinsic rhythms of activity (over periods of 24 hours and also about 1½ hours) in the systems g these three states. In health there is a regular series of transitions from one to another, the sleep cycles of fig. 3. A high level of ory input or mental activity promotes wakefulness and disrupts the usual cycles. Different drugs can influence all three states, ıs independently.

3.2 Sleep Habits of Adults

The average for most adults is 7½ (SD approx 1½) hours per night with occasional dozing during the day. Elderly subjects tend to have highly fragmented sleep, but overall they obtain more than younger adults by spending longer in bed at night and also by sleeping more during the day (*Johns et al.*, 1970). However, there are greater differences between the sleep habits of individual elderly subjects than there are between young adults. There may be a return to the polycyclic pattern of childhood sleep as degeneration of the central nervous system progresses. Boredom and social isolation also play an important part in determining the sleep habits of many elderly people.

4. Needs For Sleep

The perennial question, 'how much sleep do I need?', has proved difficult to answer in specific terms. As the onset of sleep has a powerful influence over the phase of many other rhythms of bodily function, an important need arises for sleep to begin at about the same time each day as a phase-setting mechanism. However, it is doubtful that the usual 7½ hours of sleep are required for this reason alone.

During sleep there is some sort of restorative process in which there is anabolism of macromolecules within the central nervous system and perhaps elsewhere in the body (*Oswald*, 1970). The degree of this anabolism may depend on the quality of sleep which is not related in any simple manner to its duration. Some healthy subjects obtain between 1 and 3 hours sleep per night and do not sleep during the day, without suffering any obvious ill-effects (*Jones and Oswald*, 1968; *Meddis et al.*, 1973). Other subjects sleep for 9 or 10 hours per night, in some cases using extra time in bed and asleep as one way of coping with or escaping from the harsh realities of daily life. Their needs for prolonged sleep may be more psychological than physiological (*Hartmann*, 1973).

There may also be intrinsic differences in the relative levels of arousal-promoting and sleep-promoting activity in 'long' and 'short' sleepers who are distinguishable from birth (*Kleitman*, 1963). Thus, the pattern of sleep and wakefulness in any one subject is determined by the interaction of many influences – biological, psychological, social and environmental.

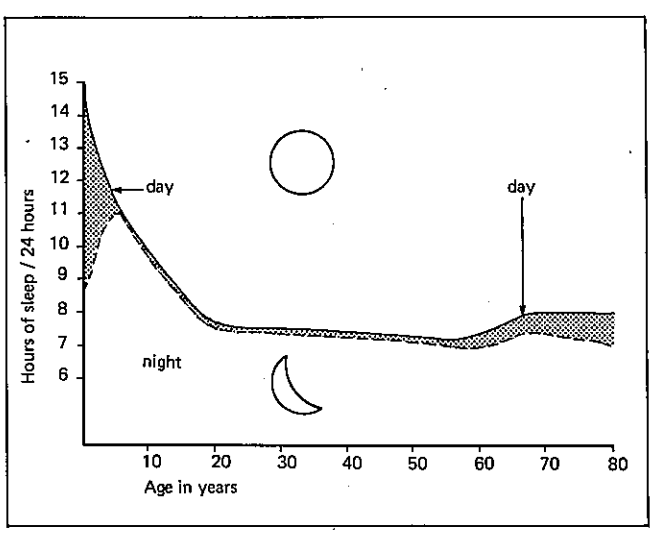


Fig. 5. The average duration of sleep per 24 hours obtained at different ages.

4.1 Effects of Sleep Deprivation

The effects of purposeful sleep deprivation for several days have been studied in the laboratory (*Naitoh et al.*, 1971). There is a progressive burden of drowsiness and a tendency to have frequent brief periods of sleep, called micro-sleeps, during which performance at a task and psychological functioning deteriorate markedly. Given the motivation, a subject can overcome these effects to some extent but he loses his normal capacity for sustained performance (*Wilkinson*, 1965).

In general, sleep deprivation experiments have not provided much information about the basis of the need for sleep. Partial sleep deprivation involving, for example, a purposeful reduction from 8 to 6 hours of sleep per night does not have much effect on the ability to perform tasks the next day (*Wilkinson*, 1968; *Webb*, 1973). Indeed, the effects of prolonging sleep beyond the usual amount may be similar to those of reducing it for a few nights (*Taub and Berger*, 1973). It must not be assumed that the same reduced amount of sleep obtained intentionally or by sleep deprivation on the one hand and obtained as a result of insomnia on the other hand will have the same effect because there may well be a difference in the quality of that sleep (see section 6).

4.2 Effect of Selective Deprivation of REM or Stage 4 Sleep

After a subject has been deprived selectively of either REM or stage 4 sleep there is an excess or rebound of that

particular stage during the recovery sleep which follows on the next few nights (*Agnew et al.*, 1967). This rebound has been an important factor in leading many sleep researchers to believe that there must be specific needs for each stage of sleep. Several hypotheses have been proposed (*Oswald*, 1970; *Hartmann*, 1973), and many experiments have been designed to discover what these needs might be. In general, this has been an unrewarding pursuit (*Johnson*, 1973).

Following the reports of an experiment by *Dement* (1960), it was widely believed in the 1960's that specific deprivation of REM sleep for several nights would produce a reversible state of psychosis in previously healthy subjects. This has proved to be incorrect (*Greenberg et al.*, 1970). Indeed, some depressed patients are improved by REM sleep deprivation over a period of about 2 weeks (*Vogel et al.*, 1968). An excess of REM sleep has been thought to be causally related to the delirium which is seen in drug-withdrawal states, especially in alcoholism (*Feinberg*, 1968). This is uncertain also because delirium which occurs under different circumstances, after cardiac surgery, is associated with an absence rather than excess of REM sleep (*Johns et al.*, 1974b).

The all important characteristic of sleep, its quality in terms of how well rested the subject feels and how well he performs next day, has proved difficult to measure objectively. The fact that sleep is initiated rapidly, is seldom interrupted by spontaneous awakenings, has a regular series of REM-NREM cycles and feels subjectively to be sound sleep, are more important criteria of the quality of that sleep than is the presence of a particular proportion of REM or stage 4 (*Johnson*, 1973).

5. Nature of Insomnia

Insomnia is primarily the sympton of not being able to sleep when or as well as the subject believes he should. Thus, it is a highly subjective phenomenon, dependent on the subject's expectations and self-awareness of his behavioural states as much as on the objective characteristics of his sleep. However, most people would agree that insomnia involves taking a long time to fall asleep initially, waking up frequently and for prolonged periods during the night, or waking up too early in the morning. Often there is more than one of these manifestations of insomnia in the same subject. Another important feature of the insomniac's sleep is its variability. A few night's poor sleep tend to be followed by a much better night (*Karacan et al.*, 1973).

Insomnia is one of the most common of all symptoms; it is present in 5 to 10% of 'healthy' young adults (*Johns et al.*, 1971a), in at least 20% of all patients seen at a general hospital (*Johns et al.*, 1970), and in 80% or more of patients suffering from acute psychiatric illnesses of various types (*Detre*, 1966; *Ward*, 1968). The prevalence of insomnia increases with age and is higher in women than in men.

The various physiological and pathological mechanisms which produce insomnia under different circumstances may be explained in terms of the concepts of sleep and wakefulness outlined in section 2.2. The differences between normal sleep habits and insomnia are more quantitative than qualitative (*Johns*, 1974). Insomnia might be produced by:

- A relative increase in the organised activity of the arousal-promoting system
- A decrease in the activity of the sleep-promoting system, particularly the NREM sleep system
- A change in the biological rhythms involved in the interaction between the sleep and arousal-promoting systems
- Some combination of the above.

Many factors have been associated clinically with insomnia, reported subjectively and in most instances also studied objectively in the laboratory. These factors may be classified into three groups:

1) Factors that are environmental and extrinsic to the patient
2) Factors that are intrinsic to the patient
3) Drugs which affect the central nervous system (see section 7).

5.1 Factors Extrinsic to the Patient

5.1.1 Noise

This does not commonly cause sleep disturbances which are either prolonged or severe enough to bring the patient to a doctor. Most people can adapt, for is not only the intensity of noise but also its novelty and its significance or meaning for the particular subject at that time which is important (*Oswald et al.*, 1960). Someone who is fearful of being attacked or robbed at night may be awoken repeatedly by soft noises. Thus, sensory input continues to be analysed to some extent during sleep. If the intensity of sensory and associated psychic input is high enough the arousal-promoting system will produce a state of wakefulness.

5.1.2 Hot or Cold Climates

Most people modify their environment, for example, by the appropriate choice of bed-clothes, or they adapt to seasonal changes over a period of a few weeks. However,

may be more common in the tropics than in climates.

igh Altitudes

ia is a prominent symptom of mountain sickness urs at elevations much above 10,000 ft (*Williams,* 'pobaric hypoxia may directly affect the sleep- system and the increased work of breathing may ase the sensory input to the arousal-promoting

tors Intrinsic to the Patient

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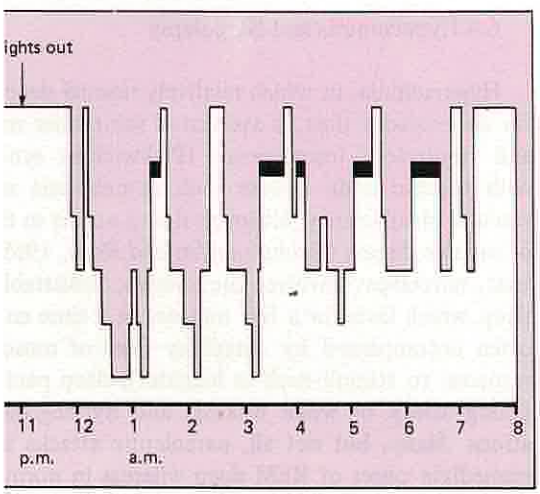
of the increase in insomnia with advancing age be related to general degenerative changes within l nervous system (*Feinberg and Carlson,* 1968). any increase in the level of arousal-promoting hether by psychic or by sensory input, will have ffect on sleep in the elderly than in young adults.

Psychological Tension and Emotional Distress

specially common in neurotic disorders associated ty, depression, hostility or guilt bereavement and ure' living. Young adults without overt physical atric illness who are poor sleepers have been the laboratory. Such people usually have minor psychological disorders which make them prone to chronic feelings of inadequacy and tension (*Monroe,* 1967; *Johns et al.,* 1974a). Compared with good sleepers of their own age they have higher heart rates, higher central body temperatures and more frequent vasoconstrictions in their fingers during sleep (*Monroe,* 1967), higher levels of adrenocrotical activity during the day and night (*Johns et al.,* 1971b), and lower arousal thresholds to external stimuli during sleep (*Zimmerman,* 1970). These differences are thought to represent long-term differences in the level of arousal-promoting activity in the central nervous system.

Attempts to demonstrate differences in the proportion of each stage of sleep between good and poor sleepers have yielded conflicting results (*Monroe,* 1967; *Kales,* 1969; *Karacan et al.,* 1973). If consistent differences do exist they are probably less important characteristics of poor sleep than are the frequency of arousals to wakefulness or stage 1, and the frequency of transitions from one sleep stage to another during the night (*Johnson et al.,* 1970). A typical pattern of sleep stages for a poor night's sleep is shown in fig. 6.

Some poor sleepers have more difficulty in falling asleep initially than in staying asleep, others the reverse. There are differences of personality between these two types of poor sleeper, related to the ease or difficulty with which the day's mental activity is inhibited rather than proceeding unabated when the subject is trying to fall asleep (*Johns et al.* 1974a).



Cycles of sleep stages in a middle-aged insomniac. The e falling asleep is increased and there are more awaken- n healthy subjects of the same age. The proportions of h sleep stage are within normal limits but if hypnotic to be taken, delta-wave and REM sleep would often be

5.2.3 Major Psychiatric Illnesses

These include, for example, psychotic depression, acute schizophrenia, mania and anorexia nervosa. The severity of insomnia can often be correlated with the degree of non-specific emotional arousal or psychotic turmoil which the patient is suffering at the time (*Kupfer et al.,* 1970; *Takahashi et al.,* 1972). The main cause of this insomnia is thought to be hyperactivation of the arousal-promoting system (*Mendels and Hawkins,* 1968). However, there may also be nutritional, biochemical or endocrine changes associated with psychotic illness which reduce the primary capacity of the sleep-promoting system, or at least the circadian rhythm in its activity.

The proportions of stage 4 and REM sleep are often reduced in the acute stage of illness, but neither these changes nor the other features of the insomnia are specific for particular psychiatric diagnoses.

5.2.4 Organic Disorders of the Central Nervous System

These include cerebral arteriosclerosis, neoplasia and presenile dementia (*Feinberg and Carlson,* 1968). Patients who

are in non-rousable coma after head injury often continue to show cyclic changes in their EEG and EOG which resemble the normal sleep stages. The absence of these changes is in fact a very poor prognostic sign (*Bergamasco et al.*, 1968).

5.2.5 Heart Disease

Heart Disease might be expected to influence sleep by several mechanisms:

1) By a direct effect on cerebral circulation and hence on neuronal metabolism

2) By changing sensory input as a result of altered cardio-pulmonary function or chest pain

3) As a result of the psychological tension associated with acute episodes of heart disease.

Either left or right heart failure is associated with insomnia (*Rohmer et al.*, 1967). Indeed, insomnia may sometimes be the initial symptom in the development of left ventricular failure, appearing before crepitations can be heard at the lung bases during the day (*Wheeler and White*, 1945). Angina without heart failure produces less sleep disturbance (*Karacan et al.*, 1969b). Individual attacks of chest pain tend to be associated with REM sleep (*Nowlin et al.*, 1965), although ECG changes indicating myocardial ischaemia also occur during stage 4 sleep when there is relative bradycardia (*Rosenblatt et al.*, 1973).

5.2.6 Other Conditions

Other conditions with which insomnia is often associated include thyrotoxicosis (*Oswald et al.*, 1972), Cushing's syndrome (*Krieger et al.*, 1972), fever (*Karacan et al.*, 1968) and normal pregnancy especially in the last trimester (*Karacan et al.*, 1969a). Nocturia is a very common symptom among poor sleepers who do not have gentito-urinary disease. However, sleep does not appear to be affected much by nocturia caused by prostatic hypertrophy (*Johns et al.*, 1970).

Musculo-skeletal pain with various forms of arthritis may well disturb sleep, but this has not yet been studied in the laboratory. The epigastric pain which wakens the duodenal ulcer patient early in the night is not necessarily associated with insomnia at other times.

6. Nature of Other Sleep Disorders

Other disorders of sleep have been studied in the laboratory and the results reviewed recently (*Kales and Kales*, 1974).

6.1 Enuresis and Somnambulism

Both enuresis and somnambulism (sleep-walking) have been found, rather surprisingly, to begin after partial arousal from stage 4 sleep rather than from REM sleep (*Broughton*, 1968).

6.2 Nightmares and Night Terrors

Nightmares in adults are associated with REM sleep and may occur with increased frequency during the first few days after withdrawal of REM-suppressant drugs (*Oswald and Priest*, 1965). However, night tremors which are similar to nightmares except for the intensity of autonomic and motor activity, tend to be associated with delta-wave sleep (*Fisher et al.*, 1973). Adults who report having frequent nightmares usually have other evidence of psychological disorder (*Hersen*, 1971), but do not necessarily suffer from other forms of sleep disturbance (*Johns*, 1974).

6.3 Snoring

A person who snores loudly seldom disturbs his own sleep but may severely disturb someone else's. The snoring noises are made by the relaxed soft palate and posterior faucial pillars during NREM sleep (*Robin*, 1968).

6.4 Hypersomnia and Narcolepsy

Hypersomnia, in which relatively normal sleep continues for an excessive time, is associated sometimes with obesity and respiratory insufficiency (Pickwickian syndrome) or with organic brain disease such as neoplasia or cerebrovascular insufficiency, although it also occurs in the absence of organic disease (*Rechtschaffen and Roth*, 1969). By contrast, narcolepsy involves the sudden, irresistable onset of sleep which lasts for a few minutes at a time and which is often accompanied by cataplexy (loss of muscle tone in response to stimuli such as laughter), sleep paralysis when falling asleep or when waking, and hypnogogic hallucinations. Many, but not all, narcoleptic attacks involve the immediate onset of REM sleep whereas in normal subjects REM sleep occurs only after a period of NREM sleep. Narcolepsy usually develops before the age of 30 and probably has a genetic basis (*Kales and Kales*, 1974).

The management of these various sleep disorders is discussed in section 8.2.

s and Sleep

lrugs influence the pattern of sleep and wakeful- not always to the patient's benefit. In practice, ; of hypnotic drugs must be assessed in terms of ria. These include:

ctive and subjective effects of their short-term on the onset and maintenance of sleep in normal ects and insomniacs

cts of their long-term use in insomniacs and the lopment of tolerance to the usual doses

cts of their short- and long-term use on the dis- ition of sleep stages, particularly on REM and 4 sleep

ir tendency to produce dependence and drug- drawal insomnia

icity

-effects, including hang-over effects and inter- ons with other drugs

morphogenicity

ncial cost.

nt years sleep researchers have placed consider- asis upon the effects of drugs on the relative of each stage of sleep, particularly of REM sleep 1968; *King,* 1972). As noted above, the import- hese stages remains uncertain. Probably of far portance is the finding that tolerance to many develops quickly – often within a week of con- e. The same dosage which begins by being an aid on becomes ineffective and, worse still, prevents t from sleeping as well as he might without the *es et al.,* 1974). However, the patient is encour- ntinue taking it because his insomnia will be even ing the initial period of drug-withdrawal. It is t insomnia should be caused frequently by the s which have been prescribed to treat that

le information has been gained from the study of effects of drugs on sleep in normal subjects, but utmost importance that these effects should also l in insomniacs and over periods of weeks rather . So far, little of this tedious and expensive, long- rch has been carried out, especially among elderly s who comprise the majority of people using drugs in the community. The effects of inter- e of hypnotics, for example taken once or twice for prolonged periods, have not been studied at thalidomide tragedy emphasises the need for testing before any such drugs are made available l use, especially during pregnancy.

7.1 Barbiturates

Various derivatives of barbituric acid have been marketed as hypnotics over the past 70 years. They are usually in the form of a soluble sodium salt although a calcium barbiturate (cyclobarbitone calcium) is available for patients on a strict, low-sodium diet. The barbiturates are rapidly absorbed from the gastro-intestinal tract and are distributed throughout the body, having a marked depressant effect upon the whole central nervous system and, to a lesser extent, also upon skeletal muscle, smooth muscle and cardiac muscle (*Sharpless,* 1970). Barbiturates are metabolised by hepatic microsomal enzymes at a rate which increases after contact with the drug for only a few days. This increased rate of metabolic breakdown and an adaptation of the central nervous system to the effects of the drug are the basis for the rapid development of tolerance (*Remmer,* 1969; *Sharpless,* 1970).

7.1.1 Effect on Sleep Patterns

When first taken in the recommended dosage for insomnia (100 to 200mg), amylobarbitone sodium, butobarbitone, pentobarbitone sodium, quinalbarbitone sodium, cyclobarbitone calcium or secbutobarbitone sodium will each tend to reduce the time taken to fall asleep (especially if this is prolonged), to prolong sleep and to reduce the frequency and duration of awakenings during the night. There is little difference in the number of hours for which each of these drugs will affect sleep. The proportion of TEM sleep is reduced for the first few days and then sometimes returns to baseline levels (*Evans et al.,* 1968; *Kay et al.,* 1972). These effects are dose-related and *Kales* (1969) has reported that chronic insomniacs taking 300mg pentobarbitone sodium per night continue to have markedly reduced amounts both of REM and of delta-wave sleep for as long as they take the drug.

After only a few days use of a barbiturate, drug-withdrawal insomnia becomes a problem with frequent awakenings and a rebound of REM sleep, often with disturbing dreams or nightmares (*Oswald and Priest,* 1965). By continuing to take the drug this much worsened insomnia is avoided but the sleep obtained is little better than that before the drug was taken in the first instance (*Kales et al.,* 1974). The dose may be increased in an attempt to improve sleep and eventually a chronic state of intoxication ensues, with tremor and confusion during the day and insomnia at night (*Whitlock,* 1970). It takes many weeks after drug-withdrawal before these effects disappear (*Oswald and Priest,* 1965).

7.1.2 Side-Effects

A hang-over effect continues for many hours into the next day after a single hypnotic dose of a barbiturate. This may impair performance at skilled tasks during the day. However, the hang-over is less marked in patients who might take such drugs than in normal people who have been the experimental subjects for several investigations of these effects (*Malpas et al.*, 1974).

Considering their widespread use in the past, hypersensitivity reactions have been uncommon. The bullae which occur in acute poisoning are not specific for barbiturates (*Ridley*, 1971). Barbiturates reduce the effects of oral anticoagulants by increasing their metabolic clearance; the effects of alcohol on the central nervous system are potentiated. The elderly and patients with cerebral arteriosclerosis may become confused and disorientated at night when taking barbiturates. However, side-effects such as headache and nausea are not much more common after barbiturates than after a placebo.

Babiturates are contra-indicated in hepatic or respiratory failure and in porphyria.

7.1.3 Toxicity

A serious indictment of barbiturates is the problem of medical management and of death after an overdose which has been a frequent occurrence in recent years (*Oliver and Helzel*, 1972). Many thousands of patients who have committed suicide by taking barbiturates might not have died if they had not been prescribed such toxic drugs. Taking all factors into account, barbiturates have ceased to have a legitimate role in the treatment of insomnia.

7.2 Benzodiazepines

The benzodiazepam derivative, nitrazepam (5 to 10mg), is widely used as an hypnotic in Europe, the United Kingdom and Australasia; a related drug, flurazepam (15 to 30mg) is also widely used in the USA. Both of these hypnotics are at least as effective as the barbiturates in the short term and have some advantages over the latter. The depressant action of benzodiazepines on the central nervous system is based, at least in part, upon a reduction of serotonin turnover in the brain (*Wise et al.*, 1972) and may be more localised to the arousal-promoting system than is the case with barbiturates (*Przybyla and Wang*, 1968). With chronic administration the blood level stabilises after about a week and it decreases over a similar period after stopping the drug (*de Silva et al.*, 1966). Benzodiazepines are eliminated via the kidney after hydroxylation and glucuronide formation. They cross the placenta to the fetal circulation and also enter maternal breast milk.

7.2.1 Effect on Sleep Patterns

Low therapeutic doses of nitrazepam (5mg) or flurazepam (15mg) have little effect either on REM sleep or on delta-wave sleep (*Gastaut et al.*, 1967; *Johns and Masterton*, 1974). With higher doses there is a minor degree of inhibition of REM sleep, which is perhaps greater with nitrazepam than with flurazepam. The reverse may be true of the inhibition of delta-wave sleep which is more prominent with flurazepam (*Kales et al.*, 1970b). After stopping nitrazepam there is a rebound of REM sleep which reaches a maximum a week or more later (*Haider and Oswald*, 1971). Flurazepam is the only hypnotic which has been shown in the sleep laboratory to have an objectively beneficial effect on the sleep of insomniacs which continues after 2 weeks of treatment (*Kales et al.*, 1970b, 1971). Although nitrazepam has yet to be studied from this point of view, it is possible that a continuing beneficial effect may also occur.

7.2.2 Toxicity

The toxicity of the benzodiazepines is considerably lower than that of the barbiturates and this is reflected in the much smaller number of deaths from overdose for each million prescriptions of nitrazepam than for the latter (*Barraclough*, 1974). Indeed nitrazepam is rarely fatal in overdosage. With the exception of drowsiness, no untoward effects were observed in one series of 27 patients who ingested acute overdoses of nitrazepam, even when up to 80 tablets were consumed (*Matthew et al.*, 1969).

The relative lack of tolerance to the benzodiazepines also makes them poor candidates for the production of physical dependence, although isolated instances of dependence have been reported with drugs such as diazepam and chlordiazepoxide and analogous compounds may therefore be tentatively suspected as having a low dependence liability (*Isbell and Chruściel*, 1970). There has been a report of a clear-cut withdrawal syndrome (with delirium tremens) occurring in a single patient about a week after the withdrawal of high doses of nitrazepam (*Darcy*, 1972).

7.2.3 Side-Effects

Nitrazepam does not alter the effects of oral anticoagulants (*Bieger et al.*, 1972). The hang-over effects of nitrazepam and flurazepam are less than those of the barbiturates and there is some evidence that flurazepam is superior to nitrazepam from this point of view (*Bond and Lader*, 1972; *Sambrooks et al.*, 1972). Some subjects, particularly the elderly, complain of intense dreams and nightmares

ng nitrazepam. However, if hypnotic drugs must
itrazepam or flurazepam are, at present, the drugs
for most patients.

loral Hydrate and its Derivatives

l hydrate was introduced more than a century ago
st synthetic hypnotic and it continues to be a
ıg for the short-term treatment of insomnia. Its
nt taste and a tendency to irritate the upper gas-
nal tract are disadvantages under most circum-
ıt may discourage its being taken to excess. It is
ed into trichlorethanol, the therapeutically effec-
ound, by both the liver and the kidney and, thus,
avoided in hepatic or renal failure. The thera-
se, in a capsule or as a syrup, is 0.5 to 2g taken
with milk and also sometimes with brandy.
tablets have been made from various derivatives
hydrate whose hypnotic properties are similar to
the parent compound; for example, dichloralphe-
50 to 1300mg), trichlorethyl phosphate (0.5 to
hloral betaine (0.87 to 1.74g). These preparations
lysed to chloral hydrate and an inactive product
stion. The disagreeable taste and gastric irritation
ore largely overcome. However, the large size of
ts sometimes presents a problem in swallowing

ffect on Sleep Patterns

l hydrate and its derivatives are effective and re-
ife hypnotics for the short-term treatment of in-
he stages of sleep are affected less by chloral
ıan by most other hypnotics and a disturbing re-
REM sleep does not occur after discontinuing the
tman and Cravens, 1973a). The sleep of insom-
mproved for the first few nights but returns to
ithin two weeks of continuous administration of
drate (*Kales et al.,* 1970b).
. hydrate and its derivatives can produce a state of
lependence which is seldom seen at present but
y become more common in the future if these
in popularity.

ide-Effects

ver effects with chloral hydrate are minimal and
ly often tolerate this and related drugs more
an barbiturates (*Bare and Pepino,* 1961). Idosyn-
tions are rare but allergic reactions include ery-
l urticaria. Chloral hydrate and related prepara-
tions modify the anticoagulant effect of coumarin drugs, accelerating their inactivation in the liver and displacing them from their binding with plasma albumin (*Orme et al.,* 1972).

7.4 Other Non-Barbiturate Hypnotics

There are several other drugs which are marketed as hypnotics. Some have achieved a phase of popularity in recent years only to be relegated to less important ranks as disadvantages became apparent.

7.4.1 Glutethimide

One such drug is glutethimide (250 to 500mg) which is a piperidinedione derivative related structurally to phenobarbitone (*Sharpless,* 1970). It has no advantage over the barbiturates either in its short-term effects, its long-term use or its toxicity in overdose (*Kales et al.,* 1970c; *Goldstein et al.,* 1971).

7.4.2 Methyprylone

Methyprylone (200 to 400mg) is another hypnotic which is related chemically to glutethimide and which has hypnotic and addictive properties, side-effects and toxicity similar to those of the barbiturates (*Rickels and Bass,* 1963; *Kales et al.,* 1970c).

7.4.3 Methaqualone Plus Diphenhydramine

Tablets containing both methaqualone (150mg) and diphenhydramine (25mg) were the most frequently prescribed hypnotics in a large general hospital in Melbourne between 1967 and 1970 (*Johns et al.,* 1971c), but since then nitrazepam has gained that position. When first introduced, methaqualone was believed to present fewer problems than the barbiturates when taken in overdose, but this has not been substantiated by later clinical experience. In addition, non-fatal side-effects of methaqualone plus diphenhydramine have been among the most frequent of all such reports in the United Kingdom (*Dunlop,* 1970).

7.4.4 Carbromal

Brominated monoureides such as carbromal have been regarded in the past as mild and relatively safe hypnotics. Carbromal (250mg) is marketed in combination with pentobarbitone sodium (100mg) and has been popular in Australia for some years (*Johns et al.,* 1971c). The combination appears to be an effective hypnotic in the short-term but has not been evaluated in long-term studies. Free bromide is released after ingestion of carbromal (*Sharpless,* 1970), and

Table I. Comparisons between commmonly used hypnotic drugs. The magnitude of each effect is dose dependent. ++ = marked effect; + = moderate effect; ± = slight effect; 0 = insignificant effect

Property	Barbiturates	Nitrazepam	Flurazepam	Chloral hydrate and related compounds	Methaqualone	Glutethimide	Methyprylone
Effectiveness in initiating and maintaining sleep:							
a) For the first few nights;	++	++	++	++	++	++	++
b) After 2 weeks treatment	0	+?	+	0	0	0	0
Inhibition of REM sleep, at least initially	++	±	0	0	+	++	++
REM rebound after drug-withdrawal	++	+	0	0	+	++	++
Inhibition of delta-wave sleep	±	+	++	0	±	+	0
Toxicity in overdose	++	±	±	+	++	++	++
Dependency liability	++	±?	±?	++	++	++	++

hence there is a danger that long-term use will lead to bromism. This danger should lead to the relegation of preparations containing brominated monoureides, along with the bromides of sodium, potassium and calcium, to a position of historical interest rather than practical importance in the treatment of sleep disorders.

7.4.5 Antihistamines and Anticholinergics

Some antihistamine and anticholinergic drugs have sedative properties without the need for a doctor's prescription. For example, methapyrilene hydrochloride (25mg) in combination with hyoscine (scopolamine) hydrobromide (0.125mg) has been found to be as effective as 100mg phenobarbitone in elderly insomniacs (*Feinblatt*, 1958). However, REM sleep is inhibited by hyoscine and chronic intoxication does occur with this drug (*Sagales et al.*, 1969; *Thakkar and Lasser*, 1972). Consequently the ready availability of such hypno-sedative drugs over-the-counter is probably undesirable.

7.4.6 Ethchlorvynol

Ethchlorvynol (0.5 to 1g) is a halogenated tertiary acetylenic alcohol whose hypno-sedative properties have received little attention from sleep researchers. It is metabolised rapidly so that blood concentrations fall to undetectable levels after about 3 hours (*Alergi et al.*, 1962). Physical dependence has developed in patients taking 1.5g daily.

7.5 Antidepressants

Both major groups of antidepressants, the tricyclic compounds and the monoamine oxidase inhibitors, affect sleep in normal subjects and in patients suffering from depression.

7.5.1 Tricyclic Antidepressants

Some tricyclic antidepressants such as imipramine, desipramine, clomipramine and amitriptyline increase the total duration of sleep and decrease intrasleep restlessness, but cause an initial decrease in the amount and the proportion of REM sleep (*Hartmann and Cravens*, 1973b). A rebound of REM sleep occurs after ceasing these drugs. By contrast, iprindole and trimipramine do not inhibit REM sleep (*Baxter and Gluckman*, 1969). Whether or not this property makes the latter drugs preferable to the former from the point of view of the treatment of depression or of insomnia is uncertain.

7.5.2 Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors produce a profound inhibition of REM sleep beginning after a few days and lasting for as long as the drug is taken. There is a very marked and disturbing rebound of REM sleep after these drugs are stopped (*Wyatt et al.*, 1971b). The beginning of clinical improvement in depressed patients coincides with the time

r REM sleep is abolished by phenelzine, although robably not a causal relationship between these *nleavy and Oswald,* 1973).

nothiazines

hiazine drugs such as chlorpromazine are not used for insomnia in the absence of psychosis, nay have a role to play if anxiety is present, even potentiate the effect of an hypnotic. In normal chlorpromazine administered for several weeks a significant increase in the duration of sleep and n in wakefulness during the night without decrea- roportions either of REM or of delta-wave sleep *and Cravens,* 1973c). Chlorpromazine may be useful during the initial period of withdrawal I-suppressant drugs to prevent the exacerbation of sleep and nightmares which would otherwise

henothiazines such as promethazine (5 to 20mg) prazine (7.5 to 30mg) are marketed primarily as ines but also have hypno-sedative properties, in children. Their long-term effects in the treat- somnia have not been investigated.

ier Drugs Which Affect Sleep

t of drugs which affect sleep in some way is a long cially considering the drugs which influence REM ny of these drug effects are clinically insignificant; y not be.

mphetamine Derivatives

tamine and its derivatives such as fenfluramine ylpropion which are used as appetite suppressants atment of obesity, tend to decrease the duration nd make it more restless. REM sleep is inhibited and a rebound of REM sleep occurs when the stopped (*Lewis,* 1970).

thyl Alcohol

alcohol (1g per kg body weight) taken by healthy before going to bed also causes a moderate and inhibition of REM sleep, at least in the early e night, without affecting delta-wave sleep (*Yules* 66). However, in chronic alcoholism sleep is mar- turbed by frequent awakenings and there is very a-wave sleep (*Johnson et al.,* 1970).

7.7.3 Hot Milk Drinks

A hot milk drink taken by middle-aged subjects at bedtime has been found to increase the duration of their sleep and to decrease wakefulness during the night, as measured objectively in the laboratory (*Brezinová and Oswald,* 1972). The mechanism for this action is unknown.

7.7.4 Miscellaneous Agents

The proportion of REM sleep obtained by healthy subjects is actually increased by a few drugs such as reserpine, lysergic acid diethylamide, L-tryptophan and 5-hydroxytryptophan.

There is some evidence for the existence of a small-molecular-weight organic molecule (perhaps a peptide) in normal plasma and cerebrospinal fluid, the concentration of which increases after sleep deprivation. The substance prolongs behavioural and EEG signs of sleep when injected into animals (*Fencl et al.,* 1971). More experimental work is required however, before the clinical significance of these findings can be evaluated.

8. Management of Sleep Disorders

8.1 Insomnia

Both the medical profession and the pharmaceutical industry are guilty of promoting the idea, whether consciously or not, that modern medical science has a drug for the successful treatment of every condition. We and our patients rely too heavily upon the prescription and taking of hypnotic drugs. The favourable response to a placebo by many patients with insomnia is good evidence that potent drugs are not always required (*Nicolis and Silvestri,* 1967). Much benefit can be gained simply by determining what are the patient's sleep habits, explaining how normal habits are variable, and reassuring him that no serious harm will follow, for example, from the loss of some sleep. Many patients have unreasonable expectations about their sleep, and there anxiety about not sleeping may be worse than the insomnia itself.

8.1.1 Re-Establishment of Normal Sleep Habits

The sleep of many patients who have been taking hypnotics, particularly the barbiturates, continuously for many months or years will be improved by gradually withdrawing those drugs over a period of a month or 6 weeks during which time chlorpromazine may be needed to control drug-withdrawal symptoms, including insomnia. Once this difficult transition period has ended, hypnotics may no lon-

ger be needed. Regular times of going to bed, exercise in the early part of the day and a hot milk drink at bedtime can help to re-establish normal sleep habits. Some people simply have to learn to live with the fact that they will usually sleep for only about 4 hours per night.

Simple relaxation exercises which could be taught by an interested physiotherapist can help those patients whose main difficulty is in falling asleep initially (*Kahn et al.*, 1968). Disorders such as incipient cardiac failure or depression should be sought and treated in their own right.

8.1.2 'Electrosleep' Therapy

Various devices which deliver low-frequency electrical impulses to electrodes placed round the head have been used (mainly in eastern Europe) as a method for inducing 'electrosleep' and for treating insomnia with rapid relief, according to some poorly controlled trials (*Rosenthal and Wulfsohn*, 1970). However, others have failed to demonstrate any effect of the impulses on subsequent sleep (*Woods et al.*, 1965; *Empson*, 1973). Further investigations of 'electrosleep' therapy are required before it could be recommended.

8.1.3 Use of Hypnotic Drugs

If the insomnia is likely to be short-lived (associated, for example, with a family crisis) and does not respond to explanation and reassurance, then prescription of an hypnotic in limited quantities and for a limited period is justified. At present the drugs of first choice are nitrazepam (5 to 10mg) or flurazepam (15 to 30mg). However, chloral hydrate (0.5 to 2g) or a related compound such as dichloralphenazone (650 to 1,300mg) may be preferred by some patients. The effectiveness of chloral hydrate and its derivatives is limited to a period of about a week if taken continuously; their effectiveness and also that of other hypnotics when taken intermittently has not been established. There is no good reason to prescribe barbiturates.

All hypnotics should be treated as drugs of psychological and physiological dependence. However, patients whose main difficulty is in falling asleep initially may become dependent on hypnotics less frequently than those who also wake up during the night (*Clift*, 1972).

8.2 Other Sleep Disorders

8.2.1 Somnambulism and Night Terrors

Medical advice is less commonly sought for sleep disorders such as somnambulism and night terrors than it is for insomnia. However, drug treatment of somnambulism is seldom required. Benzodiazepines which suppress delta-wave sleep (e.g. diazepam or flurazepam) may help, but this has not been clearly established. Somnambulism in children is often outgrown as they mature and is not necessarily associated with psychological disturbances, although this may not be true in adults (*Kales et al.*, 1964a).

The same conclusions also apply to night terrors in children and adults. In the latter diazepam has been found to decrease the frequency of attacks (*Fisher et al.*, 1973).

8.2.2 Hypersomnia

Hypersomnia must be evaluated from the point of view of a possible psychological disorder, or the presence of cardiopulmonary disease or organic disease of the central nervous system. The patient's previous sleep habits, his age and social circumstances must be taken into account before treatment with central nervous system stimulants is begun, as these drugs are best avoided for long-term use unless strongly indicated.

8.2.3 Narcolepsy

Narcolepsy can be a very disabling condition and, once a definite diagnosis has been made, a trial period of treatment with dexamphetamine is justified. Imipramine and phenelzine have also been used with some success (*Akimoto et al.*, 1960; *Wyatt et al.*, 1971a).

8.2.4 Enuresis

Enuresis in schoolchildren who do not have organic disease of the urinary tract or elsewhere has been treated successfully with imipramine, but there is a tendency to relapse after the drug is withdrawn (*Miller et al.*, 1968). However, improvement with the drug is not related to changes which it causes in the stages of sleep. Psychological support and measures other than drug treatment continue to be important in the management of enuresis (*Katz*, 1972).

References

A list of references cited is available from the editor on request.

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