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An Overview of Sleep Research:

Past, Present and Future

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Introduction

This chapter may be regarded as a revision of the chapter on the "Psychophysiology of Sleep and Dreams" that appeared in Volume III of the first edition of the *American Handbook of Psychiatry*, A gulf of nearly a decade separates the two. In the original chapter, the 258 citations listed in the bibliography represented a reasonably

complete coverage of work in the so-called modern era of sleep research inaugurated by the discovery of REM sleep. However, in the intervening years, perhaps ten thousand publications dealing with some aspect of sleep have appeared. In the face of this avalanche, our goals must be much more circumspect and modest than reviewing the field of sleep research. Furthermore, Volume VI will appropriately have two chapters devoted to aspects of sleep. The other chapter will be devoted mainly to clinical descriptions and issues. Considering all this, we have elected to give a somewhat personalized overview of the sleep -research field with special emphasis on issues that seem particularly relevant to psychiatry. We have also tried to fulfill an interpretive function, one of putting some things into perspective. In this regard, we feel that understanding of material presented under the rubric, "process view," is mandatory. We feel it is only through this

conceptualization of the realities of sleep mechanisms, that the findings of sleep research can be meaningfully applied to such diverse problems as hallucinations, thought disorders, cataplectic seizures, insomnia, sleep apnea, and so on.

Another issue is tangentially raised by Frederick Bremer, the great Belgian neurophysiologist, in his introductory remarks to the proceedings of the First International Congress of the Association for the Psychophysiological Study of Sleep (APSS). He says that the congress

> . . . marks the date when 'sleep research' became a discipline unto itself. In the long way of man's endeavor to understand his body and his soul, the search for the neurophysiological mechanisms underlying the sleep phenomenon began very late, as if we had been paralyzed by an obscure feeling of awe in the face of these obligatory pauses in our busy life and by the magic appearances of the dream phantasmagoria.

Bremer may have repressed his prior acquaintance with the work of Sigmund Freud, but the point we wish to underscore is the notion of sleep research as a discipline unto itself. In the United States at least, sleep research has clearly been the foster child of psychiatry. Much of the work on sleep mechanisms has been conducted in the guise of clarifying the role of these mechanisms in mental aberrations. However, as will be seen in this chapter, there are a number of concerns that have to do only with sleep both on a basic and a clinical level. A case in point is the sleep apnea-insomnia syndrome recently described by Guilleminault et al. This is clearly an organic sleep

disorder. Yet, we may presume that many of these patients will find their way to the psychiatrist's consulting room. Who or what discipline is really responsible for such a patient? We have just about reached the point in time where the foster child is grown up and should either be formally adopted to share in the support and heritage of its foster parents, or should be cast out into the world, entirely on its own, to make its own way, to establish its own heritage, etc.

Before going to more specific topics, we would like to recommend a number of general references. Books and symposia dealing with sleep continue to be published at the rate of several per year. *The Sleeping Brain,* edited by Chase, brings the field up-to-date in a number of specialized areas. Webb has edited a book that ties together the work of a decade by having investigators comment upon earlier experiments in the light of present-day knowledge. Also of recent vintage are two volumes with entirely different purposes by Freemon and Dement.[2] In addition, the National Institute of Neurological Diseases and Stroke has established information networks that include the Brain Information Service at UCLA. In addition to the monthly "Sleep Bulletin" and "Sleep Reviews," the service has begun publishing a yearly volume entitled *Sleep Research,* which will include the proceedings of the annual APSS meetings, and complete yearly cumulation of "Sleep Bulletin" and "Sleep Reviews." Other more general references will be cited from time to time throughout the chapter.

Historical Perspectives

Sleep and wakefulness are essentially behavioral states and, as such, involve the whole organism. Further, they represent functional changes vastly extended in the temporal dimension. Scientific observation is ordinarily either cross-sectional or longitudinal, but the very essence of research on sleep is that it is simultaneously longitudinal *and* cross-sectional.

Perhaps the major factor that limited the ultimate validity of the earliest "laboratory" work on sleep was the natural assumption that sleep was a single totally uniform state. With the often ignored exception of the occasional fleeting disturbance of a dream, sleep was viewed as the "off" condition of the organism and, accordingly, it was felt that a *single* observation of some variable would suffice to describe the behavior of this variable for the entirety of the nocturnal sleep period. A great many interpretations were made on this basis. For example, Pietrusky published a "definitive" study of eye position during sleep in human subjects. He made single observations on three hundred individuals. From these data he concluded that the characteristic stationary resting position of the eyes during sleep was in divergence. In addition, this conclusion may have been predisposed in the sense that Pietrusky saw divergence during sleep as an inevitable consequence of predominant ocular convergence during wakefulness. By nightfall, he reasoned, the more fatigued internal recti could

not maintain the midposition against a slight tonic pull of the less fatigued lateral recti. We now know that the eyeballs *do not* maintain a single characteristic resting position during sleep. Actually, much of Pietrusky's data could have been duplicated by making observations on one individual at three hundred different points in a single night. Any position in which we might find the eyeball is simply one of the relatively brief pauses separating the countless episodes of slow and rapid motility.

Thus, any description of sleep must also take the temporal dimension into account. In this sense, sleep is something like a river— basically the same, yet different at every point depending upon the shape of its bank, the size of projecting boulders, the presence or absence of tributaries, the traffic upon it, the rate of flow, and so forth.

Obviously, a moment-to-moment description of the entire mammalian organism over the entire sleep period is an enormous task. It is possible that some aspects of the description will be quite trivial. However, we must guard against premature assumptions that this or that function is not important, or worth the effort of thorough study. As we shall see later in this chapter, certain physiological variables that are quite easy to record during sleep, but have not been closely scrutinized in recent years because of a lack of interest, are today the subject of a second look and, in some cases, have pointed the way to whole new investigative realms. A case in point is respiration during

sleep. Long taken completely for granted, the revelations of the discoveries involving the sleep apnea syndromes® have made us ask how we manage to continue breathing when we fall asleep and have made us realize how vulnerable this vital function really is during the complex functional adjustments that characterize the incredible transition from wakefulness to sleep.

In addition, there is a natural tendency for scientific investigators in any field to favor experimental approaches—direct attacks upon mechanism and function—at the expense of patient, comprehensive, unbiased passive observation. Again, sleep research is an outstanding example of a general principle: when pure description is not the goal, certain dramatic transients are easily overlooked among the myriad variables that constitute the behavior of the whole organism in time. There were innumerable experimental studies on the mechanisms of sleep before anything like the true nature of mammalian sleep was fully comprehended—that is, before the existence of rapid eye movement (REM) sleep was known. It is a great mystery how REM sleep was so long overlooked, given the techniques available in many studies, and particularly the fact that it can be seen with the naked eye! One explanation, as we have implied above, may lie in the fact that descriptive work generally holds second-class citizenship vis-a-vis experimental work, and the latter is, by definition, narrow (focused) and biased (hypothesis testing).

The EEG and the ARAS

The somnolent state has occupied the attention of laboratory scientists for more than a hundred years. During this time, the one thing that, more than any other, stimulated research was the development of electroencephalography (EEG). This tool permitted continuous observation of the electrical activity of the brain during sleep without disturbing the sleeper.

Berger quickly noticed after his discovery of the presence of brain waves in humans that they always underwent qualitative changes when passing from wakefulness to sleep or vice versa. As is well known, Loomis's group at Harvard and Blake's group at the University of Chicago produced an exciting series of papers that presented relatively detailed descriptions of the various EEG patterns during sleep in humans. These workers did not oversimplify their observations. Although they used sampling procedures, they nevertheless recognized dramatic differences in sleep EEG patterns as functions of time of night and time from sleep onset.

In the thirties and forties it was generally held that EEG waves represented a kind of integrated display at the scalp level of unit activity. Therefore, it was felt that the important parameter in sleep and arousal was EEG synchrony, assuming that frequency and amplitude are generally inversely related. Thus, it was logical that neurons would be discharging slowly and synchronously in deep sleep.

The work of Magoun's group strengthened this notion.'' EEG desynchronization (cortical activation) was equated with arousal. Degree of cortical activation was assumed to depend upon the activity level in a hypothetical ascending extralemniscal system in the brain stem, the so-called ascending reticular activating system (ABAS). For these workers, the whole continuum of sleep and arousal was presumed to be controlled by a unitary mechanism residing in the brain-stem core.

Further, the ARAS was known to receive fibers from all sensory pathways. Thus, its activity could reflect the amount of stimulation impinging upon the organism. By interposing the ARAS between external stimulation and the cerebral cortex, one could hypothesize a certain amount of organismic independence from immediate sensory stimulation since the ARAS could amplify, modulate, and reverberate input. This formulation seemed to explain so much and seemed so amenable to experimental manipulation in laboratory animals that it was reified before all the descriptive facts were available.

The ARAS concept also allowed for variation in the "depth" of sleep. Thus, the bigger and slower the EEG waves, the deeper the sleep. This was also consistent with the notion that cortical units were discharging slowly and synchronously, in contrast to their presumed patterns in response to the evocations of wakefulness. Figure 8-1 depicts this concept of the continuum

of sleep and wakefulness.

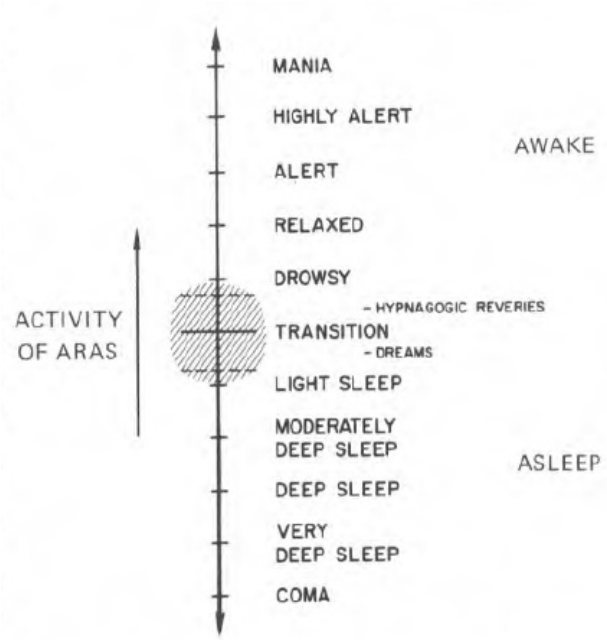

Figure 8.1.
The vertical continuum of human existence.

Several studies were also done that presented evidence supporting a relationship between EEG patterns and arousal threshold, f Here again, the relationship was reified before all the evidence was gathered. For example, in their otherwise superb *Atlas of Electroencephalography,* the Gibbs eschewed numbers or letters to name the EEG stages of sleep, preferring instead a nomenclature based on the depth of sleep.

Figure 8-2 presents classic examples of the typical EEG patterns seen during human sleep and will serve to make the point that the current classifications of sleep rhythms are not very different from the major descriptive categories set forth by the Loomis group. These workers originally used letter designations: the letter “A” designated waking alpha rhythm; “B” through “E” corresponded roughly to our EEG sleep Stages 1 through 4.

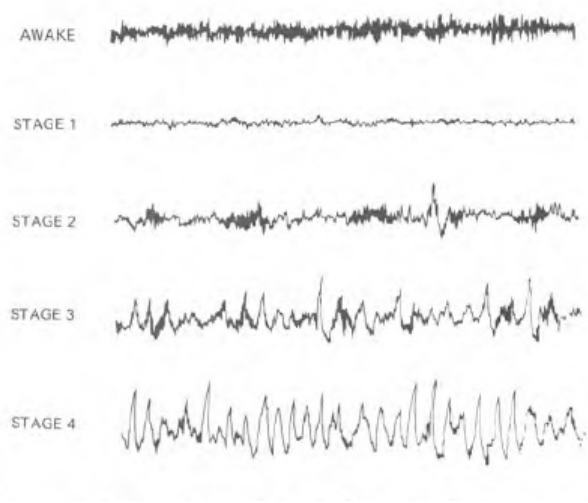

Figure 8.2.
Examples of the recorded tracings of EEG stages of sleep for the same subject over a period of a single night. The recording paper was moving under the pens at one-third the standard speed, which means that the waves are somewhat pushed together. However, this also means that only one third as much paper is needed during the night, a considerable saving in eight hours of continuous recording.

The top line shows the ten-per-second alpha waves characteristic of the Awake EEG. Their mean amplitude, for comparison with the sleep patterns, is about fifty μv.

The second line (Stage 1) shows a mixture of low voltage, irregular, relatively fast waves. The sample of Stage 2 in the third tracing shows the characteristic waxing-waning bursts of regular waves (sleep spindles) lasting one to two seconds. The frequency of the spindle waves is about twelve to fourteen per second, which causes them to be somewhat blurred at this paper speed. Nonetheless, they stand out sharply from the low voltage, irregular background rhythms. A moderate amount of high-voltage, slow activity is seen in the Stage 3 tracing. Stage 4, shown in the bottom line, is characterized by continuous high-voltage, slow activity. The frequency is about one per second.

REM Periods and the Temporal Course of Events during Sleep

We have pointed out that EEG patterns during sleep have long been known to vary throughout the sleep period. Nevertheless, a thorough study of the temporal course of events during sleep did not develop until Aserinsky and Kleitman made their original observations on the occurrence of rapid, binocularly synchronous eye movements during sleep in human adults. This discovery, together with the additional observation that dream recall was very likely when such eye movements were present, fundamentally changed the focus of attention; now the temporal course of events throughout the night became critical. Intense interest in the temporal position and physiological concomitants of the rapid eye movement dream periods led to continuous monitoring over many hours instead of intermittent sampling. The ink writing electroencephalograph or polygraph was the perfect instrument for such work because it enabled continuous monitoring not only of brain-wave patterns but of eye movements as well, *without* disturbing the sleeper. Furthermore, the permanent paper record could be scrutinized carefully at a later date. One of the first reliable EEG instruments was available in Nathaniel Kleitman's laboratory at the University of Chicago, and with it we were able to inaugurate a period of intense observation of a relatively small number of physiological variables. This observation was aimed at a detailed, minute by minute description of the eight-hour nocturnal sleep period in man.' Because of the importance we naturally attributed to

brain processes in sleep, EEG patterns were emphasized.

It is really unclear why the so-called Dement—Kleitman classification of sleep stages utilizing numbers became so popular. We always felt that it was really trivial whether numbers or letters were used. The reason may have been that the Dement-Kleitman classification was the first relatively precise description of brain-wave patterns during sleep. There were fairly specific descriptions of frequency, amplitude, and wave forms, which permitted scoring patterns fairly reliably into one of the four stages. In addition, these stage definitions helped in dealing with the huge mass of data that always accumulated from all-night sleep recordings before the advent of computer scoring.

It was soon apparent that all sleep epochs would fit comfortably into these four levels. More importantly, it was also obvious that the four stages seemed to alternate in a kind of cyclic fashion. With rapid eye movement periods as guideposts, repetitive sequences were clearly seen. Further understanding of the relationship between rapid eye movement periods and dreaming led to the first longitudinal generalization about the nature of sleep, the so-called basic rest activity cycle (BRAC).

The characteristic all-night EEG changes were viewed as cyclic alternations in depth of sleep. Moreover, central nervous system activity at

the peak of the cycle (signaled by the appearance of low voltage, relatively fast EEG patterns) seemed consistent with the concomitant psychological experience of dreaming. In turn, such psychological activity was presumed to be responsible for other manifestations occurring at the peak of the cycle such as rapid eye movements and certain other physiological events. Thus, in 1958 it seemed that the only aspect of the rapid eye movement (REM) period that might give it importance for the human organism was its apparent association with dream activity. Although interesting quantitative data were compiled on lengths and locations of REM and Stage 4 periods, there was, as yet, no concept of two kinds of sleep.

Two States of Sleep

REM Sleep versus NREM Sleep

Several observations led to a drastic modification in the monolithic cyclic concept of sleep. First was the finding that rapid eye movement periods also occurred in the laboratory cat, which stimulated much subsequent experimental work. In the next year, Jouvet and Michel made one of the most remarkably simple and far-reaching observations in the history of sleep research. Jouvet and Michel found that the electromyographic (EMG) was quite active during slow wave periods, but when EEG activation with rapid eye movements appeared, EMG activity was totally suppressed! Berger

confirmed this finding in man. Thus, there was for the first time a strong suspicion that sleep was not a unitary state. These data are especially significant since every precedent favored closer scrutiny of the brain and diminished scrutiny of peripheral events; yet Jouvet and Michel had the temerity to observe the electrical activity of the muscles. Up to that point, most researchers assumed that EMG activity would more or less parallel depth of sleep and level of EEG activation.

Finally, Jouvet and his colleagues discovered a very unique electrical activity in the pons of the cat during REM sleep. They initially referred to this activity as "spindles," but later recognized it as bursts or clusters of individual monophasic sharp waves, or spikes. Brooks and Bizzi found the same activity in the lateral geniculate nucleus, and Mouret, Jeannerod, and Jouvet completed the implication of the visual system in REM sleep by describing these waves in the visual cortex. Even in human scalp recordings, it is possible to identify unique features in the EEG of REM sleep. Schwartz was the first to see bursts of peculiar waves that had escaped the notice of everyone else. These waves were related to rapid eye movements and have come to be known as saw-tooth waves. Thus, it became clear that some very unique phenomena were part of the spontaneous electrical activity of the brain during REM sleep, in addition to nonspecific arousal or hyperarousal.

Sleep researchers now realized that sleep was two processes. This was

truly a revolutionary shift in viewpoint. It ran counter to the personal experience of sleep and was a complete departure from all previous thinking about sleep. Oswald was probably the first to actually state this radical new notion in print, but we think that Jouvet probably deserves the most credit because of the impact of his epochal paper, which appeared later in the year. Jouvet summarized a tremendous amount of anatomical, physiological, and behavioral work, and clearly established the brain-stem origins of REM sleep.

Thus, the regularly recurring REM period was recognized as one kind of sleep, and all the rest, albeit encompassing several very different EEG patterns, was recognized as another kind of sleep to which the term, nonrapid eye movement (NREM) was applied. Though outwardly very similar in terms of recumbency, quiescence, increased response threshold, etc., these two kinds of sleep are totally dissimilar when observed more closely. Indeed, as we all know, and as has been demonstrated repeatedly, nearly every physiological variable observed longitudinally during sleep shows markedly contrasting behavior as a function of REM periods versus NREM periods.

The Concepts of State and Stage

Some confusion still exists regarding the idea that REM sleep is a state and all other sleep (four stages) also comprises a state. The term *state* usually refers to a condition in which something exists that is qualitatively different

from other possible conditions in which it may exist. A specific condition or state is usually recognized by the necessary presence of one or more attributes that are essentially absent at other times. For example, when water exists in the frozen state, it possesses attributes of solidity and rigidity that are present at no other time. In complex living organisms, the taxonomic problem of defining states becomes, to some extent, a matter of judgment and consensus. As a rule, a single variable will not suffice to define a state; a cluster of attributes whose simultaneous and repeated occurrence is highly unique must be present. It is commonly accepted that there are two, and only two states of sleep. As noted above, they are called REM and NREM sleep and they appear to be present in nearly all mammals.

The word *stage* usually refers to a relatively precise, but arbitrary subdivision in the course of a continuously progressing quantitative change. Thus, water in the liquid state between 0° and 10° centigrade could be called Stage 1, from10° to 20° could be called Stage 2, and so on. It is obvious that almost any number of stages could be defined arbitrarily within a state. In the case of the sleeping human, only four stages defined by the EEG have been commonly accepted as subdivisions of NREM sleep. There are *no* commonly accepted subdivisions of REM sleep.

To be useful, stage designations should have functional or organizational significance. The putative functional significance of the NREM

EEG stages is that they represent levels in a NREM continuum of depth of sleep. These stages also show quantitative changes in several clinical conditions.

Are there stages in REM sleep? It may be presumed that no stage subdivision of REM sleep has been widely accepted because a clear-cut functional significance does not exist, or has not yet been conclusively shown to exist. Certain divisions of REM sleep have been used from time to time to facilitate an experimental approach. Most frequently, such a division is used for the study of the correlation between a REM sleep-associated variable and some aspect of dreaming. For example, epochs of REM sleep have been differentially classified according to the absolute frequency of individual eye movement potentials, heart rate changes, respiratory changes, so forth.

The realization that two entirely independent states of being alternated during the period of bodily quiescence (sleep) gave rise to two kinds of questions. One set of questions dealt with the biochemical underpinnings of the two states. These issues were extensively addressed by the Lyon group. Their early work led to the proposals of Jouvet that NREM sleep might be dependent upon serotonergic neurons, while REM sleep might involve catecholaminergic systems.' The second group of questions concerned the age-old problem of the function of sleep. If one could distinguish two kinds of sleep, what then were their respective functions? It was necessary to

repudiate the total sleep deprivation studies because they had confounded the effects of the loss of both REM and NREM sleep. It was felt that functional clarity would come only as a result of selective sleep deprivation.

The first such study involved the selective deprivation of REM sleep. The early experiments were rather successful in eliciting the postdeprivation REM rebound, which seemed to suggest some sort of need for REM sleep. In addition, there was a feeling that the rebound served a quantitative makeup function. While clarification of the specific role of REM sleep in the biological economy of the mammalian organism has remained controversial, the mere fact that one could conceive of a possible need for a certain amount of REM sleep led to an augmented concern with quantification of sleep states and stages. Parenthetically, there was also a notion that Stage 4 might have some unique functional significance and it was also subjected to quantitative manipulation.

Accordingly, great consternation developed when Monroe first presented the results of his study of inter-rater reliability in the scoring of sleep stages. To wit, he found that the numbers (minutes of Stage 4, REM, etc.) everyone had been presenting as experimental data did not have a generally reliable meaning. Monroe had distributed copies of exactly the same all-night sleep recording to a number of laboratories, and the results showed significantly different values for the sleep states and stages among the

laboratories.

Primarily as a result of this debacle, the UCLA Brain Information Service sponsored a specific project to develop a standard manual for the scoring of human sleep stages. Under the chairmanship of Allan Rechtschaffen and Anthony Kales, a committee was formed to set forth absolutely precise definitions of the sleep states and stages so that anyone, at least in theory, should get identical results scoring human adult sleep records. This manual was completed and published in 1968.

The "Standard Manual" not only details definitions of the sleep stages, but illustrates standard techniques and procedures for human sleep recording as well. Instructions are included for recording the three chief modalities used in sleep research, EEG, EOG, and EMG. Ample figures are presented in the manual for illustrating all the criteria and special rules for scoring sleep stages. To give a general idea of the thoroughness of the manual, we abstract from one of the sleep stage definitions:

> Stage 1: This stage is defined by a relatively low voltage, mixed frequency EEG with a prominence of activity in the 2 to 7 cps range. The faster frequencies are mostly of lower voltage than the 2 to 7 cps activity. Stage 1 occurs most often in the transition from wakefulness to the other sleep stages or following body movements during sleep. During nocturnal sleep, Stage 1 tends to be relatively short, ranging from about 1 to 7 minutes. The highest voltage, 2 to 7 cps activity (about 50 to 75 μv), tends to occur in irregularly spaced bursts mostly during the latter portions of the stage. Also during the latter portions of the stage vertex sharp waves may appear . . . (whose)

> amplitude is occasionally as high as 200 μv . . . Stage 1 requires an absolute absence of clearly defined K-complexes and sleep spindles . . . Stage 1 . . . is characterized by the presence of slow eye movements . . . Rapid eye movements are absent. Tonic EMG levels are usually below those of relaxed wakefulness . . . When the amount of the record characterized by alpha activity combined with low voltage activity drops to less than 5% of the epoch and is replaced by relatively low voltage, mixed frequency activity, the epoch is scored as Stage 1.

The beauty of this manual is that it enables everyone to say that "this epoch is REM sleep, this epoch is Stage 2, this epoch is Stage 4, this epoch is wakefulness . . ." and so on.

There are many implications underlying what become arbitrary decisions about stages, but such peripheral problems usually develop when temporal quantification is involved. Thus, it is true that an epoch containing eye movements and sleep spindles both, may be scored Stage 2, but it is obviously true that this epoch is not pure Stage 2. If transitions in sleep, and we will say more about this later, can occur at rates greater than once every thirty seconds, then it is obvious that the scoring is not ultimately precise.

A similar scoring manual has recently been published for the scoring of sleep stages in infants. This manual was more difficult to prepare because the criteria and the actual descriptive phenomenology of sleep in newborn infants is much more complicated than in human adults.

Investigators have worked on similar standardization in other animals,

but very little progress has been made. Ursin has proposed a two-stage division for NREM sleep in cats. Adey, Kado and Rhodes have described sleep stages in the chimpanzee and Weitzman et al. have described sleep stages and sleep cycles in the monkey, but precise criteria have not been widely accepted. Kales et al. and Kahn and his colleagues have described sleep in the elderly and it is clear that there are differences, particularly in that the Stage 4 criteria would not apply in the elderly. Whether these problems of precise definitions and quantification will be resolved in the same way that they have been resolved in the past, or whether new ways of processing this kind of data will simply take over and obviate the need in this area remains to be seen.

Limitations of the T100 State Notion of Sleep

Although development of the concept of two kinds of sleep was a major advance, it was inevitably carried too far. In some way, the notion of two kinds of sleep was transmogrified so that these states became things in their own right. People began to assume, a priori, that what was true for one state absolutely could not be true for the other. For example, since dreaming is clearly associated with REM sleep, dreaming cannot be associated with NREM sleep. Or, if serotonin is the neurotransmitter for NREM sleep, it cannot play a role in REM sleep. Jouvet has, in a sense, recognized and avoided this conceptual error in proposing that serotonin plays a priming role for the

onset of REM sleep. Of course, REM sleep and NREM sleep represent the same brain doing two somewhat different things. Thus, the notion of mutual exclusivity is almost as if people regarded a car that is moving and the same car standing still as two entirely different and unrelated entities.

In addition to such problems for biochemical approaches, the notion of two totally different states of being definitely affected approaches to the problems of sleep function. Because the phenomenological aspects of REM and NREM sleep seemed so divergent, researchers felt that their functions ought to be equally divergent. This kind of mythology grew up where we assumed the selective loss of NREM sleep would lead to sleepiness, whereas the selective loss of REM sleep would lead to excitation and hyperarousal. Because sleep loss in total sleep deprivation is around 75 percent NREM sleep, we assumed the overt consequences of total sleep loss primarily reflected the loss of NREM sleep. We further assumed that REM sleep loss contributed some excitation and thus diluted the effect of sleep deprivation. Accordingly, if the baseline sleep in some animal were hypothetically characterized by 50 percent REM sleep and 50 percent NREM sleep, total sleep deprivation would have essentially no effect on waking behavior because the two opposite consequences would cancel each other. Further, we could assume that if an animal had only NREM sleep, it would be extremely vulnerable to total sleep loss since the only effect would be depression of function and sleepiness.

An attempt to test this latter supposition was made by sleep depriving adult chickens in our laboratory. Adult chickens have only NREM sleep. We observed that chickens did appear to succumb to total sleep loss somewhat more quickly than mammals, e.g., rats and cats. However, we felt that the findings were really the result of anatomical considerations: i.e., the chicken, having only two feet, could not walk a treadmill or remain physically active as long as most mammals that have four feet.

At this point, we would like to mention two observations that will exemplify a host of findings that do not support the extremes to which the "two kinds of sleep" position has been car-ried. The first is an as yet unpublished* study by Paul Naitoh and Lavern Johnson who totally sleep deprived subjects for two full days and then deprived selectively of REM or NREM Stage 4 during the recovery period. They found that regardless of the procedure the recovery function proceeded at the same rate, probably being dependent *only* on total amount of sleep time.

The second is the casual but very startling observation that the sleepiness of a narcoleptic patient, which is in no way distinguishable from the drowsiness of someone who has suffered prolonged sleep loss, can be reversed if he has ten to twenty minutes of pure REM sleep (the characteristic sleep onset REM period of the narcoleptic patient). In other words, there is no cortical synchronization, no spindles, just the furious rapid eye movements,

twitches, and implied neuronal “storm” of REM sleep. Yet, the tiredness and sleepiness is reversed, as it would be by ten to twenty minutes of NREM sleep —a normal nap.

We mention these things not to suggest that the old theorists who felt that REM and NREM were really manifestations of a unitary process were right, but merely to suggest that there is much more to the problem of two kinds of sleep than meets the eye. There are a great many things going on, some of which are common to *both* of the defined states of sleep and some of which are not.

Interspecific Generality of the Two States of Sleep

In addition to the move toward more rigorous analysis of human sleep, another great push in the last decade was a far reaching phylogenic description of sleep.[3] Such research probed the evolutionary and interspecific generality of sleep behavior. One striking finding from this large body of data is the widespread interspecific similarity of mammalian sleep. It is now accepted that in most mammals and many avian species polygraphically defined wakefulness, NREM sleep and REM sleep always appear and are at least qualitatively and sequentially comparable across species. Of course much more descriptive and experimental work exists and will continue on various quantitative sleep differences' between species.

Ontogenic Studies of Sleep

In another vein, cutting across phylogeny, a vast developmental description of sleep has come into being. One major theme of such investigations was that the electrophysiological and behavioral variables, which in adult organisms help to distinguish among the states of sleep, were of inconsistent value in determining behavioral states in young organisms. For example, adult human slow-wave sleep (Stages 3 and 4) is characterized by high voltage, slow (delta) EEG patterns, regular respiration, and tonically moderate EMG activity. In infants these variables often bear very different and inconsistent interrelationships. One may see, for example, delta activity with irregular respiration and irregular but low EMG activity. Such disassociated patterns in common sleep variables necessitate handling infant sleep records in a different manner than that used for adults. The way sleep in young humans is scored may be regarded as using what we call a process view of sleep. (We will deal more extensively with this process view in another section.) While adult sleep is defined by constantly recurring patterns in many physiological processes, developmental sleep researchers recognize that patterns may not consistently appear in infancy. The adult patterns develop from very different and inconsistent constellations seen in young organisms. Consequently, in studying infant sleep, physiological variables are studied concurrently but regarded as independent processes. The relative importance of each index is established by the investigator,

depending on the questions he wishes to ask.

The Process View of Sleep

The foregoing material provides an appropriate introduction to a consideration of what we may call a process view of sleep. While of heuristic value, we have seen that the notion of state and, in particular, two sleep states does have certain limitations. Today many workers would agree that sleep states are really the outward manifestations of a number of discrete processes that are going on simultaneously but with as yet unspecified degrees of independence. The beginning of this systems concept of sleep could probably be dated to the Lyon Conference on the Neurophysiology of the States of Sleep in 1963 when Prof. Guiseppe Moruzzi made some extemporaneous remarks (duly recorded and transcribed) to the effect that it would be helpful in describing REM sleep to distinguish between phasic (short-lasting) and tonic (long-lasting) activities. Thus, although REM sleep was generally considered as a single "something," Moruzzi's suggestion formally recognized the fact that there were at least two attributes of REM periods that could be dealt with more or less independently. The further development of this line of thought has led to a relatively new point of view that is best set forth by a consideration of REM sleep.

Independent Processes in REM Sleep

Full-blown REM sleep is defined in most mammalian species when we can note the simultaneous occurrence of at least three distinct classes of events. Perhaps the most essential and characteristic process of REM sleep is an actively induced, tonic, nonreciprocal motor inhibition. The most widely used and convenient indicator of this inhibitory process is a continuous recording of the electromyogram, or EMG. Suppression of EMG activity is highly correlated with the onset of REM sleep (see Figure 8-3). EMG suppression is also highly correlated with other indicators of active motor inhibition, for example, suppression of electrically induced reflexes and a number of measures as studied by Pompeiano and his associates' in cats. According to Pompeiano, during REM sleep there is a tonic hyperpolarization of alpha motor neurons; and if the cataplectic attack in narcoleptic patients is representative of the effectiveness of this inhibitory process (see also section on "Tonic Motor Inhibition and Cataplexy-Narcolepsy") REM sleep is a time of profound motor paralysis in which tendon reflexes cannot be elicited and in which voluntary movement is totally impossible. In cats, the presence of motor inhibition during REM sleep is also confirmed by an extreme flaccidity.

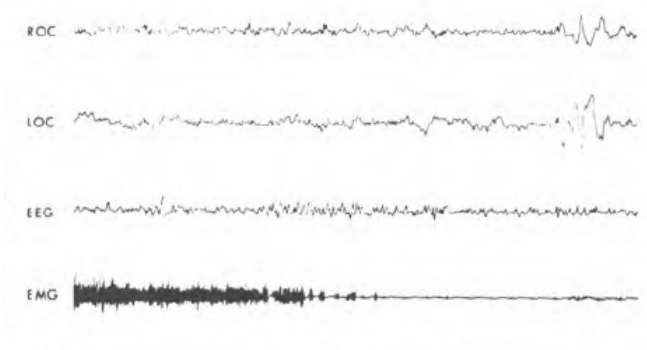

Figure 8.3.
This figure illustrates the transition from Stage 2 sleep to REM sleep. Note that the EMG suppression precedes the appearance of rapid eye movements by several seconds.

Derivations: ROC—monopolarelectrooculogram from right outer can thus; monopolarelectrooculogram from LOC: left outer canthus.

EEG—monopolar electroencephalogram derived from C3/A2;

EMG—electromyogram from placements over digastric muscle.

There is a dream that has been experienced by most people. It is the dream of trying to run, usually to escape some great danger, and being completely unable to move, or of moving slowly, with great difficulty as if one's limbs were weighted with lead. It is quite likely that this dream represents a breakthrough into dreaming consciousness of an awareness of the true neurophysiological condition, much as a narcoleptic is aware that he cannot move during an attack of sleep paralysis.

The second process is central nervous system (CNS) arousal or

activation. It is a well-known fact that in many respects, the brain in REM sleep appears to be aroused or awake. We must, therefore, postulate some sort of nonspecific arousal process or system that operates more or less tonically during REM periods. It is still a matter of great puzzlement whether the observed CNS arousal is true wakefulness or a totally different process that merely resembles wakefulness in terms of most of the nonspecific measures of CNS activity levels such as brain temperature, EEG activation, cerebral blood flow, and so forth. Certain differences between wakefulness and REM sleep could, of course, be quantitative. Thus, atropine might block EEG activation during waking behavior but not during REM sleep at one dose, but would block EEG activation in both states at a higher dose. Early studies suggested different pathways by showing that lesions in the reticular formation brought about prolonged EEG synchronization in wakefulness, yet, when REM periods occurred, normal EEG activation was seen. This is not so clear in humans because the EEG patterns in REM sleep do not resemble patterns seen during the waking state. However, there is still some controversy about just where the REM sleep EEG actually belongs from a conceptual point of view. Is the REM sleep EEG a combination of activated patterns plus superimposed saw-tooth slow rhythms, or is it really a different spectrum more analogous to NREM Stage 1? The subjective descriptions by narcoleptic patients of the transition from unequivocal wakefulness directly into REM sleep lead us to feel that perhaps REM arousal is truly the same

arousal process as in wakefulness. If the narcoleptic patient is interacting verbally with a bedside observer, the transition appears to be a gradual pre-empting of the waking sensorium by internally generated sensory input. Thus, the narcoleptic on the verge of full-blown REM sleep, with certain aspects of this state—namely, EMG suppression and rapid eye movements—already established, is still clearly awake in terms of the usual definitions of wakefulness.

The third process characteristic of REM sleep is called *phasic activity.* At the present time, there is no widely accepted definition of this activity. The underlying neurophysiology is far from clear, and different investigators will think of different things when the term is used. In its most global definition, phasic activity merely refers to short-lasting events. The exact time limits for this definition have not been specified nor would it be practically useful to do so. Generally we are thinking of phenomena lasting for a second or less. These events may, of course, occur in bursts. The most important aspect of this phasic activity derives from the assumption that phasic activity is generated exclusively from *within* the brain.

What are some examples of phasic activity? The most dramatic and the first to be observed was, of course, rapid eye motility. The rapid jerks of the eyeballs are binocularly synchronous and occur in bursts or singly and in all directions and sizes of arc. This activity has been described in the cat and

numerous other mammals as well as the human adult and infant.

Other things we can mention are muscle twitches, sudden changes in pupil diameter, sharp fluctuations in penile tumescence, cardiovascular irregularities, and phasic, middle-ear contractions. The latter were uniquely studied in the cat until recently when Pessah et al. published their beautifully thorough observations demonstrating middle-ear muscle activity in human REM periods.

Finally, the most intriguing and widely studied phasic events are the discrete bursts of high amplitude, biphasic sharp waves in the electrical recordings from the pons, oculomotor nuclei, lateral geniculate nuclei, and visual cortices of the cat (the PGO wave). Many investigators have speculated that these PGO waves represent the primary phasic event in that they may be the electrical sign of the basic trigger of other phasic events, e.g., eye movements, middle-ear muscle contractions, and so on. Figure 8-4 illustrates a typical example of PGO activity. Certainly, if there were a generator for PGO waves, this generator might stimulate many areas of the brain where a potential change resembling a PGO wave could not be recorded. This is suggested by unit studies that show in almost every area of the brain phasic bursts of firing which seem to be correlated fairly well with PGO waves. Thus, it is important to know whether or not every other phasic event is uniformly linked in time to the occurrence of PGO waves. Another problem is whether

or not PGO waves and the underlying neuro-physiological events are unique to REM sleep, since there are waves in the lateral geniculate that appear to be merely a response to eye movements in the waking state. Data of Brooks and Gershon raise the question of whether such eye movement potentials have the same anatomical substrate as the REM-PGO wave. Recent studies addressing this issue include a careful description of the temporal relationship between eye movements and geniculate waves and some demonstrations from thalamic stimulation that eye movement potentials are elicitable in any state, but that REM-PGO waves have a longer latency and can only be elicited during REM sleep and periods of NREM sleep that immediately precede REM sleep.

At the present time, clear relationships have been described in the cat between PGO waves and a variety of peripheral events such as eye movements, limb twitches, and, most recently, phasic contractions of middle-ear muscles in the cat. However, the relationships among these peripheral activities are not entirely clear. In addition, there are events that really lie between “phasic” (one hundred to one thousand msec.) as exemplified by the PGO wave, and tonic as exemplified by the duration of the REM period itself. Thus, the original description of middle-ear muscle activity by Dewson et al. was mainly of contractions lasting several seconds that were not necessarily related to rapid eye movements. Roffwarg et al. noted these longer contractions but referred to them as “tonic” and also not necessarily related

to PGO waves. We will consider this problem again in relation to "psycho-physiological correlations and dreaming."

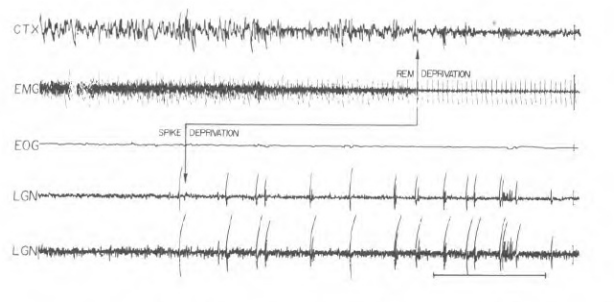

Figure 8.4.
A comparison of "spike" deprivation and REM deprivation. In the latter procedure, the cat would have been aroused at the exact onset of the REM period (B) signaled by EMG suppression and EEG activation. If the cat had been undergoing spike deprivation, the arousal would have been accomplished a little earlier (A) immediately after the first PGO spike. In this example, such an arousal would have deprived the cat of thirteen NREM PGO spikes in addition to those occurring in the REM period, and twenty-six seconds of NREM sleep.

It is important to emphasize here that there is little cross-species data to affirm (1) the apparent "pacemaker" properties of the feline PGO wave vis-a-vis other phasic events and (2) the generality of the distribution of the feline PGO wave in sleep. Nevertheless, we all assume that there is some phasic generator in all the many mammalian and avian species who have REM sleep characterized by other phasic events such as muscle twitches and eye movements. Figure 8-5 presents a highly idealized conception of such a generator. In this conception, PGO waves represent a low threshold response.

Whether or not any particular response occurs would be a complex function of the moment-to-moment excitability of the responding structure and the stimulus output it receives from the generator. The generator itself could be exceedingly simple with a rhythmic constant output, or exceedingly complex with its output varying in terms of intensity, duration, direction (to which particular structure), timing, and sequence. Given the postulated brain-stem origins of such activity, we may ask the question, is there some structure or area in which such a complex function could be housed? The desire to look at this activity in association with dreaming in humans has led to a search for some sort of PGO analogue in humans. There are three important candidates. The first is the phasic-integrated muscle potential (PIP) described by Rechtschaffen, Michel, and Metz, who observed that discharge in the eye muscle was always associated with PGO waves in the cat and decided to look at this activity in the human. Second, the phasic EMG suppression described by Pivik and Dement, which is apparently analogous to the phasic inhibition described by Pompeiano, can be seen only during NREM sleep in humans because it is observed against the tonically active EMG background. It has been confirmed by H-reflex studies that such phasic inhibition is short lasting but generalized. Third, there are EEG events that may be related to phasic activity. The saw-tooth waves of REM sleep could be human cortical or scalp derivations of phasic electrical activity, and the so-called K-complex, seen more frequently in NREM sleep, may represent a kind of response to some

spontaneously occurring internal event. We will say more about this later.

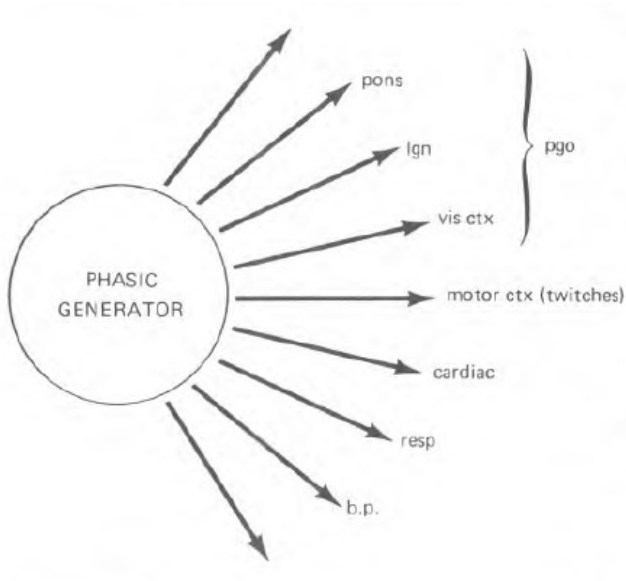

Figure 8.5.
Diagrammatic representation of the phasic event generator.

Independent Processes in NREM Sleep

What about NREM sleep? Most people think of NREM sleep as slow waves and spindles in the EEG (see Figure 8-2), and further feel that these imply deactivation of the cortex. However, we might ask the question, what is the absolutely essential difference between being awake and being asleep (NREM sleep)? In our opinion, after considerable reflection, the salient

feature of wakefulness is the environmental engagement of the organism. It sees, hears, and responds to the world around it either behaviorally or perceptually. The onset of sleep (normally NREM sleep) always entails the cessation of the above perceptual activities. There is a fairly discrete point somewhere in the transition from wakefulness to sleep where the organism essentially, though perhaps not in every detail, stops perceiving its environment. It becomes in one instant blind, deaf, dumb, and numb. The important point, and of this we are quite certain, is that the moment of perceptual shutdown is *not* the moment at which slow waves and spindles appear. Therefore, the significance of spindles and slow waves in the EEG may not be crucial to the onset of sleep, convenient though they may be as signs of NREM sleep.

The moment of sleep (i.e., the cessation of perception) is apparently quite abrupt. While there may be important predisposing changes leading up to it, and consequences of its occurrence leading away from it, the point of sleep onset itself seems relatively easy to determine within a second or two. For example, suppose we ask an individual to sit with his eyes taped open and to make a motor response when a light flash is presented. At some point he will not respond. The moment of sleep is best defined by such a point of perceptual disengagement. We have recently used this technique to demonstrate pathological lapses in patients complaining of excessive sleepiness. Immediately after such a failure the EEG patterns can still show

waking patterns, such as alpha rhythm. Thus, we could conceivably abolish slow waves and spindles without abolishing the process of perceptual disengagement. Accordingly, we must acknowledge that it is not clear if slow waves and spindles are processes that really begin at the point of response inhibition and only build up enough to appear in the EEG a few minutes later or are entirely separate and perhaps redundant processes. But until proven otherwise, we must think of slow waves and spindles as meaningful although often belated signs of a central inhibitory state. However, aside from the kind of behavioral study we have mentioned, even the more sophisticated neurophysiological techniques, such as unit activities studies, have not shown changes in firing patterns that are commensurate with the vast functional differences among states. It may be, however, that such studies compare unit activity at the onset of sleep (i.e., after perceptual changes but before the conventional signs such as slow waves and spindles) with the sleep stage a few minutes later when slow waves and spindles have appeared.

In our opinion, the best sign of the exact moment of sleep appears to be the breakdown of the ability to maintain visual fixation, which is usually signaled by the appearance of a slow drifting of the eyes. If the transition is prolonged, it is typical to see rhythmic, to-and-fro, slow, horizontal movements that resemble a sinewave when recorded by conventional polygraphic electrooculographic methods. According to other investigators, pupillary myosis in dim light may also be such a precise sign, although others

have suggested that relative myosis is a sign of “drowsiness” in the waking state.

Another possible alteration in NREM sleep that could, by stretching a point, be called an independent process has to do with memory mechanisms. It seems reasonably clear, from the work of Portnoff et al. and the unpublished results of Kamiya and his colleagues, that sleep either erases short-term memories or that long-term memory mechanisms do not operate in NREM sleep. These changes could possibly be invoked to account for the blackouts or amnesic episodes that are often experienced by narcoleptics.

Dissociative Aspects of Normal Sleep

As we have shown, it is possible to take the phenomenology of normal sleep and conceptually divide it into independent processes. However, the real test is whether these processes can truly be dissociated from one another on a temporal basis. This is crucial to the issue of whether states are entirely different things or whether they are mere manifestations of the simultaneous occurrence of independent processes.

The best illustration of the process view in normal sleep is phasic activity. Phasic activity, as exemplified by the PGO spike in the cat, is not limited to REM sleep. PGO spikes typically occur in NREM sleep. Thus, what occurs in, is true for, REM sleep also occurs in, is true for, NREM sleep. The

most characteristic time in NREM sleep when PGO spikes appear is about ten to thirty seconds prior to the onset of the REM period (see Figure 8-4). To illustrate how absolute this is, we looked at the beginning of more than two thousand REM periods distributed among sleep periods of about thirty cats in our laboratory and failed to find, in normal intact animals, a single instance where REM sleep (as defined by EEG activation closely followed by EMG suppression and eye movements) ever occurred before at least a few PGO waves (usually ten to thirty) were discharged in the preceding NREM interval. Phasic activity in the form of PGO waves is actually far more distributed throughout NREM sleep than most people realize and more than we have already described.

Although absolutely characteristic of REM periods in the cat, it is also true that phasic activity in the form of PGO waves may be present in more than 50 percent of the total amount of NREM sleep, at least in some cats. In addition, intervals of NREM sleep in the cat in which there are absolutely no PGO waves at all are relatively brief, for the most part no longer than two or three minutes. Discharge rate of PGO spikes during REM periods varies from cat to cat, ranging from about forty per minute to more than one hundred. The discharge rate during epochs of NREM sleep is highly variable, although well below the rates seen during REM periods. The total number of PGO spikes per day in the cat has been estimated to vary between ten thousand and twenty thousand. Approximately 15 percent of this total typically occurs

in NREM sleep as defined by slow waves and spindles in the EEG and the presence of tonic electrical activity in the neck muscles. Most of the other phasic activities tend to be less prominent in NREM sleep, but the truth of the matter is that we have not looked at them closely. Thus, there may be occasional rapid eye movements in NREM sleep, occasional fluctuations in heart rate, penile tumescence, and so on, but we have simply not emphasized these findings.

In human subjects, there is also plentiful evidence that phasic activity is widely disseminated throughout NREM sleep. For example, Rechtschaffen and Chernik have reported an almost continual discharge of phasic-integrated muscle potentials or "PIPs" during NREM periods as well as REM periods. Pivik and Dement have reported a similar distribution and intensity for phasic EMG suppressions. Finally, K-complexes, if they represent phasic activity, are also distributed throughout much of NREM sleep.

If we look at tonic EMG suppression, we find that it, too, can precede the onset of the REM period, often by a minute or more. Thus, we can have intervals of NREM sleep that are characterized by what is usually considered the sine qua non of REM sleep. In one of the early studies of long-term REM sleep deprivation, we observed that the gap between EMG suppression and EEG activation (NREM Stage 2 to REM patterns) underwent a steady enlargement. Penile tumescence, which appears to be a consistent

concomitant of REM periods in humans and monkeys,' has been reported to occur in NREM sleep in humans if REM sleep is prevented from occurring.

Conclusions

The upshot of this section's discussion is that we can conceptualize individual processes existing within or as part of the two states of sleep. In REM sleep, we can speak of motor inhibition, CNS arousal, and phasic activity. Obviously, this list is arbitrary; there are other processes, too. In NREM sleep, we can speak of the control of cortical rhythms, higher processing or inhibition of sensory input, and perhaps control of long-term memory processes or consolidation. Throughout the remainder of this chapter we will see many of the implications and ramifications of the notion that sleep comprises many temporally linked processes.

Phasic Activity and the Selective Deprivation of REM Sleep

With the realization that there were two kinds of sleep came the realization that total sleep deprivation might be an approach that confounded the effects of two entirely different deficits. Accordingly, the first attempt was made to study the effect of selective depriva-tion of REM sleep by arousing subjects at the onset of REM periods. The experiments produced some anecdotal findings from the subjects in the area of behavioral disturbance,

but, more important, there was a marked “rebound" in REM sleep time in the all-night sleep recordings immediately after the nights of REM sleep deprivation.

These results suggested that there might be a specific “need” for REM sleep, the rebound on recovery nights representing a “compensation,” and, because of this need, it was further suggested that prolonged REM sleep loss might lead inevitably to some psychological dysfunction or even more serious organic impairment if carried on long enough. The actual temporal organization of the physiological concomitants of REM sleep (EMG suppression closely followed by EEG activation and rapid eye movements) made it relatively easy to carry out deprivation experiments by awakening organisms at the precise onset of each successive REM period, or by placing them in special situations where the motor inhibition of a developing REM period led to an arousing consequence. Thus, the state of REM sleep could be sharply, almost surgically eliminated while leaving NREM sleep essentially intact, and the effects of this “extirpation” could be systematically observed with the hope of clarifying what normal REM periods accomplished for the organism.

A sort of philosophical underpinning or justification for this kind of experiment was that the processes of evolution and natural selection would not have allowed this “thing” (REM sleep), with its unique physiology and

neuroanatomical substrate, to achieve universal distribution among most mammals of all ages unless it held some very important advantage or vital function. An initial offshoot of the very first attempt to understand the function of REM sleep was the hypothesis that REM sleep (dream) deprivation might lead to insanity, a formulation markedly influenced by psychoanalytic theories about the psychology of the dream process and metaphorical organization of the psyche. In the early 1960s, probably because of the absence of a biochemical knowledge as well as the above *Zeitgeist,* there was a premature reification of the so-called hydraulic model of REM sleep, with its associated metaphorical constructs of REM pressure, REM reservoir, compensatory rebound, REM quota, and so forth. However, in recent years, there has been an explosive increase in knowledge about CNS metabolic processes. It is therefore no longer appropriate to explain REM deprivation-compensation in metaphorical terms. The REM rebound is a very real and intriguing response and must have a biochemical mechanism.

The Stanford University Sleep Laboratory has been in the forefront of the struggle to understand REM sleep, at least in terms of man- , cat- , and rat-hours devoted to selective REM-deprivation studies. A number of experiments undertaken by the Stanford group were essentially open-ended, i.e., the end point was not defined in advance. Rather, organisms were to be selectively deprived of REM sleep until clear-cut effects were seen. It was confidently expected in the beginning of these efforts that if the procedure

were carried on long enough it would be life threatening, and that prior to this terminal eventuality, serious derangements of behavior would be observed. A number of spectacularly long (up to seventy consecutive days) deprivation experiments were carried out in laboratory animals.

As early as 1965, we were forced to conclude, despite the dramatic and highly consistent alterations in recovery sleep (enormous REM rebounds) that REM periods in the adult animal did not serve a vital function, and that the organism could probably live indefinitely without them. This conclusion was published in several places (see 66, 67) including Volume III of the first edition this *Handbook* in 1966. “These results strongly suggest that REM sleep does not perform a vital function in the adult cat.”

The possibility that there might still be some harmful effect of REM sleep loss in susceptible individuals was tested by REM-depriving schizophrenic patients." In human studies, chronic administration of monoamine oxidase inhibitors was found to completely suppress REM sleep and when administered for many months with periodic testing of the REM suppression did not produce adverse psychological effects. In some instances, REM sleep was completely suppressed for as long as a year. The overall results in animals and man indicate that REM sleep deprivation per se is not harmful and support the conclusion reached by Vogel that REM suppression does not lead to psychosis. In a roughly similar vein are the findings of Kales

et al. in their sleep studies of long-term barbiturate addiction. To be sure, withdrawal from any of these REM suppressive drugs, particularly after prolonged usage, is likely to be fraught with difficulties, but the absence of discernible REM periods for a year or more would seem to eliminate in a most conclusive manner the possibility that these periods in themselves serve a vital function, or that their prolonged absence would play a role in the genesis of psychotic disturbances. It is important to emphasize this point very strongly because it is our impression that aphorisms such as "dreams preserve sanity" and "loss of dreaming may lead to insanity" are still very much preserved in the collective psychiatric consciousness.

There remains one problem to solve in this area however. All of the work cited earlier was done from the point of view of regarding REM sleep as a thing that could, in fact, be extirpated. Our discussion of the so-called process view of sleep should suggest that this concept of REM deprivation might be questioned. For a variety of reasons, we have turned our attention toward phasic activity to illuminate the function of sleep. The basic assumption to be tested is that the function of REM sleep is to permit the efficient discharge of phasic events (PGO spikes). It is difficult to justify this assumption in neurophysiological or biochemical terms, but it is equally hard at the present level of knowledge to refute it on these terms.

If we recall that nearly 15 percent of the total number of PGO spikes are

discharged in NREM sleep and that every REM period is preceded by NREM-PGO spike discharge, we can see that REM sleep deprivation per se cannot solve the problem. In the first place, as REM sleep deprivation proceeds, there is the well-known effect of an increasing number of REM periods that must be interrupted. Since a finite number of PGO spikes occur before each arousal, it is obvious that the total number can become very large. Secondly, there is evidence that the "intensity" of PGO spike discharge increases in *both* REM and NREM sleep as a function of prior REM deprivation. Thus, at some point, the daily count of NREM-PGO spikes would presumably equal the total number discharged during REM periods in a typical baseline day. In other words, if the function of REM sleep was somehow involved in phasic activity, the function would be *totally* fulfilled in NREM sleep. At this hypothetical point, no further deprivation effect would accumulate even if the selective deprivation of REM periods were continued indefinitely.

These arguments led to a painstaking series of experiments that essentially consisted of making the REM deprivation arousal a little earlier so that the NREM- (or pre-REM-) PGO spikes would also be prevented along with all those normally occurring within REM periods.

This procedure is illustrated in Figure 8-4. A glance at the illustration shows that if the animal is aroused at the precise moment indicated by the left arrow a more effective "spike deprivation" is accomplished than if he is

aroused at the onset of the REM period (right arrow). Several cats were deprived in this manner for two consecutive days. In addition, the same cats served as their own controls by undergoing a "standard" REM deprivation procedure for an identical amount of time. The latter procedure produced the usual result in terms of a REM rebound and increased number of REM periods. The spike deprivation procedure, which was essentially conventional REM deprivation plus the elimination of additional NREM-PGO spikes, produced a picture that was identical to a longer period of REM deprivation. In other words, there were larger REM rebounds. These results are illustrated in Figure 8-6. They clearly, albeit indirectly, support the hypothesis that the essential ingredient of REM periods is phasic activity.

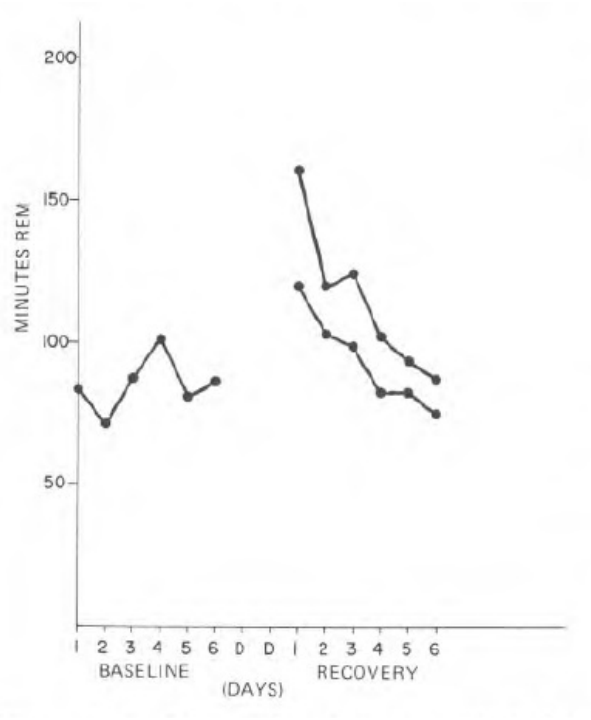

Figure 8.6.
The results of classical REM sleep deprivation versus spike deprivation in one representative cat. The minutes of REM sleep per day on an eight-hour schedule (baseline) are plotted on the left. The upper curve on the right shows the daily REM times immediately after two days of spike deprivation (D), and the lower curve is after two days of REM deprivation.

The point of all this discussion is that conclusive tests of whether or not there is a need for REM sleep have not yet been done. While the "PGO spike hypothesis" may seem a little far-fetched (i.e., what useful function do PGO spikes perform?) it is still a possibility that must be ruled out before we can conclude there is no need for REM sleep or any of its processes. The same

consideration applies to the long-term administrations of powerful REM suppressant drugs, e.g., monoamine-oxidase inhibitors (MAOIs), since careful monitoring in cats has not been done to see if there has been a buildup of phasic activity (PGO spike) discharge in NREM sleep. In short-term studies of MAOI in cats, there appears to be a complete suppression of PGO spike activity, but most observations have been casual at best, and only of a few days duration. Finally, there is still the difficult question of whether absence of the PGO waves per se means that the phasic activity function is not being discharged. This latter is further considered in the section on "Phasic Activity and a Theory of Psychosis."

Tonic Motor Inhibition and Narcolepsy with Cataplexy

It has been noted that motor inhibition is an important process associated with REM sleep. We will see that the syndrome of narcolepsy with cataplexy may be regarded as a disorder involving abnormal occurrences of this and other REM sleep components.

Narcolepsy is always characterized by recurring episodes of daytime sleep. Such sleep episodes may be related to fatigue, boredom, monotony, or drug ingestion, but are most characteristic of the illness when they occur in inappropriate situations. Cataplexy is often involved in narcolepsy. Cataplexy is defined by a rapid loss of voluntary muscle control leading to partial muscle

weakness or a complete body collapse. The cataplectic episodes are usually quite short, lasting only one to ten seconds and rarely as long as one minute. Cataplectic attacks are characteristically precipitated by sudden strong emotion, most typically laughter and anger, although being startled, fear, and other emotions may be involved. Cataplexy may also occur without any precipitating emotion on rare occasions.

The mechanism of this generalized motor inhibition is not clear. Pompeiano and his co-workers' have shown, however, that the tonic inhibition of REM sleep descends from the brain stem to the spinal cord in the ventral halves of the lateral fasciculi. Rostrally, there is evidence that the locus coeruleus is involved in REM sleep inhibition, and caudally the lumbar spinal cord has been implicated. Such inhibition may involve cholinergic mechanisms since from a behavioral and global point of view generalized motor inhibition can be produced by focal injection of cholinomimetic drugs into the pontine reticular formation.'' Similar nonreciprocal inhibition can also be produced by electrical stimulation of areas such as the orbital cortex and the ventromedial medulla in the lightly anesthetized cat. However, most individuals who are investigating these phenomena assume that the medullary inhibitory area of Magoun and Rhines is some sort of final common inhibitory pathway.

Other manifestations of the narcolepsy-cataplexy syndrome are the so-

called auxiliary symptoms: sleep paralysis, hypnogogic hallucinations, and disrupted nocturnal sleep. Sleep paralysis consists of episodes of paralysis occurring at sleep onset or at the end of a sleep period. Patients report that they maintain consciousness during these episodes. Although the episodes are not precipitated by emotion, they are often associated with great anxiety generated by the helplessness, which usually persists for several minutes. Hypnogogic hallucinations are intense and vivid, often frightening hallucinations occurring at the onset of sleep. Finally, narcoleptic patients may experience multiple arousals and frightening dreams during the night.

Thus, just as we conceive of motor inhibition and endogenous sensory input (presumably heralded by phasic activity) as REM sleep processes, we can also conceive of narcolepsy-cataplexy as a disorder involving the uncoupling or disassociation of such processes from the normal wakefulness-sleep cycle.[4]

Phasic Events and the Psychophysiology of Dreaming

An area of sleep research that has certainly received both theoretical and practical implementation by the notion of independent processes within sleep is the psychophysiology of dreaming. This area is concerned with the physiological activities that correlate with (a) the presence or absence of dreaming in humans and with (b) specific elements of dream content within

the overall dream episode. The ultimate goal is to understand the special CNS events that are specifically involved in the genesis of complex hallucinatory experiences during sleep and, by implication, hallucinations that occur abnormally during wakefulness.

In the beginning, this seemed to be a relatively simple problem. The discovery of REM sleep and the early work that showed a startlingly high incidence of dream recall when subjects were aroused from REM sleep periods and a contrastingly low incidence from NREM periods (see 275) seemed to settle the issue. The terms, REM sleep and dreaming sleep, were treated as being exactly synonymous, and it seemed that further investigations of the "unique" neurophysiology of the REM state would lead eventually to a description of the brain processes giving rise to the remarkable hallucinatory experiences of dreaming. The concept of a sharply differentiated physiological substrate underlying the two basic sleep states reinforced these expectations.

Unfortunately, the conceptual identity of REM sleep and dreaming was soon undermined by a steady flow of results that continued to show that a substantial amount of dream recall could be elicited from NREM sleep arousals. An attempt was made to develop definitions based on quality and quantity of dream recall so that, although one could not say that mental activity was not totally absent in NREM sleep, one could say that it was

quantitatively different from that which occurred in REM periods.

However, when investigators looked at the discriminability of REM and NREM reports, it was clear that many NREM reports could not be discriminated from REM reports defined as "full-blown" dream recall. This was particularly true when the reports were elicited from sleep onset NREM. In other words, it appeared that intense, complicated, bizarre, emotional, hallucinatory experiences could occur at the onset of sleep as well as occasionally in other NREM stages.

This situation posed a dilemma for those who were interested in the neurophysiological substrate of dreaming and hallucinations; but a way out of the dilemma suggested itself when it was realized that certain events thought to be ineluctably linked to REM sleep also occurred in NREM sleep. These events were the PGO waves or phasic activity. Their typical occurrence in the NREM sleep just prior to REM periods is illustrated in Figure 8-4, but the waves or spikes also occur in a widely disseminated fashion throughout NREM intervals.

It was almost inevitable that the PGO spike should become the focus of attention when investigators began to look for a single "marker" that could account for dreaming in both REM and NREM sleep. In terms of looking for more specific events *within* REM periods, the suggestion was made quite

early that the dream was experienced as “real” and the major problem would be to find the neural events that were effectively substituting for sensory input. The brain-stem generation of PGO spikes as described by Brooks and Bizzi and Jouvet, and the apparent distribution of this activity along the visual-oculomotor pathways definitely suggested a quasi-sensory function. Furthermore, these studies clearly showed that the rapid eye movements in the cat were precisely related to PGO spikes, and it was already known that arousals at the very moment when eye movements were being executed within REM periods frequently provided the very best recall of dreaming. Thus, a major shift in viewpoint occurred in the area of dream psychophysiology that suggested that phasic activity would be a much better predictor of dream recall and, hence, a better correlate of dreaming than REM periods. Taking individual rapid eye movements as phasic events, Molinari and Foulkes have carried out an elegant study that compares tonic (REM periods) and phasic events as dream correlates. All of these considerations have subsequently guided what might be called the search for the perfect indicator of dreaming.

It is obvious that phasic activity (short-lasting events) can be conceptualized *within* REM periods in essentially all mammals including humans since the rapid eye movements themselves are phasic events. There is also no problem in identifying phasic activity in NREM sleep in animals where cortical and subcortical recordings can reveal PGO spikes or bursts of

unit discharge. The big problem is to find a phasic event that satisfactorily cuts across sleep states in the human. It should also bear some analogous relationship to the feline PGO waves. K-complexes in the EEG certainly qualify as phasic events, but they do not occur in the EEG of REM sleep. Parenthetically, Pivik and his colleagues have studied the possible relationship of K-complexes and NREM dream recall. They found no simple relationship. Body movements, respiratory changes, heart-rate changes and other relatively nonspecific physiological variables have been examined from this point of view.

The search for a really useful indicator of the presence of phasic activity in the human, particularly during NREM sleep has turned up three promising candidates. The first was described by Pivik and Dement. It is essentially seen as a brief (two hundred to five hundred msec.) suppression of the tonic EMG activity in NREM sleep (see Figure 8-7). Utilizing electrically induced reflex activity, Pivik and Dement were able to show that the phasic EMG suppressions were coincident with active motor inhibitory influences. Similar phasic EMG suppressions were found to occur in the cat during NREM sleep and were often coincident with a NREM-PGO spike (also Figure 8-7). Because of the latter relationship, it seemed reasonable to postulate that the phasic EMG suppressions represented a human analogue of the phasic inhibitory process described in cats by Pompeiano. Although not usually detectable in REM periods because of the absence of the tonic EMG background, on the rare

occasions that this background is *not* totally suppressed plentiful phasic EMG suppressions are easily seen *within* REM periods most commonly in connection with rapid eye movements.

The relationship of phasic EMG suppressions in NREM sleep to recall of mental content was tested by Pivik. Significant results were not obtained. Parenthetically, another relationship has been discovered that elevates the status of EMG suppressions beyond the level of laboratory curiosity. Guilleminault et al. have shown that the motor discharge in *nocturnal myoclonus* frequently follows phasic EMG suppression.

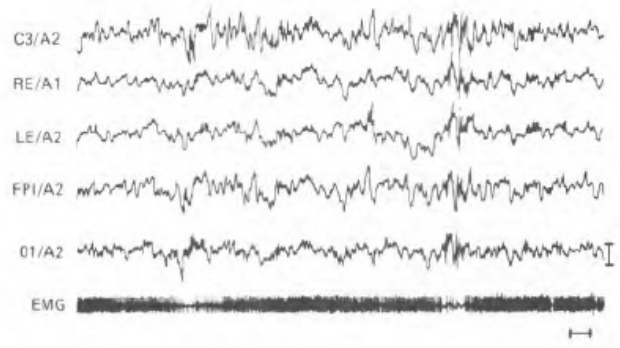

Figure 8.7.
This figure shows phasic (short-lasting) EMG suppression occurring in Stage 3 NREM sleep. Note that a K complex (C_3/A_2) occurs simultaneously with the phasic muscle suppression.

Derivations: all EEG placements use the standard ten-twenty system;

RE/A_1—right eye recorded from right outer canthus;

LE/A_2—left eye recorded from left outer canthus;

EMG—recorded from placements over diagastric muscles.

Calibrations: horizontal one second; vertical fifty μv.

The second phasic indicator is the phasic integrated potential or PIP reported by Rechtschaffen et al. in 1970. These discharges are recorded from ordinary disc electrodes placed near the eye, but the authors were not certain exactly which muscles were involved. However, they felt that the PIPs were exact homologues of similar discharges recorded in the cat that were, in turn, precisely related to PGO spike discharge in both REM and NREM sleep. The

human PIPs have the advantage of being easily seen in both REM and NREM sleep. In the former state, they are clearly related to rapid eye movements although they also appear (as do PGO spikes in the cat) in the absence of ocular deviations. They are distributed throughout NREM sleep, although the discharge rate is clearly higher immediately preceding REM periods than immediately after.

A series of reports by Rechtschaffen and his colleagues' explicated relationships of periorbital PIPs to mental activity in both REM and NREM sleep. These studies also developed a new concept about phasic activity and dreaming, which will probably be very important in guiding future investigations. Four arousal conditions were described by the authors: (1) a "tonic" condition that was characterized by a brief (several seconds) burst of periorbital EMG activity without PIPs; (2) a phasic condition characterized by periorbital PIPs without tonic periorbital EMG activity; (3) a phasic-tonic condition when both of the foregoing were present; and (4) a control condition in which there has been no PIPs or tonic activity for at least one minute. Hundreds of arousals were carried out in these exhaustive studies. The responses were rated in terms of presence or absence of recall of mental content, amount of recall in content reports, and amount of distortion, implausibility, and bizarreness in these reports.

In NREM sleep, the presence or absence of PIPs did *not* predict the

presence or absence of mental content. The latter was, however, significantly predicted by the tonic periorbital activity. PIPs alone were not correlated with an increased probability of obtaining mental content over the control condition. However, if content was present, PIPs were correlated with experiences judged to be bizarre. Similar relationships obtained in REM periods although the tonic condition was not recordable, ostensibly because of the REM associated motor inhibition. We may infer that it exists because tonic potentials have been recorded directly from the inferior rectus muscle during REM sleep in humans.

These studies are extremely relevant to the psychophysiology of dreaming, and, once again, they have introduced a further refinement in conceptual organization of sleep physiology. Thus, there appears to be a process involving sustained activity of a few seconds duration during which thoughts, associations, vague images, etc., are raised to hallucinatory intensity. The correlate of this process is what the Rechtschaffen group call "tonic EMG activity." It is important to avoid confusion when a clear distinction is made between this process which lasts only a few seconds, and the use of the word tonic to describe changes that are sustained throughout the entirety of the REM period as described in the previous section.

A second process, which is indicated by PGO spikes in the cat and PIPs in the human, seems to represent neural events that contribute to distortion

and bizarreness by loosening and disrupting associative connections. Thus, phasic activity per se does not appear to be an indicator of the presence of dreaming, although it is clearly implicated in the overall dream process. This refinement contributed by the Rechtschaffen group makes it possible to understand how activity that seems so characteristic of REM periods and, by implication, so important to dreaming does not predict NREM dream recall.

Finally, there is a very interesting report by Pessah and Roffwarg describing middle ear muscle activity during sleep in human subjects. This activity parallels the occurrence of other phasic events, notably rapid eye movements, but represents a refreshing departure from the visual system that has been so intensively studied. In the cat, there is an almost one-to-one correlation between PGO spikes and phasic discharge in the tensor tympani. This is true in both REM and NREM sleep. However, it is clear from studies of the cat, particularly those of Dewson et al., that a similar dichotomy probably exists for middle ear muscle activity, i.e., very brief phasic discharges versus somewhat longer (several seconds) contractions. The tonic contractions were not necessarily related to rapid eye movements or PGO spikes. In human subjects, the recording technique utilizing acoustic impedence and AC amplifiers does not lend itself to this type of differentiation.

The most fascinating aspect of this work is perhaps the data suggesting a relationship to dream imagery in the auditory sphere (Roffwarg, personal

communication).

Conclusions

Obviously, the neural processes that give rise to sights, sounds, feelings, and thoughts during sleep are very complex. It would seem that this complexity is infinitely beyond the information carrying capacities of PGO spikes. Even the recognition of additional activities beyond the punctate PGO waves or PIPs (i.e., Rechtschaffen's periorbital tonic discharge) falls far short of the presumed complexity. However, it is quite possible that there is a single indicator that "turns on," independent of REM or NREM sleep, when dreaming is present, and that it has little to do with specific hallucinatory percepts. Accepting the Rechtschaffen group's results at face value, the indicator does not appear to be phasic events that are analogous to PGO spikes. A better candidate would appear to be the tonic periorbital potentials. However, at the present time, these EMG discharges lack specificity in terms of attempting to identify some underlying unique neural events. It seems clear that "events of intermediate duration" and phasic events are more likely to coexist in REM periods. In NREM periods, it is obvious that the dream process can occur (tonic potentials) without concurrent phasic activity. In this instance, the associated experiences are presumably coherent and rational or at least more so than we are accustomed to expecting in typical dreams. It may even be that the sleeping subject does not label the experiences as dreams. If the

"intermediate" tonic potentials are absent in NREM sleep, suggesting the absence of dreaming, phasic activity may do nothing unless it actually arouses the individual. If ongoing hallucinatory activity is present, the phasic discharge derails it, disrupts it, etc., and thus may contribute those qualities which we find most characteristic of the average dream. This whole formulation is based on minimal evidence, but, as will be seen, it accounts for certain behavioral correlates of PGO spike discharge in wakefulness better than any yet proposed.

Psychophysiology of Dream Content— the "Scanning" Hypothesis

In addition to indicators of the presence or absence of dreaming that will satisfactorily account for the relative incidences of dream recall in REM and NREM sleep, there is a concern about indicators which will "predict" specific content. For example, if there was a high heart rate in a REM period one might expect to elicit a frightening or exciting or nightmarish dream upon awakening the subject.

Most of the work in this specific area has focused around one controversial, empirical finding, namely, that a direct relationship exists between the rapid eye movements and hallucinated visual images of REM dreams. The correlation of specific items of content or emotion with other peripheral measures has been suggested but not extensively investigated.

Much of the latter work is reviewed in a paper by Roffwarg in which he also discusses and dispenses with a number of issues he feels are "irrelevant" to the eye movement dream relationship in human adults such as occurrence of rapid eye movements in newborn infants, decorticate humans and animals, the nonspecificity of certain neural events during REM periods, etc.

The basic procedure in investigations on eye movement mentation relationships involves arousing subjects during REM periods with the arousal specifically related to a temporal sequence of rapid eye movements measured with horizontal and vertical eye leads. This electro-oculogram (EOG) gives a precise record of the temporal sequence of eye movements leading up to the arousal. An interrogator, who awakens the subject, asks questions about the dream experience and from the dreamer's answers attempts to predict the sequence of eye movements leading up to the awakening. Actually, a detailed prediction is impossible unless the implied eye movement sequence is very characteristic. Thus, if the dream imagery is all in the vertical plane, the interrogator might predict eye movements only on the vertical plane and this could be ascertained from the EOG. On the other hand, the kind of activity that is associated with a few seconds of frantic looking around in all directions is impossible to dissect and describe with any accuracy at all simply because of its intensity and complexity.

Alternative procedures involve (a) attempting to match a limited

number of EOG tracings with their associated dream narratives, say five of each, and (b) limiting the prediction to the final eye movement that immediately precedes the awakening.

In the early phase of correlating eye movement patterns and dream content, there were several reports that supported such a relationship, culminating in the very positive report of Roffwarg and his colleagues.

A number of years passed before the relationship was specifically tested by other investigators. Moskowitz and Berger, utilizing a matching procedure, found that their results were not significantly better than chance. Jacobs and his colleagues,' using DC EOG techniques, also found no relationship. Finally, Krippner et al. added negative data from a single subject. Thus, the original optimistic and potentially biased reports were not confirmed.

The most recent study by Bussel et al. adopted a number of control procedures that helped to clarify the issues. It is clear that the sheer difficulty of obtaining dream recall of sufficient detail and accuracy so as to permit a correct prediction is a major source of error. Any forgetting or inaccurate reporting will make a correct prediction impossible. Bussel et al. conclusively exposed this error source by carrying out their study using EOGs and recall from wakefulness as well as REM sleep. They showed that the ability of an interrogator to predict the direction of the last eye movement based 011

recall of visual imagery and gaze fixation from REM arousals was minimally accurate, but significantly better than chance, given a large number of data points. *Further, the level of accuracy and significance was exactly the same in the waking trials!* Thus, it is clear that any study that purports to test this relationship with all its inherent difficulties must be based on a large amount of data. It is our opinion that there will be continued attempts to work on this problem in the years to come, and that the evidence favoring a relationship will begin to mount.

In spite of the relatively few studies, the possibility of a relationship is more than a laboratory curiosity. It is an important issue on two counts. In the first place, the establishment of such a relationship would allow judgment as to whether the dream actually occurred as sensed by the dreamer. Although dreaming is widely reported, the certainty of its occurrence is in doubt. Even the correlation between eye movements and the dream report would not be absolute proof, but the principle of parsimony would allow no other conclusion if we awaken a sleeping subject and he claimed that he was watching a ball thrown up and down, and, prior to the arousal, we had recorded up-and-down eye movement deflections. Secondly, a lack of correlation between neurophysiologically determined events such as eye movements and the dream experience would seriously undermine the axiom that events in the mind have physical and potentially measurable counterparts in the brain soma.

Dreams

The basic unity underlying much of what is described under this heading is the use of polygraphic monitoring of sleep to define sleep states and the utilization of this information for anatomical, physiological, pharmacological, biochemical, and, in particular, psychological correlation. In general, research in this field is called sleep *and* dream research. Thus, it seems worthwhile to discuss dreams briefly and to ask what has been learned about dreaming as a result of laboratory sleep research.

In the twenty-plus years since the discovery of REM sleep, a number of quantitative aspects of the occurrence of dreaming have been clarified. Certainly there is much more dreaming per se than pre-REM investigators thought. We now know something about the time course of the dream; and we have much more data on the content and characteristics of typical dreams and dreams in a variety of personality types and pathological subjects; and we know something of the effects of presleep and ongoing stimuli on these variables. However, much of this work was conducted in the late 1950s and early 1960s. After that it would seem that the dream subsection of modern sleep and dream research "attained a plateau from which it seems steadily more difficult to reach higher ground." This opinion, which is in some ways as shattering to the smugness of current sleep research as the statement that "the emperor has no clothes," was made by Foulkes in a remarkable position

paper delivered at the 1973 meeting of the Association for the Psychophysiological Study of Sleep (APSS). As Rechtschaffen cautioned a number of years ago, "if we do not keep our attention on the psychology of the dream, we might find out a lot of the biology without knowing very well what it is the biology of."

Foulkes addressed himself to such questions as "what do dreams mean?" and "why do we dream what we do?" and "why are dreams the way they are?" and so on. And he concludes that almost 110 progress has been made since Freud's monumental efforts to answer these questions. In his book, *The Interpretation of Dreams,* Freud propounded both a theory of dream formation and a method of dream interpretation. It was Foulkes's thesis, unchallenged by any of his discussants that either the modern techniques of sleep research have not enabled investigators to confirm or refute Freud's theories or that ingenious investigators have not pursued these questions with tenacious vigor. The situation appears to be one in which those who use the technique of dream interpretation remain unconcerned with its ultimate validity and continue to confuse meaning and causality while those who carry the banner of science and research cannot or will not devise direct experimental tests of psychoanalytic theories about dreaming.

With the exception of certain investigators who have utilized content analysis with outstandingly productive results, money, talent, and dedication

are relatively absent in the areas outlined by Foulkes.

Although, the content findings can be quite interesting—e.g., women dream more often of strangers than do men and so on—again, the important questions about dreaming are not addressed. That is, there must be a set of rules for determining dream content that can be "discovered."

It seems possible that a carefully systematic study of the effects of external stimuli on dream content might reveal some of the rules by which one set of psychic percepts are transformed into another set of dream percepts. In a recent study by Augustyn et al., characteristic auditory stimuli were presented during REM sleep. It is of interest that the transformations and incorporations of these stimuli into dream content were about half visual and half auditory. Why did the sound of a locomotive whistle produce the image of a train in some dreams and only the sound of a train in others? It is not unthinkable that there is some reason for these differences, some explanation to be found.

Moreover, to what extent will physiological state, e.g., hunger, thirst, stress, determine dream content? This aspect has been studied with equivocal results, f but the studies have been only preliminary and far from systematic.

Finally, innumerable studies of REM sleep deprivation have demonstrated a so-called physiological need for REM sleep (i.e., REM

rebound), and investigators, assuming the identity of REM sleep and dreaming, have postulated a similar need for dreaming. Rut little attention has been directed to simply the psychological need or excuse for dreaming. What, if anything, do dreams do for us in and of themselves, regardless of their physiological correlates? This question and those and asked by Foulkes are the kinds of problems that should generate more investigation in the future.

It seems obvious that much future work is needed to establish and clarify the role of the psychological side of dreams and the psychic economy of the organism. The dream must regain its status as a psychological event, while at the same time retaining its position as a neurophysiological process.

Selective REM Sleep Deprivation and Schizophrenia

As was noted earlier, an almost inevitable consequence of selective REM sleep deprivation is a usually substantial REM sleep increase, above baseline levels in the immediate postdeprivation (recovery) period. In the nondrug technique, which utilizes continual instrumental interruptions of REM periods at their beginning, the size or degree of the rebound is a function of the duration of the deprivation period. Thus, for extended periods of deprivation in healthy animals, the REM rebound certainly seems to be an inevitable response. Ry interrupting REM periods, some sort of biochemical-

metabolic-physiologic process is set into motion that drastically alters the REM-NREM ratio in favor of REM sleep.

We do not recall any instance in a normal cat or rat where a REM rebound failed to appear after two or more days of REM sleep deprivation. In addition, substantial REM rebounds appear after certain drugs that suppress REM sleep are withdrawn such as amphetamines, monoamine-oxidase inhibitors, and barbiturates. Certain exceptions have been noted. If REM sleep is substantially reduced in the cat by diphenylhydantoin or by electroconvulsive shock, no rebound appears. Finally, on certain occasions, the development of a febrile illness has been observed to interfere with an expected REMS rebound.

It must be emphasized, however, that the rebound is never a linear function. Dement et al. have summarized their extensive REM deprivation studies in animals and have reported that there appears to be a limit to the size of this rebound in two ways: the REM percentage in their studies was rarely above 70 percent even during a lengthy, *ad libitum* sleep period; and in cats, at least, after twenty-five to thirty consecutive days of deprivation, no further increases in recovery function could be detected. Such lengthy periods of REM sleep deprivation have not been done with humans, but in several cases,' subjects were REM sleep deprived as completely as possible for ten to fifteen consecutive nights and monitored during the day to rule out napping.

In these subjects there were spectacular shifts in the structure of sleep to allow for a great increase in total REM sleep time and REM sleep percentage.

There is, however, some problem when relatively brief durations of selective REM sleep deprivation are carried out in human subjects—"normal human volunteers." In the first study of REM deprivation, there was a questionable response in one subject, who was REM deprived for four nights, although he was not monitored during the day. The size of the rebound varies considerably in human subjects, but a number of nonspecific factors usually play a role. For example, there is the structure of human sleep with widely spaced REM periods such that if the morning awakening occurs a little prematurely or after a long NREM period, the REM percent is artifactually reduced. In addition, humans generally experience a certain amount of NREM sleep reduction that tends to interfere with the expression of REM sleep. It was felt by Dement that these problems would have little effect when REM sleep deprivation periods were extended beyond the usual two to five nights and the evidence to date, which is minimal to be sure, suggests that this is true. However, such lengthy durations are difficult to accomplish in psychiatrically disturbed subjects and, therefore, data in these subjects must be compared to data in normal humans who have undergone short durations of REM sleep deprivation. It is in this area that some question arises, i.e., will all "normal" humans show a rebound in REM sleep following deprivation, or are there some apparently normal individuals who lack this attribute or

capacity? Cartwright et al. feel that a group of "noncompensators" exists with distinguishable personality traits on the basis of failing to rebound after three nights of deprivation. In addition to those mentioned above, possible artifactual causes of rebound failure are sleeping during the day, improper deprivation procedure, covert drug ingestion (for example, neo-synephrine nose drops), and failure to carry out recovery monitoring long enough. With regard to the latter, there is clear evidence that a rebound can be delayed. As a test of the ultimate validity, one of the Cartwright noncompensators was REM deprived a second time by the Stanford group with twenty-four-hour monitoring and prolonged recovery studies. The rebound failure was confirmed, but the patient was apparently an ambulatory schizophrenic.

All during the decade when speculation was rife that REM sleep deprivation might play a role in the pathogenesis of the psychotic state, there was a feeling that the REM deprivation technique ought to be applied to schizophrenic patients as a crucial test of this notion, the expectation being that such a procedure would drastically worsen their condition. It was indeed this expectation, not to mention the substantial complexities of such an experiment, that probably caused many investigators to hesitate. Nonetheless, the first reports by Azumi et al. and Zarcone et al. of REM sleep deprivation in schizophrenics appeared in 1967. The former group selectively REM deprived three "chronic schizophrenics" for five consecutive nights. Two of the three patients did not experience a rebound. The latter group has

carried out extensive studies of this phenomenon. In their overall program, they selectively REM deprived actively ill schizophrenics, remitted schizophrenics, and nonschizophrenics for two nights; and in one actively ill patient, REM deprivation was carried on for eight nights with the aid of nighttime amphetamines. This, group attempted to reduce some of the confounding variables by keeping phenothiazine medications absolutely constant throughoutthe period of study and by carefully delineating the clinical state of the patient population. The observations focused on two groups of chronic schizophrenics with evidence of deterioration in occupational and social functioning. The patients in one group were experiencing active symptomotology, hallucinations, thought disorders, bizarre motor activity, and affective abnormalities. The continuing symptomotology was accepted by these patients and seemed to explain their situation and seemed, in a way, to communicate their anxiety. The second group of schizophrenics was as clinically differentiated from the first as possible, consisting essentially of patients with no active symptomatology whatsoever. All patients were subjected to two consecutive nights of selective REM sleep deprivation with prior baseline and subsequent recovery recordings. A major consideration in these studies was the fact that one patient was actually in both groups as a result of clinical change, and thereby served as his own control. The latter particularly applies to the possibility of a coincidence between some genetic failure in the mechanism subserving the

REM rebound and the schizophrenic state. Nine patients were studied in the activity ill group, and eight failed to show a postdeprivation rise in total REM sleep time (REM rebound). The ninth showed a small rebound that was not nearly as great as that seen during remission. Over an entire five-night recovery period, they averaged only 5 percent makeup of the REM time lost on the two deprivation nights. One patient, a hebephrenic who constantly hallucinated, was REM deprived for an extended period of eight consecutive nights and he also failed to show the usual compensatory REM rebound. On the other hand, the patients in remission, including the one who had been studied while actively ill, all showed substantial rebounds averaging over 200 percent makeup following deprivation. Normal controls and nonschizophrenic control patients, while showing considerable variability, averaged a 50 to 60 percent REM sleep makeup.

The studies of the acutely ill patients appeared to be in marked contrast to the report of Vogel and Traub and to the study of De Barros. The foimer investigators carried out the REM deprivation procedure with five chronic schizophrenics for seven nights by awakenings and by administration of nighttime phenobarbital and amphetamines. Four of these patients were taking phenothiazines and all patients had an increase in REM sleep above baseline levels in the postdeprivation recovery period. De Barros carried out the REM deprivation for three nights each in six chronic schizophrenics and reported that all six experienced a “REM rebound.”

The whole question of REM rebound in acute schizophrenic subjects was further investigated by Gillin and Wyatt. These investigators have concluded that actively ill schizophrenic patients do indeed fail to have a normal REM rebound following deprivation of REM sleep. They did not study patients in remission. Their studies were exceedingly careful and represent very strong support.

Without making interpretive comments on this phenomena, we believe the failure of REM rebound is a valid concomitant of schizophrenia in at least the acute phase, and, because of this, it is in some way related to the active psychotic process. If the relation to the clinical state, i.e., normal or excessive rebound when the psychotic process was in abeyance, was confirmed it could be a very meaningful correlate. Certainly, in view of the difficulty of achieving some satisfactory pathogenic explanation of schizophrenia, this phenomenon warrants further investigation. Gillin and Wyatt present an extensive discussion of their findings in this area and in other areas relating to a general theory, which will be discussed in the succeeding section.

One of the early interpretations made by Zarcone et al. to account for the rebound failure was based on a somewhat metaphorical notion of a phasic activity quota either being discharged in REM sleep or building up. It was speculated that phasic activity was being discharged in the waking state in the “actively ill” patients and therefore nothing “built up” to instigate the REM

rebound. The process view of sleep says nothing about any kind of quota. However, if it is the reduction in phasicactivity that is implicated in the REM deprivation recovery phenomenon, certainly the phasic activity could be discharged at other times. One of the ways of accounting for the limit to the REM deprivation effect is that eventually as much phasic activity is occurring in NREM sleep as originally occurred in REM periods. There is obviously a strong resistance to such a disassociation. Otherwise, there could be no REM deprivation effect since phasic activity would immediately shift to NREM sleep.

Phasic Events and a Theory of Psychosis

It is not easy to generate enthusiasm or even interest about a theory of psychosis in these days that have seen so many prior proposals. One of the most recent is a hypothesis put forth by Stein that involves the endogenous production of 6-hydroxydopamine in schizophrenics. Behavioral effects in humans have obviously not been studied, but Stein feels that certain behavioral effects in rats are analogous to pathological processes in schizophrenics.

The theory that will be discussed in this section has one unique aspect. It is based on the notion expressed by many theorists that dreams represent nonpathological psychotic activities. Such activities are nonpathological

because all of us dream and because what we do in our dreams is safely sequestered in the minds of our paralyzed bodies. This view further holds that the mechanisms underlying the dream state and the dream experience must also be involved in the psychotic activities considered by most to be pathological. The notion that dreams and psychoses are related has had many proponents. For example, we have the statement, "We ourselves, in fact, can experience in dreams almost all the phenomena to be met with in insane asylums", which is attributed to Wilhelm Wundt. Hughlings Jackson said, "Find out about dreams and you will find out about insanity." The pursuance of this general notion is based upon an abiding faith that somehow the psychotic state and REM sleep-dream processes are related.

The various theoretical convolutions and ramifications of this notion have been considered at length in at least two papers, and we will remain concerned here as much as possible only with the empirical facts.

The basic tenet of this theory or hypothesis is that psychosis represents some aspect of the dream process intruding into the waking state. Such an intrusion would not have to be the experience of full-blown hallucinatory dream images in wakefulness, although it could at times. We already know that the dream process, insofar as it is related to sleep mechanisms, is complex and involves at least several independent systems. Thus, the disorganization of the psychotic state could be produced by the intrusion of

only one of those systems.

The PGO spike was actually discovered by Jouvet and his colleagues, who were the first to undertake' brain-stem recordings during REM sleep in the cat. The Lyon investigators were also the first to show that the PGO waves could be entirely dissociated from normal REM periods. Matsumoto and Jouvet found that REM periods in the cat were abolished by high doses of reserpine, but that PGO spikes were continuously discharged throughout the interval of REM suppression. Although the reserpinized state was clearly not wakefulness, it was clearly not REM sleep. A more impressive demonstration, however, came from this group when Delorme et al. showed that administration of the serotonin depletor, parachlorophenylalanine, was followed by a release of PGO spikes in what was both behaviorally and polygraphically an apparently normal waking state. Similar findings for reserpine have been reported by Brooks and by Monachon et al. The observations of the Stanford group on PCPA administration were focused on a detailed account of the behavioral correlates of waking PGO spikes and a careful description of the changes in sleep states and PGO spike distribution as the treatment progressed. Both of these areas gave information that could be effectively related to observations in human subjects and patients.

Repeated direct simultaneous scrutiny of both behavior and subcortical EEG has made it absolutely clear that the occurrence of a PGO spike during

wakefulness in the PCPA treated animal, or, better yet a burst of spikes, is associated with a behavioral response in the complete absence of any external sensory event. There is some remaining controversy about whether or not these behavioral responses in the cat could be said to resemble full-blown hallucinatory experiences. Probably not. They appear to be more appropriately described as intrusions and disruptions of the ongoing perceptual-behavioral stream. The affected cat does appear, when left to his own devices, almost continually preoccupied with these internal disturbances; and in this regard, he is uncannily reminiscent of the preoccupied psychotic. Occasionally, there is a brief, wild, agitation that seems to correlate with a very intense burst of spike activity, but, on the whole, the behavior of the cat is much more of an orienting, searching, distracted, repeatedly disrupted kind of behavior. Often, it is as if someone was pounding or knocking on the wall of the cage, and the cat was searching for the source of the disturbance. Other behavioral disturbances have been reported in PCPA treated animals,-- but are still somewhat controversial. The key principle is that the cat's behavior during PCPA administration is no longer totally determined by the events in the real world, and it is no longer a series of completely "rational" responses to events in the real world. Something continually intrudes and that something appears to be the phasic event of REM sleep.

The sleep changes associated with chronic PCPA treatment in the cat

are also worth noting. There is a transient insomnia that usually develops on the third day of PCPA treatmentBASELINE

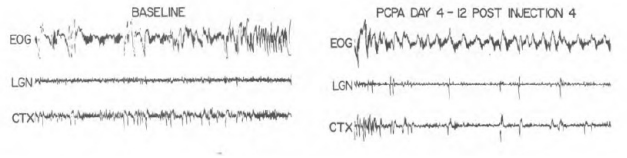

Figure 8.8.
Emergence of REM-type PGO waves into wakefulness following four days of PCPA treatment.

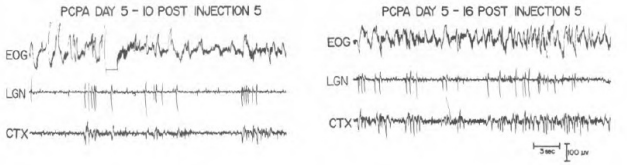

Figure 8.9.
The development of more dense waking PGO activity late in chronic PCPA treatment.and lasts three or four days. Then, there is a return of considerable amounts of both REM and NREM sleep. A major difference between normal sleep and PCPA sleep is that the number of PGO spikes during PCPA-REM periods is greatly reduced while the overall number during NREM periods is greatly increased. The major overall effect appears to be a kind of dissemination or complete lack of regulation of the spike activity so that it is discharged with approximately equal intensity in all behavioral states. This intensity is somewhat lower than in the normal cat where most of the PGO spike activity is concentrated in REM periods.

A final pertinent observation in these PCPA treated animals involves REM sleep deprivation. All changes can be quickly reversed by administration of 5-hydroxytryptophan (5-HTP). In the chronically PCPA treated cat, REM sleep deprivation does not appear to elicit a rebound. This is illustrated in

Figure 8-10. On the other hand, if REM deprivation is carried out in the cat, and PCPA is given only during the recovery period, the REM rebound is greatly enhanced until the fullblown PCPA effect is evident. The parallel of this rebound failure in the PCPA cat and the diminished or absent response to selective REM deprivation in acute schizophrenics discussed in the last section is obvious.

Neurochemical Regulation and Basis of the PGO Spike

There seems to be broad agreement that serotonergic neurons are involved in the regulation of phasic activity. This regulation appears to be inhibitory. Certainly, a primary effect of the inhibition of serotonin synthesis is the correlated reduction of serotonin in all brain areas and the emergence of waking PGO spikes. Lesions in the raphe nuclei that destroy substantial numbers of serotonergic neurons lead to exactly the same dual effect. In the case of PCPA, the effects are reversed by small amounts of 5-HTP; in the case of lesions, they are not.

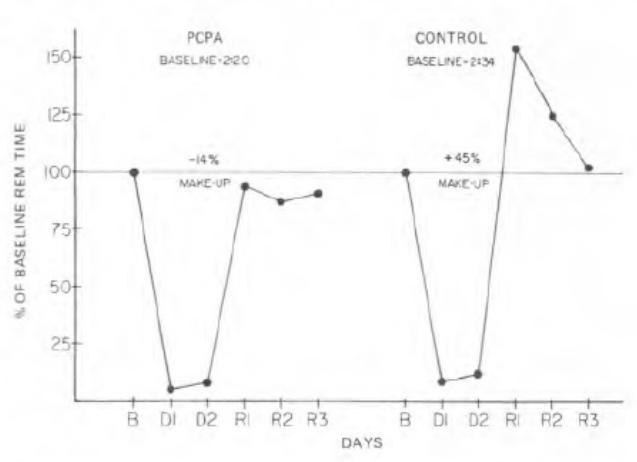

Figure 8.10.
Rebound failure in a cat chronically treated with p-chlorophenylalanine (PCPA). The daily REM time values in this cat during the two deprivation periods are expressed in percent of the baseline REM sleep time. Since there is usually a small reduction in the daily REM time after an animal has been stabilized on PCPA, 100 percent of baseline actually represents a different value in the PCPA condition versus the control condition. These values are indicated on the graph in hours and minutes. As can be seen, although this cat was averaging two hours, twenty minutes of REM sleep per day on a twelve-to-twelve schedule (twelve hours on treadmill—twelve hours in recording cage) in the PCPA condition, two days of deprivation resulted in no makeup at all. The REM rebound following the similar period of deprivation prior to the administration of PCPA was of normal size.

Further aspects of the neurophysiology of PGO regulation were described by McGinty and Harper[5] who measured firing in raphe units in relation to PGO waves. These units continued to fire at all times in wakefulness and NREM sleep. They became quiescent when NRE-MPGO waves appeared and remained so throughout the following REM sleep period.

Unpublished results by Jacobs and Dement[6] indicated that electrical stimulation of the raphe nuclei had the effect of blocking PGO waves in normal cats.

Jouvet and his colleagues have felt that PGO waves are catecholaminergic. Their major evidence is that lesions in and around clusters of catecholaminergic cell bodies tend to be followed by a reduction or disappearance of PGO waves. In addition, alphamethyl-Dopa, which is metabolized to the false transmitter alphamethylnoradrenaline, rapidly and effectively suppresses PGO spike activity.

The most damaging evidence against this notion are the several studies with alphamethylparatyrosine (AMPT) which selectively inhibits the tyroside hydroxylase and leads to a depletion of noradrenaline and dopamine. This compound is nephrotoxic, however. In an effort to overcome this nephrotoxic effect, Henriksen and Dement administered AMPT to cats by intravenous drip in a dosage calculated to be supramaximal and saw that there was a modest increase in the amount of slow wave sleep and, more importantly, an increase in the amount of REM sleep. Thus, it is very difficult to attribute the PGO discharge to catecholaminergic neurons. Furthermore, Haefely and his colleagues have elaborated an hypothesis that catecholamines are actually involved in the inhibition of PGO spike activity.

The Stanford group has pointed out that REM sleep is acutely susceptible to disruption by pharmacologic intervention in the normal animal.Thus, it is difficult to study the neurochemical basis of any single component. If a drug treatment blocked tonic muscle inhibition, produced nausea or discomfort, or raised the arousal level, it would probably block the occurrence of REM sleep, and therefore, secondarily, it would also block the appearance of PGO waves. Given the opportunity of producing a dissociation of PGO waves from REM sleep by PCPA treatment, this phasic activity can then be studied without concern about other REM components. Thus, Jacobs et al. have studied waking PGO waves following PCPA treatment after administering the following presumptive receptor blockers: pimozide, a dopamine receptor blocker; phentolamine and phenoxybenzamine, alpha-adrenergic blockers; propranolol, a beta-adrenergic blocker; and atropine, a cholinergic blocker. The results were dramatically unequivocal. None of the four catecholamine receptor blockers had a significant effect on the PGO wave discharge. On the other hand, atropine, in very low doses in chronic PCPA cats totally blocked the occurrence of PGO waves and the effect could be partially reversed by eserine. Henriksen et al. administered atropine to REM deprived normal cats and found that bursts of PGO waves were blocked while REM periods per se and muscular twitching were not.

Interest in a postulated relationship between PGO waves and hallucinations stimulated electrographic observations on cats treated with

hallucinogenic drugs. It might be expected that the administration of hallucinogenic compounds would be accompanied by a discharge of PGO waves in wakefulness, particularly if hallucinatory behavior ensued. This does not appear to be the case. Henriksen et al. have administered hallucinogenic doses of LSD and, following the lead of Jones, have also given tropolone, a catechol-o-methyl transferase inhibitor, to cats. Fullblown hallucinatory behavior was easily produced, but in no case was this behavior accompanied by clear-cut discharge of typical PGO spikes. These data may not support the alleged role of PGO spikes in hallucinatory conditions, but neither do they completely disallow it. In the Jones preparation, PGO spikes were not precisely coincident with hallucinatory behavior, but they did appear in wakefulness immediately after the abnormal behavior had subsided.

Parallel Studies in Humans

PCPA has been given to human subjects by Wyatt et al. These authors felt that it did not produce the appearance of severe behavioral abnormalities or hallucinations. Boelkins carefully observed the behavior of three monkeys given PCPA in a quasi-natural environment. He did not report hallucinations or maniacal behavior. On the other hand, he did observe certain inappropriate responses as well as substantial depression.

It is well-known that phenothiazines have an ameliorative effect in

psychotic, nondepressed humans. Cohen et al. have recently reported that chlorpromazine administered to the PCPA cat at the height of the PCPA effect with insomnia and waking spikes will immediately reinstitute sleep and suppress PGO spikes.

A consistent effect of PCPA in the cat is a change in the REM-NREM ratio of PGO spike intensity. In other words, the intensity goes down in REM sleep and up in NREM sleep as compared to baseline. Wyatt et al. have examined this ratio in human subjects receiving PCPA using PIP discharge as the indicator of phasic activity. They found a comparable change in the REM-NREM-PIP ratio.

If one assumes that some part of the psychotic process is due to faulty regulation of phasic events, this is tantamount to assuming that a serotonin defect exists. This suggests that a test of the overall hypothesis would be treatment of psychotic humans with a compound that might offset this defect. In just such a trial, Wyatt has shown modest improvement in schizophrenic patients given 5-hydroxy tryptophane.

Finally, a very exciting preliminary report has appeared by Watson et al. to the effect that the periorbital phasic integrated potentials (PIPs) show a definite relationship to the psychotic process in acute schizophrenics. During the initial and most severe phase of the psychosis in two acute schizophrenic

patients, PIP activity in NREM sleep was greatly increased while activity in REM sleep was somewhat decreased.

A puzzling but consistent finding in chronically treated PCPA cats, who show substantial amounts of REM sleep in twenty-four-hour continuous polygraphic monitoring, is that selective deprivation of this REM sleep does not induce the typical REM rebound. Such deprivation was accomplished by interrupting each REM period by hand awakenings just as EMG suppression begins. In the preceding section, we have discussed similar failures to find rebound after REM sleep deprivation in acute schizophrenics. The parallel is obvious.

Interpretive Remarks

As we have said earlier, the basic tenet of the theory under consideration is that psychosis represents some aspect of the dream process intruding into the waking state. We have speculated elsewhere that what intrudes is phasic activity, or whatever is analogous in humans to the feline PGO spike. If this is assumed, then we may postulate some defect in serotonin metabolism or function, assuming further that serotonin has the same phasic event regulatory function in humans that it appears to have in cats. The animal model or analogue of this hypothesis is the chronically treated PCPA cat. When we look at schizophrenics for parallels to the findings in the PCPA

cat, we find a sufficient number to keep the hypothesis viable.

There are two sources of confusion, however, that should be considered. The first has to do with overly simple notions about the consequences of dream processes intruding into wakefulness; the second has to do with overly simple notions about the neurophysiology of these dream processes. With regard to the former, we have repeatedly emphasized that overt behavioral manifestations of serotonin depletion and PGO spike release, though definitely present, are minimal. It is clear that a PGO spike does not make a cat "see" a nonexistent mouse. Rather, if anything, the cat is relatively calm but preoccupied, internally distracted from a smooth interaction with the environment. A misunderstanding of these findings and the consequent erroneous expectations may have beclouded observations of humans and monkeys receiving PCPA treatment. Investigators might have seen changes in behavior had they been looking for less dramatic manifestations than full-blown maniacal hallucinations. In addition to the possibility that it is only part of the dream process rather than the whole dream that intrudes, there is also a complication having to do with the possible consequences of combining, or attempting to combine, waking and dreaming functions. We know that PGO spike generation in the brain stem gives rise to responses in the lateral geniculate nucleus during REM sleep. Of course, during sleep there is a great reduction in retinal input. There is no data to tell us what happens when retinal and brain-stem inputs "collide" at the lateral geniculate

receptors.

With regard to the second source of confusion, there is a tendency to regard the PGO spike as the sine qua non of dreaming and hallucinations. We can already introduce two qualifications. The first is drawn from the Rechtschaffen experiments described in the section on "Phasic Activity and the Psychophysiology of Dreaming." If one assumes that the PIP is the human analogue of the PGO spike, it is reasonably clear that PGO spikes are not the generators of dream and hallucinatory imagery. Another process or other processes seem to be more crucial. The only clue to the latter is the "tonic periorbital EMG discharge." The problem with this indicator is that it is essentially nonspecific. Tonic upsurges in periorbital EMG can be individualized in sleep, but not in wakefulness where EMG levels are normally quite high. This leaves the PGO spike or phasic activity process with only a disruptive role. The question we cannot answer at the present time with any assurance is whether both of these processes or just phasic activity are released into the waking state by serotonin depletion. The behavior of the PCPA cat would suggest that it is just phasic activity. Even so, we can assume that such intrusive jolts to the entire brain would, by themselves, have very serious consequences for the human stream of consciousness. A second qualification has to do with the significance of the actual PGO wave as an electrical, potential change. In this regard, it is merely a response—an electrical sign of underlying cellular events. Referring back to Figure 8-5, we

can conceive of a “generator” that initiates all phasic activity from muscular twitches to bursts of unit discharge in the hippocampus. In certain areas of the brain for purely structural reasons, relatively synchronous bursts of discharge in a pool of units give rise to a PGO spike. The point is that if we do not see PGO spikes, it does not prove the absence of phasic activity. Such a point receives experimental support from the work of Henriksen et al. who gave atropine to cats deprived of REM sleep for five consecutive days. They found that periods of atonia with concurrent prolonged EMG suppression continued to appear, although atropine blocked cortical desynchronization. During these atonic periods, there were typical phasic events such as muscular twitches, rapid eye movements, and even single PGO waves. However, atropine blocked the bursts of PGO waves characteristically associated with eye movement bursts in normal cats. Thus, in this instance, it was demonstrated that phasic activity can occur in the absence of its electrical sign (PGO spike). Given this possibility, we may reconsider the work with hallucinogenic preparations in the cat wherein it was noted that induced hallucinatory behavior was not accompanied by PGO spike discharge. We may make two interpretations: (a) that the PCPA-induced behavioral abnormalities, associated with PGO spikes in the waking state, are fundamentally different neurophysiologically from whatever events give rise to the behavior in cats treated with tropolone plus L-DOPA and other known hallucinogens; or (b) phasic activity was indeed released by these

compounds, although PGO waves per se were not. Parenthetically, there is plentiful evidence that these hallucinogenic pharmacological manipulations do effect serotonin metabolism.

Conclusions

We have tried to summarize and explicate findings that implicate sleep mechanism in the pathogenesis of psychotic behavior. At least one basic biochemical defect is postulated that is in the serotonin system. Evidence for the serotonin hypothesis independent of sleep is summarized by Gillin and Wyatt. The sleep studies essentially deal with the mediating mechanisms and attempt to explain why a serotonin defect might produce the puzzling manifestations of a schizophrenic psychosis rather than something else. Thus, whatever else it might do in the CNS, serotonin is assumed to regulate the phasic activity of REM sleep and prevent its release in the waking state. A breakdown in this function is postulated to result in phasic discharge in wakefulness and NREM sleep. This, in turn, produces behavioral abnormality, increased manifestations of NREM disturbance, and, somehow, a failure to produce the usual response to selective deprivation of REM sleep.

Biochemistry and Cellular Neurophysiology

It is clearly beyond the scope of this chapter to review the voluminous

cellular neurophysiological and biochemical literature that deals with sleep. Furthermore, these two disciplines utilize technical refinements that are sometimes difficult for outsiders to readily comprehend. Nonetheless, they represent the points at which understanding of brain mechanisms has been pushed the farthest and is most replicable and precise. To the extent that sleep mechanisms are biochemical and neurophysiological, it is therefore appropriate to indicate some current trends and well-established findings in these areas. Our additional purpose is to highlight several of the developments that seem most relevant to psychiatry. We have, in previous sections, alluded to some of the most crucial biochemical and neurophysiological issues in sleep research, but the interested reader should consult one or more of the following reviews'' as well as the BIS summary, *Neuronal Activity in Sleep* by Hobson and McCarley.

Suspicions that something "wet" or biochemical as opposed to "dry" or electrophysiological was involved in sleep certainly dates at least as far back as Pieron's search for some blood-born hypnotoxin.

It is now generally accepted that neural circuits control wakefulness, NREM, and REM sleep, and also that electrophysiological studies of such circuits have not yet yielded the best explanation of control processes. However, this may soon change since many exciting findings are now coming from single unit work. To date, though, most progress has come from

studying the neurochemistry of the monoamines and sleep. This is true partly because much is known about the biosynthesis of these compounds and because better techniques of localization and estimating turnover are available.

In terms of putative neural transmitters, acetylcholine has certainly received a great deal of early research attention (see). However, it is probable that work with this tertiary amine did not receive the recognition it should have vis-a-vis monoamines because anatomical localization with histofluorescent techniques is currently possible only for serotonin and the catecholamines.

Modern biochemistry of sleep may be said to have begun with Jouvet's observations on the reserpinized cat. Jouvet found that depletion of monoamines led to the disappearance of the states of sleep. He found that this effect was reversed by both 5-hydroxtryptphan, a precursor of serotonin, and by L-DOPA, the precursor of dopamine and noradrenalin. Jouvet suspected that serotonin had something to do with NREM sleep and catecholamines with REM sleep. At that time Swedish investigators were developing histofluorescent techniques that led to the localization of serotonergic and catecholaminergic cells and their projections. It was then that Jouvet developed the serotonin hypothesis of NREM sleep on the basis of raphe lesion and neuropharmacological experiments; other studies had already

implicated catecholamines, the pons, and nucleus locus coeruleus as crucial for REM sleep. Jouvet and his colleagues observed the effects of specific attacks upon serotonergic neurons. They achieved pharmacological specificity with acute administration of the serotonin depletor, parachloro-phenylalanine (PCPA), and anatomical specificity with stereotaxic lesions. Both of these attacks led to insomnia or a great reduction in total sleep time and the emergence of PGO activity in the waking state. Our laboratory focused on chronic PCPA administration.These data have been reported elsewhere. Very briefly, we found that PCPA reduced serotonin concentrations in all parts of the brain (o to 10 percent of controls) by the fifth PCPA-treatment day. During the first twenty-four hours after the beginning of PCPA administration, REM time generally stayed the same or increased. NREM was slightly reduced. Near the end of the third day, total sleep dropped precipitously and often reached zero for limited periods. Minima were generally seen on the fifth day of PCPA treatment. After two or three days of very low values, a marked recovery in total sleep time began, reaching approximately 70 percent of the baseline values even during continued administration of PCPA.

One of the clearest findings was the emergence of PGO activity throughout NREM and the waking state. Such activity could be seen at each point in the pons-geniculate-occipital-cortex circuit. As this activity appeared in the waking state, the overall rate of spike discharge began to drop in REM

sleep. Accompanying PGO waves in the waking state were behavioral effects, such as orienting behavior that occurred during bursts of PGO waves. Such behavior occasionally assumed the organization and the intensity of an hallucinatory episode. These observations led to the hypothesis that serotonin regulated REM sleep's endogenous sensory stimulation and that some defect in such a regulation mechanism is associated with psychotic behavior. Several clinical studies have lent some support to this notion by showing some reciprocity between REM sleep and the severity of psychotic symptoms. (See for a review.)

However, it must be noted that the PCPA serotonin-sleep literature does indeed have ample examples of negative and/or hard-to-reconcile findings.

Unit Activity during Sleep

The study of single brain cells in animals while they go through wakefulness-sleep cycles has become a popular tool to further investigate neurophysiological differences with respect to wakefulness, NREM sleep, and REM sleep.

In one sense these studies confirm the qualitative differences between NREM and REM sleep. In general, unit studies have demonstrated that many cells have slower discharge rates during NREM sleep compared with wakefulness and REM sleep. However, some cells that have relatively slow

firing rates during wakefulness may increase discharge rate during NREM sleep. In REM sleep, most cells have high firing rates, often equal to or greater than wakefulness rates. Firing usually occurs in bursts during REM sleep and these bursts are often in temporal association with other short-lasting phenomena (phasic events) such as rapid-eye movements and fasciculation of skeletal musculature. However, neurons in the amygdala and the dorsal raphe nucleus have been shown to depart from this pattern; these cells slow their firing rates during REM sleep.

In another sense, unit data also point to the difficulties inherent in regarding NREM and REM sleep as distinct, mutually exclusive states. First, it is possible to experimentally dissociate EEG characteristics from behavior. Harper has shown that unit activity slows to NREM sleep rates during atropine-induced EEG synchronization and during the immobility response induced by inversion and restraint. These data are noteworthy since they demonstrate that when behavioral sleep is dissociated experimentally from EEG patterns or from locomotor inactivity some electrophysiological indices (unit firing rates) follow sleep patterns and others (say, eye movements) follow wakefulness patterns.

These kinds of observations have led investigators of unit activity to pursue more and more precise temporal relationships between unit firing patterns and macroscopic components of sleep states.

This trend in unit research will undoubtedly continue. Many workers are probing brainstem areas in search of direct associations between sleep processes and unit activity patterns. However, in order to comprehend at the unit level the complex changes in state, such as the transition from NREM to REM sleep, it would seem that even more elaborate techniques are required. For example, the finding that certain pontine neurons fire in bursts before and during REM sleep, rapid eye movements is exciting but problematic since these neurons may also fire in bursts during wakefulness and with waking eye movements. (D. McGinty, S. Henriksen, personal communications.) Such an interpretive dilemma may be amenable to a systems approach that would regard these pontine neurons as members of a component that operates in one mode during wakefulness and another mode during REM sleep. The logical strategy, then, is to simultaneously search for neuronal firing patterns that could characterize a switching mechanism to place pontine neurons related to eye movements in either the wakefulness or the REM sleep mode. Such an approach may require simultaneous recordings in two or more areas as well as a detailed analysis of any interstate differences in the temporal relationships between unit activity and eye movement.

The Importance of Circadian Rhythms for Sleep Research

We have noted that up to about i960, sleep was considered by most researchers to be a unitary state. Anything that was true of a part of sleep was

assumed to be true for all of sleep, allowing for some quantitative variation. We have also pointed out some of the pervasive consequences of the discovery that sleep was, in a most far-reaching and fundamental way, at least two entirely different things. At one stroke, nearly all of the opinions about sleep were invalidated. At best, most of the conclusions had to be applied exclusively to NREM sleep and, at worst, entire categories of physiological study had to be reexamined.

A major point of this chapter is that, analogous to early sleep researchers facing the conceptual ramifications associated with the discovery of REM sleep, sleep researchers will now have to deal with the implications of circadian rhythms for sleep. It is possible that all prior theorizing and conceptualizing about sleep has been very misleading and narrow, because it has left out factors of daily oscillation. The early model for sleep studies was what might be called a "contingency model" or a "recovery model," that is, things happened because other things had happened. Sleep was thought to be a product of fatigue or so many minutes of prior wakefulness, regardless of time, day or night. This viewpoint left us with certain puzzling variabilities to account for. Because of these variabilities and methodological problems, the recovery model could not really be pursued to its extrapolated end. Nevertheless sleepiness was still thought to be the consequence of prolonged wakefulness.

Such early notions of sleep as recovery were first challenged by the jet-lag studies that simply pointed out that times of sleepiness and wakefulness certainly shifted complexly in adaptation to new time zones. The recovery model also had difficulty in accounting for the data that REM sleep periods might have some relation to clock time. Furthermore Mitler et al. presented data that directly challenged the recovery model by showing that, like the well-known, activity-inactivity rhythm, wakefulness-sleep also appears to be under the control of an internal circadian oscillator.

Recently, there has been increased interest in combining techniques of circadian rhythm research with those of sleep research to better assess the influence of daily cycles on sleep. Webb and his coworkers have led in recording sleep at different times of the day and pointing out that there is a kind of programming or tendency for REM sleep to be favored at certain times, slow wave to be favored at certain times, and so on. Such data come from looking at sleep samples in morning, afternoon, and evening. In another vein, Crowley and his coworkers' have begun to examine several variables over a twenty-four-hour period in order to begin understanding how sleep interrelates with other daily biological cycles. Such multi-variate studies are very significant since they not only combine circadian rhythm and sleep approaches, but they also adopt a process view in that components of behavioral state, such as temperature, body motility, and eye movement, are examined as separate oscillators.

To better understand the significance of combined circadian rhythm and sleep studies, it may be useful to give a cursory review of some concepts and terminology of circadian rhythms of special relevance to sleep.

It is clear that at any point in a twenty-four-hour period, we could examine an individual with respect to many biological and electro-physiological variables such as urine volume, body temperature, electroencephalogram, and even physical posture. We now use whole constellations of such variables to diagnose illness and to determine behavioral states. However, it is important to remember two facts when interpreting such data. First, each variable we choose to examine changes in amplitude over any extended period, and usually reaches a peak at the same time each day. Second, not all variables peak at the same time; there are intervals between peaks of some variables. Under most normal circumstances such intervals will be of constant duration over a number of days. Thus, each variable oscillates in a measureable phase relationship to all other variables, and, in most cases, phase relationships are constant over days.

Consider the three idealized daily rhythms (X, Y, and Z) shown in Figure 8-11. Curves like these can be obtained by taking measures of, say, urine volume, blood-sugar concentration and body temperature every fifteen minutes or so for ninety-six consecutive hours. To make amplitude compatible, we have plotted standard scores for each variable. Note, too, that

the data are double-plotted so that forty-eight-hour records can be seen by scanning horizontally, and trends over days can be seen by scanning vertically. The peaks and troughs for each curve occur at approximately the same point each day, as if the variables had their oscillations synchronized to some external environmental signal. When curves look like this day after day, the subject is considered to be entrained to the cycle of his environment. Under entrainment, phase relationships among variables are quite constant over days.

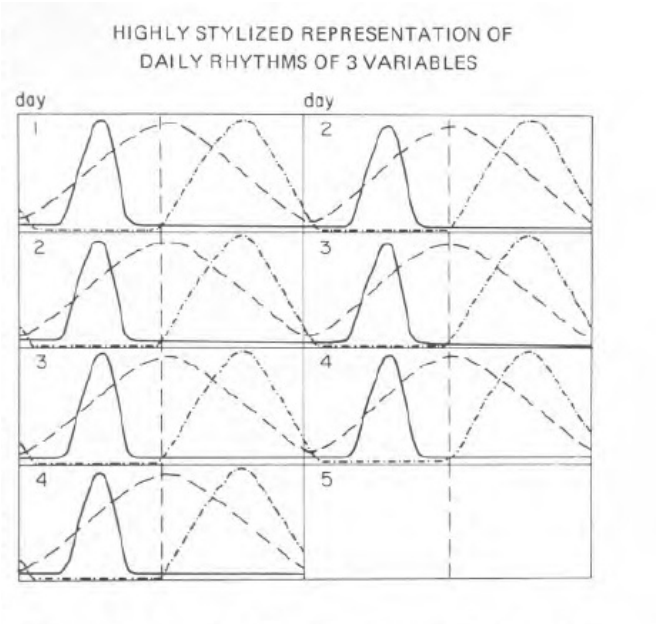

Figure 8.11.
This figure presents a double plot of three variables: X (solid line), Y (dashed line), and Z (dotted line and dashed line). Day-to-day cycles can best be seen by scanning horizontally; trends over several days can best be seen by scanning vertically. The values are standardized to allow plotting on the same scale.

Next we must consider what happens if an individual is removed from his normal environment so that he has no information about the time of day. This is difficult to achieve because only so many cues can be withheld from the subject. One strategy is to place a subject in a cave along with all the materials he needs for life. Under such constant conditions, it has been repeatedly shown that any species will maintain periodicities in most

variables. The period of each variable will be about twenty-four hours; often the periods are slightly longer, say twenty-five hours; occasionally periods of twenty-two or twenty-three hours have been observed. These periodicities or rhythms manifested under constant environmental conditions have been termed circadian rhythms fropi the Latin word *circa* (around) and *dies* (day). These rhythms are significant since they suggest that biological systems show oscillations that can occur independently of environmental signals. When an individual presents such independent rhythms in constant conditions, he is said to be free running.

If we look at variable Y in a subject who is free running, we may see a twenty-five-hour period (illustrated in.Figure 8-12). In other words, after twenty-four hours, he will not have completed his full circadian cycle. In twenty-four days he will have lost a full day according to this physiological clock. Yet, if we return temporal cues to his environment, he will reentrain to a twenty-four-hour schedule. Another subject may show a different free-running period, say twenty-three hours (illustrated in Figure 8-13). Thus, in twenty-four days, he will gain a full day.

This discussion underscores the fact that each variable we study oscillates with a period of around twenty-four hours and usually oscillates in relationship to our daily behavior. Under constant conditions such entrained cycling can disappear and be replaced by circadian cycling. The plasticity of

daily cycles is further evidenced by the many studies demonstrating that variables can entrain to artificial environmental periods ranging from about twenty-two to about twenty-six hours.

Up to now, we have been speaking about free running in one dimension. It is easy to assume mistakenly that curves for variables X and Z would look like curves for variable Y. Such an assumption ignores our second point. We said that under most normal circumstances each variable oscillates with a specifiable phase relationship to all other variables. What happens under constant conditions when we study more than one variable? Here, the time-gain or time-loss story may very quickly become complicated since variables can change phase relationships in free-run conditions. Under constant conditions, oscillators can become uncoupled. Such uncoupling of variables has been called internal desynchronization and is graphically represented in Figure 8-14.

Now we should ask if we can consider sleep a single oscillator. Probably we cannot. Sleep and wakefulness are states. As such, they are constellations of values in many variables. We conceive of sleep as low responsiveness to stimuli, recumbent posture, low and falling body temperature, electroencephalographic synchronization, etc. Sleep specialists agree on the necessary and sufficient portions of the sleep constellation. However, we are just beginning to understand what other portions of the sleep constellation

predispose to the emergence and maintenance of sleep. In the entrained human, many oscillating variables must form a stereotypical pattern prior to sleep onset.

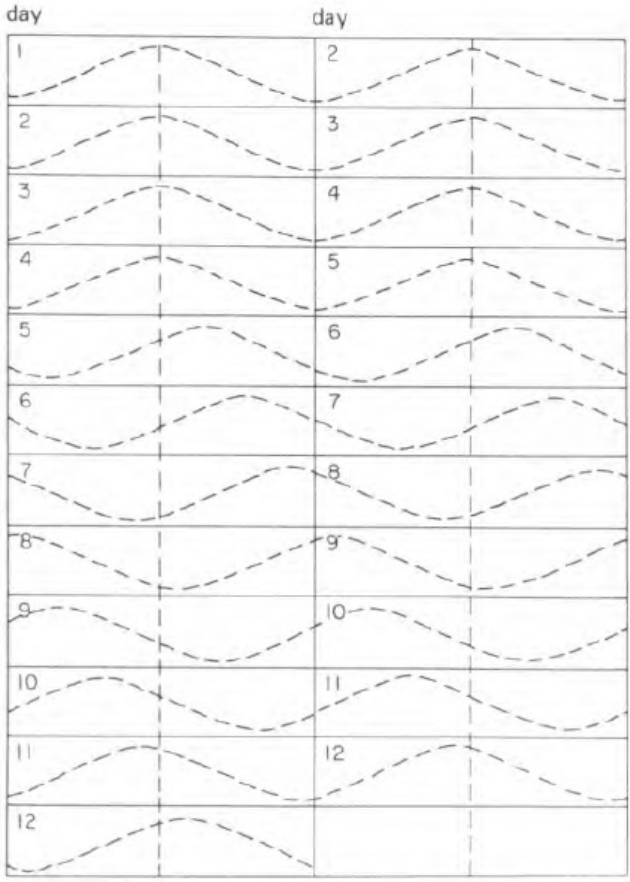

Figure 8.12.
Double plot of entrainment through day five followed by free running with a period longer than twenty-four hours in variable Y. Dashed vertical lines denote twelve noon.

Now consider what would happen if we alter the individual's environment so that everyone around him is predisposed to sleep several hours earlier than he is. Such circumstances frequently arise. For example, if we jet a subject to a different time zone, seven hours later we will produce the well-known, jet-lag syndrome. He arrives at, say, 11 p.m., local time—bedtime. Yet he cannot sleep and is restless all night. Moreover, the next day he will be fatigued and frequently predisposed to sleep. The subject may attribute this fatigue to lack of sleep during the night, but required duties may not allow him to sleep during the day. This temporary condition distinctly resembles insomnia. Several days are necessary to reentrain sleep time to the new environmental cycle, but one may need *weeks* to re-synchronize relevant physiological oscillators to their approximate former phase relationships. Thus, phase relationships change not only under free-running circumstances, but also when environmental cues have been abruptly shifted with respect to physiological time, since variables can show different rates of reentrainment.

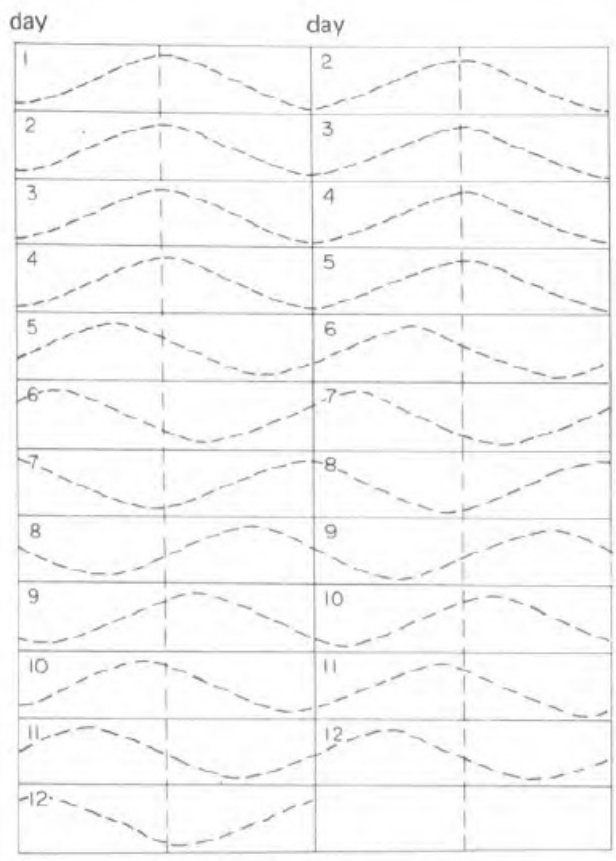

Figure 8.13.
Double plot of entrainment through day five followed by free running with a period shorter than twenty-four hours in variable Y. Dashed vertical lines denote twelve noon.

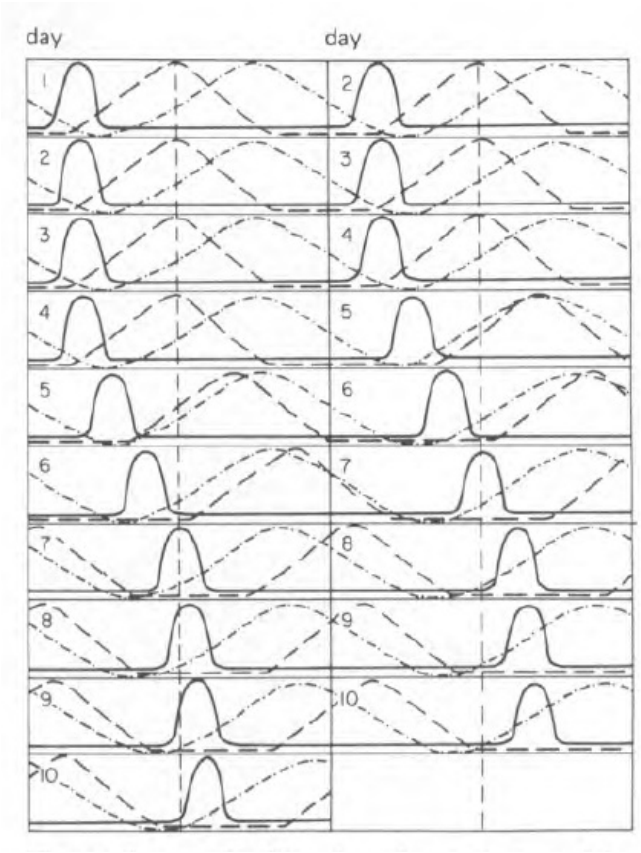

Figure 8.14.
Double plot of entrainment followed by free running in variables X, Y, and Z. Note that during the free-run period, phase relationships are different from those of the first five days. Dashed vertical lines denote twelve noon.

Fortunately reentrainment does occur, making jet-lag disruptions reversible phenomena. But suppose there are certain individuals who cannot remain entrained to any twenty-four-hour schedule. Perhaps one or more

physiological processes operate on a natural frequency too short or too long to ever remain firmly entrained to a twenty-four-hour period. Or perhaps due to some low sensitivity to social or environmental cues, he cannot entrain to existing time cues. What might such a person complain of? One guess would be chronic insomnia. The patient may show inconstant phase relationships among various variables. Let's examine the consequences of such inconstant relationships. At different times from day to day, the patient may be physiologically predisposed to some condition that *approximates* normal sleep. Occasionally predisposition to sleep might coincide with common sleep times; then the patient's complaints of insomnia would subside. At other times predisposition to sleep may occur at inappropriate times of day; then the patient might complain of nighttime insomnia, daytime fatigue, and being ineffective at work. Finally, the phase relationships among certain oscillators may preclude sleep completely; it may be days before sleep is again possible.

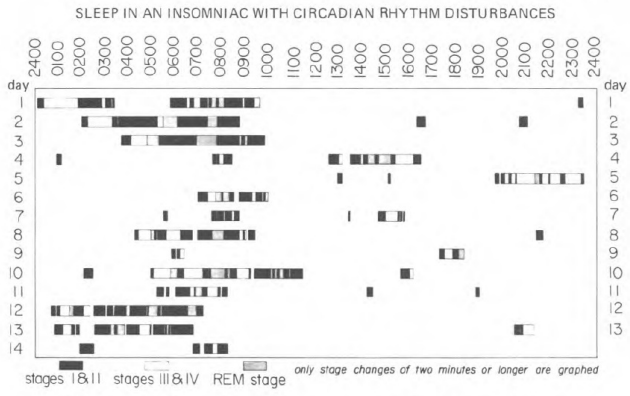

Figure 8.15.
Periods of Stage 1 or 2 sleep, Stage 3 or 4 sleep, and REM sleep plotted by time of occurrence over fourteen consecutive days in a patient who complained of insomnia. Note long periods without sleep and the inconsistent structure of the sleep periods. These data suggest that sleep may be free running and that the cycles which predispose to sleep may be internally desynchronized.

This reasoning has led us to a condition that closely parallels the symptoms frequently observed in insomnia. We have plotted for several days the sleep of an insomniac in Figure 15. During this test the patient was allowed to sleep whenever he wished. For over thirty hours we saw no sleep. At other times sleep onset occurred successively later, day after day, reminiscent of free running. But the staging structure and amount of sleep varied throughout the test. We may conclude that predisposition to sleep varies in two ways. First, predisposition slides in time, reflected by changing sleep-onset times. Second, it changes in effectiveness, reflected by varying structure and quantity of sleep. These data support the notion that sleep is

not a single oscillator but a state whose occurrence may depend on the phase relationships of other variables that oscillate in time.

Observations like these have convinced us that circadian rhythms and their relation to functional problems of sleep should be a major new research area. Very little is known now about such relationships except that sleep is favored at certain phases of the circadian oscillation. In addition to our insomnia data, a recent study in our laboratory suggests that circadian programming of sleep stages may override the conventional contingency notion that, for example, REM sleep can only occur after a certain amount of slow wave sleep. In this study, one subject lived on a ninety-minute cycle (thirty minutes of sleep and sixty minutes of wakefulness) for six days. The limited sleep period obviated the normal occurrence of REM sleep. Yet, although the subject obtained approximately five hours of sleep per twenty-four hours, REM sleep occurred during sixteen of the sleep periods. In fact, many sleep onset REM periods were seen. It is interesting to note that this simple alteration of scheduling produced sleep onset REM periods quite easily as opposed to the heroic methods of REM sleep deprivation or pharmacological manipulation utilized in the past. However, at present, we can only guess at the many consequences to sleep sequencing when phase relationships are radically altered or when the organism is free running.

Finally, it is probable that in addition to restructuring theoretical and

clinical issues in sleep, circadian rhythms will have profound implications for the areas of sleep deprivation and the biochemistry of sleep. First, in the last twenty years virtually hundreds of people have been studied before and after total sleep deprivation, partial sleep deprivation, and selective sleep deprivation. In general, data indicated that after deprivation, Stage 4 is greatly favored while REM sleep is depressed. In a careful analysis of these findings researchers have noted that after a deprivation period people tended to go to bed earlier in the day. Thus, any configuration of postdeprivation sleep was probably very much a function of the time of day rather than deprivation per se. In short, after a period of deprivation recovery sleep may look very different if it begins during normal waking hours as opposed to normal sleeping hours. In the latter case, recovery sleep shows fewer changes in structure. Thus, time of recovery sleep can account for much individual variability in the structure of recovery sleep. Second, it is usually assumed that sleep-wakefulness is biochemically controlled. We will have to explain eventually why there are well-known large circadian changes in level and turnover of biogenic amines, but very small changes in these variables as a function of state.

Sleep Disorders

In the review that appeared in the first edition of the *American Handbook of Psychiatry,* Volume III, we discussed the "chicken or the egg"

problem of mental illness and sleep. In other words, is a sleep disturbance a symptom of mental illness or is it a cause, either directly or indirectly as a precipitating stress? This question has not been entirely resolved in the last decade, although material presented earlier in a previous section suggests that sleep loss per se will not necessarily lead to serious mental, emotional, or physical breakdown. In addition, this point of view is supported by observations of volunteers who stayed awake for *more* than two hundred consecutive hours.

In Volume III, we stated that "it is virtually axiomatic that a disturbance of the mind can manifest itself in the sleeping state as well as the waking state. In fact, the former state is often the more sensitive barometer of psychic turbulence." This remains the case whether or not one assumes that the sleep disturbance is the cause of the psychiatric disorder or vice versa. Psychiatric causes of insomnia are generally thought to be anxiety, depression, or the agitation of acute psychotic episodes. Yet the question persists as to whether these are the causes or only the correlates of the sleep disturbance. Further, if a patient who complains of insomnia is found, for example, to be depressed, can we then assume that there is no other cause of the insomnia?

Although the clinical aspects of sleep are covered elsewhere in this volume, we feel that some additional discussion of sleep disturbance as a symptom is appropriate to this chapter. Such discussion can serve two

purposes. The first of these is to illustrate the point that sleep studies are often too limited in their scope to be effective clinical tools. The second involves the consideration of an approach to the patient who complains of insomnia.

In a recent survey of several hundred practicing physicians, we found that psychiatrists and internists saw a great majority of patients complaining of insomnia. It was clear that this complaint is considered an essentially psychiatric and by implication "emotional" or "psychological" problem by the medical community. We should, of course, remind our reader that sleep disturbance also includes complaints of hypersomnia, but our survey indicated that, in general, hypersomnia is considered a neurological problem. (Occasionally, however, there is a question of the association of hypersomnia and depression.)

The sleep laboratory approach to clinical sleep problems has been most vigorously advocated and pursued by Kales and his group who have made contributions in the area of insomnia,' drug dependency, sleeping pill effectiveness, sleepwalking, as well as a variety of medically related conditions such as duodenal ulcer, asthma,' hypothyroidism, etc. Others have also contributed in this area. If the psychiatrist is concerned about the complaint of insomnia on a routine basis, he should have some notion of the evolving differential diagnosis in this area; he should also have some

developing list of causes and of the techniques of evaluation as well as of treatment.

The situation is analogous to the complaint of a chronic headache: if the psychiatrist is confronted with such a patient, he will want to ascertain, either on his own or by checking the appropriate referral procedures, that certain well-known organic causes, such as brain tumor or hypertension, are not implicated. By the same token, it is very important to recognize that insomnia requires similar evaluation. At this point, rather than presenting an exhaustive description, we will consider several examples of the conditions that proper evaluation can identify. Thus, we hope to demonstrate that when a psychiatrist is confronted with a patient who complains of chronic insomnia, he cannot assume that anxiety and/or depression are his only concerns, or that the referring general physician, if one is in the picture, has ruled out all organic causes.

Sleep Apnea-insomnia Syndrome

Sleep apnea-insomnia was first described by Guilleminault et al. in 1972. Sleep apnea had been recognized prior to this discovery, but had been described almost exclusively in patients complaining of hypersomnia and accasionally in narcolepsy and in other medical conditions. Sleep apnea-insomnia was first observed in a man who had complained of insomnia for

nearly twenty years and who had sought both medical and psychiatric help for his condition. The remarkable aspect of the discovery of sleep apnea in this patient was the fact that, although he had several all-night sleep recordings using the standard sleep monitoring techniques (i.e., EEG, EOG, EMG) and although an objective sleep disturbance was duly noted, the recordings failed to implicate the true nature of the man's condition—that his respiration ceased during sleep. Appraisal of sleep apnea was made only after respiration gauges were added to the sleep recording parameters in order to investigate the claims of the patient's wife that he snored excessively.

Because of this discovery, measures of respiration (either mercury stain gauges placed on thorax or abdomen, thermistors taped near the nose or mouth, or both) are routinely included in all-night sleep recordings of insomniac patients at the Stanford University Sleep Disorders Clinic. In approximately fifty patients complaining of insomnia who have had all-night sleep recordings with respiratory measurements since the discovery of sleep apnea-insomnia, this syndrome has been identified in five patients (10 percent). While this is an extremely preliminary figure, Hauri has confirmed the presence of sleep apnea in three of his insomniac patients (personal communication).

The etiology of sleep apnea is not clearly understood at the present time, but three types of pathologic apneas during sleep have been described.

The first type is peripheral or obstructive apnea, thought to be due primarily to an obstruction of the airway caused by large adenoids, large tonsils, collapse of the pharyngeal muscles, thyroid goiter, etc. Obstructive apnea is typical of the Pickwickian syndrome. Central or diaphragmatic apnea involves a cessation of diaphragmatic movements during sleep. Thirdly, mixed apnea is characterized by a diaphragmatic apneic component followed by an obstructive apnea.

The sleep apnea-insomnia syndrome seems to involve primarily the diaphragmatic type of apnea. Figure 8-16 shows a recording of this condition. In general, we have found that insomniacs who have sleep apnea have little or no difficulty falling asleep, but complain of many lengthy nighttime awakenings, early morning awakening, and daytime fatigue. In addition, a history of nightly periodic snoring frequently suggests the diagnosis.

Most conventional treatments, whether they involve psychotherapy or chemotherapy, are ineffective in sleep apnea-insomnia. In fact, there is great danger in prescribing drugs that are respiratory depressants. Finally, it has been shown in other of the sleep apnea syndromes that cor pulmonale, cardiac failure, pulmonary artery, systemic hyperpressure, and other serious cardiovascular difficulties may arise, and there is no reason to believe that such complications will not result in sleep apnea-insomnia as well.

Restless Legs Syndrome and Nocturnal Myoclonus

Restless legs syndrome, characterized by deep paresthesis and limb movements occurring during extended muscular rest and when falling asleep, and nocturnal myoclonus— intense muscle jerks that occur primarily in the legs at sleep onset and throughout the sleep period—are often associated and may induce severe insomnia. Furthermore, the severity of the illness may often lead to the development of depression and suicidal ideation in these patients. Here, then, is the case of an insomniac in whom depression can be diagnosed, but whose insomnia (and indirectly depression) stem from a neurologic disorder.

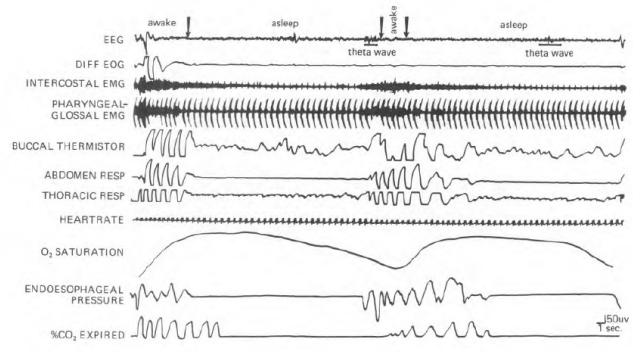

Figure 8.16.
Polygraphic recording of sleep apnea episode recorded in a patient complaining of insomnia. Note that the EEG tracing shows periods of wakefulness when the patient breathes. When sleep ensues, breathing again ceases.

In general, one can obtain a very good indication of nocturnal myoclonus from the history of the patient, but polygraphic sleep recording with the usual sleep parameters, as well as various limb muscles, is necessary to make the diagnosis. We have performed such recording on one patient who complained of both restless legs and nocturnal myoclonus, a seventy-year-old woman who had a thirty-two-year history of insomnia. A remarkable feature of her recording was the fact that the myoclonic jerks in her legs often coincided with short EMG suppressions recorded from the digastric muscle (see Figure 8-17). Pivik and Dement® have also recorded similar short-lasting EMG suppressions during sleep and have hypothesized that the EMG suppressions might be an indication of phasic events during NREM sleep. It is possible, then, that the myoclonic jerks of nocturnal myoclonus represent an abnormal response to phasic event discharges that occur in NREM sleep.

Restless legs syndrome has been treated with some success with tocopherol, vitamin E. Our patient has reported relief with 5-hydroxytryptophan, which we have utilized on an experimental basis.

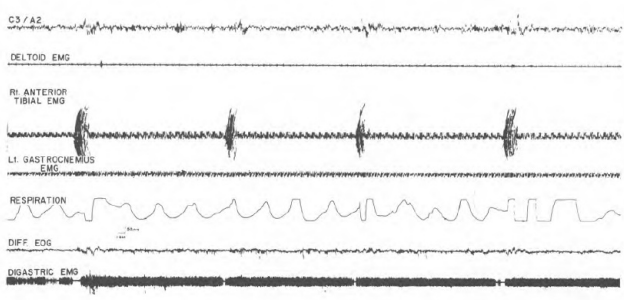

Figure 8.17.
Nocturnal Myoclonus. Note the violent phasic EMG activity in the anterior tibialis associated with K-complexes in the EEG and with phasic suppressions of digastric EMG activity. Such twitches are disruptive of sleep and can lead to insomnia.

Pseudoinsomnia

When certain obvious factors have been ruled out, such as sleep apnea, drug dependency, and nocturnal myoclonus, one is left with a very large question mark with regard to patients who complain of insomnia. These patients have been evaluated by a number of workers. Kales, in particular, emphasized significant elevations in MMPI scales. However, the question we ask is, what is really going on in the sleep of such patients? To answer this question, we have routinely conducted all-night sleep recordings utilizing standard parameters as well as respiratory and other variables on all insomniac patients who are referred to us. Thus we have studied a heterogeneous population rather than a highly selected group.

To date, we have evaluated approximately fifty patients with *no* obvious cause of their insomnia. We have looked at objectively recorded sleep parameters, such as total sleep times, sleep latency, number of arousals, etc., as well as a number of subjective assessments of the complaint both before and after the sleep laboratory experience. In Figure 8-18, we present a histogram in which each bar represents a mean sleep latency of four or more nights in the laboratory, rank ordered from longest to shortest. It can be seen that a number of patients, but by no means all, have sleep latencies that must be regarded as normal. Further, many of these latencies are under thirty minutes, which we use as a kind of rule-of-thumb cutoff for abnormal sleep latency. All of the patients complained that sleep onset was delayed and many complained that it took them "hours" to fall asleep.

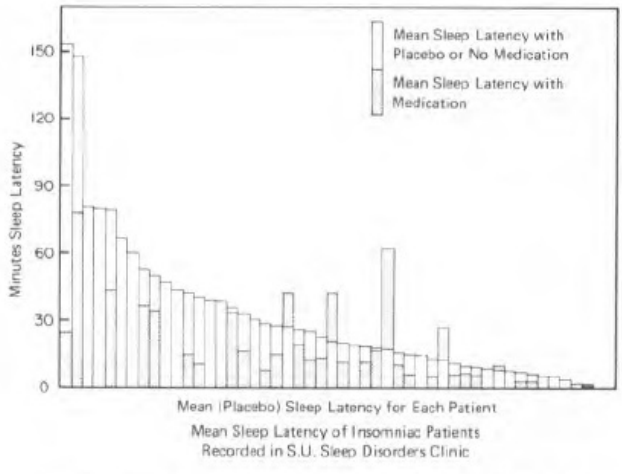

Figure 8.18.
This figure is a rank order histogram showing the average sleep latencies of fifty insomniac patients recorded at the Stanford University Sleep Disorders Clinic for at least two consecutive nights with no medication or placebo (white bars). Certain patients were also recorded on at least two nights when the hypnotic medication (stipled bars), either Dalmane, fifteen mg or thirty mg; Sinequan, fifty mg; or GP41299 (an experimental hypnotic), one hundred mg.

It is interesting to note that although all patients complained of sleep latencies longer than sixty minutes, in only seven patients was this complaint confirmed! Only eleven patients had sleep latencies between thirty and sixty minutes. The majority of patients fell asleep in less than thirty minutes on placebo in spite of the fact that they had complained of severe difficulty falling asleep.

Figure 8-19 is a similar description of total sleep time. Here again, there is a wide variation in this parameter in spite of the fact that all of the patients complained that they only slept a few hours at night even during their laboratory experience. The mean for the entire group was approximately six

and one half hours, which is not abnormal when the mean age of the group is considered.

An obvious consideration, which has not been aggressively emphasized by others, is that an understanding of insomnia will surely require looking at more than these obvious factors. That is, in patients who fall asleep immediately and sleep adequately long periods without significant interruptions, we must look elsewhere for the cause of their complaint. "Elsewhere" may be in more subtle physiological measures, such as heart rate, body temperature, and other parameters as originally described by Monroe;[219] or it may be in more subtle dysfunctions of perception of sleep; or in the use of of the complaint as a symptom when the patient is anxious and/or depressed; and, finally, it is clear that such patients should also be evaluated from the point of view of circadian rhythms. Every good judgment cries out that it is a heterogeneous group.

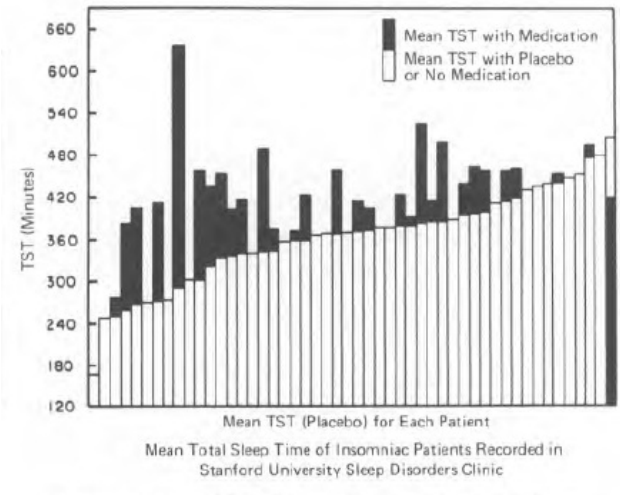

Figure 8.19.
This figure is a rank order histogram of TST on placebo or no medication nights (white bar) and medication (black bar) nights in the same patients shown in Figure 8-18.

Although all patients complained of less than six hours sleep, this complaint was confirmed in only twenty-one patients on placebo nights. Of the remainder, fourteen had mean TST between six and seven hours and the rest had a mean TST over seven hours. Thus, again, the complaint was not reflected by the sleep recording.

Another interesting finding illustrated by this figure is the effect of sleeping medications on TST. The efficacy of the medication seems to be less as the subjects sleep longer on placebo nights. In other words, the longer an insomniac sleeps, the less likely he is to be significantly helped in terms of increased TST by hypnotic medications.

Night Terrors

A final mention should be made of a disorder that is very dramatic, but probably not overly fraught with psychological significance. This is the night

terror or pavor nocturnus. Work in this area has been done by Fisher et ai 93,94 Broughton, Gastaut, and others. This disturbance appears to involve some physiological-biological defect. According to Fisher, there is no detectable premonitory sign of the abrupt onset of the night terror. We wonder if it is not precipitated by a burst of phasic activity arising in NREM sleep. Fisher has treated the night terror syndrome effectively with diazepam.

Implications for Sleep Research

With regard to the field of sleep research, it is clear that, after two decades or more in which basic research and experimental approaches to the sleep mechanisms have certainly been the predominant concern, an interest in sleep disorders is emerging that is basically independent of medical specialties, such as neurology, internal medicine, or even its foster parent psychiatry, but which combines all of these areas. The classical sleep complaints of insomnia, hypersomnia, sleepwalking, bedwetting, and so on are the concern of the psychiatric sleep specialist or of anyone who is interested in the clinical aspects of sleep. In view of the fact that most clinical sleep research has been conducted under a psychiatric umbrella, it seems reasonable that the evaluation and treatment of sleep disorders as a clinical subspecialty should be regarded as a subspecialty of psychiatry. This appears to be the best option, in spite of the fact that such clearly organic problems as sleep apnea, hypersomnia, narcolepsy, and so on are involved. In a recent

paper delivered at the Association for the Psychophysiological Study of Sleep, Dement made the point that it is economically mandatory to combine sleep disorders under one specialty because of the tremendous investment required to provide monitoring equipment, twenty-four-hour coverage, and an adequate number of bedrooms to handle sleep-disorders patients. It is therefore very impractical to have a psychiatric-clinical sleep laboratory for insomnia and a duplication of this facility for what are traditionally regarded as neurological complaints.

It is also clear that we must begin to be wary of the limitations of the so-called "standard sleep recording." In patients with sleep apnea or nocturnal myoclonus, the standard sleep recording is inadequate both for description and for diagnosis. It also seems obvious that total sleep time, sleep latency, and other traditional measures are not the parameters that will effectively define the psychological and physiological discomfort that is experienced by insomniacs. In terms of examining the sleep of the insomniac patient, the surface has only been scratched. Body movements, muscle tension, cardiac and respiratory factors, gastric motility—all these areas need thorough investigation and comparison with the normal population.

The final point, which will surely receive greater emphasis in the future, however disconcerting it may be, is that sleep is not necessarily a blessing greatly to be desired and to be sought at any cost. Sleep may instead

constitute a subtle life-threatening imbalance: to accomplish the metamorphosis from the waking state to sleep may be a much more difficult adjustment than we have heretofore realized. For example, when we are confronted with a sleep apneic patient, we tend to ask the question, why do some people stop breathing when they fall asleep? It is more appropriate, knowing that the respiratory control systems are heavily dependent upon activity in the reticular formation, to ask: how do people continue to breathe when they fall asleep? This point is emphasized in a study by Lugaresi et ah, in which they document a variety of imbalances and instabilities in autonomic parameters during sleep, particularly respiration. The transition from wakefulness to sleep may be especially vulnerable. A similar behavioral instability is evident when one examines heart rate: a small movement in the waking state will barely accelerate the heart rate; yet a similar small movement during NREM sleep will produce an enormous change.

All of these considerations will become the concern of the well-trained psychiatrist of the future, and it is certainly time to get some of these items into the psychiatric residency program.

Instrumentation and Data Analysis

In this section, we would like to touch on two areas that will undoubtedly figure importantly in the future of sleep research.

First are the many advances in automatic processing of polygraphic data. As the scope of sleep observations extends in time among species and into odd locations like the moon, the sky lab, and perhaps Mars, it becomes necessary to process more and more data. Further, in addition to the classical measurement of EEG, EOG, and EMG, we have become much more interested in recording other variables when possible. In the human this includes blood pressure, cardiac functions, and respiration. In animals additional variables include primarily unit data, biochemical data by push-pull cannulae and reflex facilitation. The most important advance is use of the computer in a manner analogous to the human scorer. Systems have been developed by Itil,> by the Florida group, and by others that will perform this task. To date, while computers perform much more rapidly, they are not really able to match the flexibility and accuracy of human scorers. However, one implication is that the standards, presumably more consistent, that are used in computer scoring will in some way shape our future concepts of sleep. The computer may also be used to look at other events in the sleep period in ways analogous to that which obviated the drudgery of looking at evoked potentials. There are now programs for counting K-complexes, eye movements, and PGO spikes. Advanced techniques of pattern recognition, masking techniques, and so forth may apply in recognizing patterns of discharge, phasic activity units, and other electrophysiological phenomena. We have just begun to utilize advanced methods of data processing in this area, but we expect great

advances in the future. This may also include fairly radical departures in looking at the data. An example of this is the Stanford Slowgram and a similar approach developed by Johnson et al. in terms of delta cycles. The point is that instead of looking at the amount of Stage 4, we measure the decay in amplitude, the rate of rise, and so on. All of this can be done almost totally by a computer at the end of the night and written out. Figure 8-20 illustrates a Stanford Slowgram.

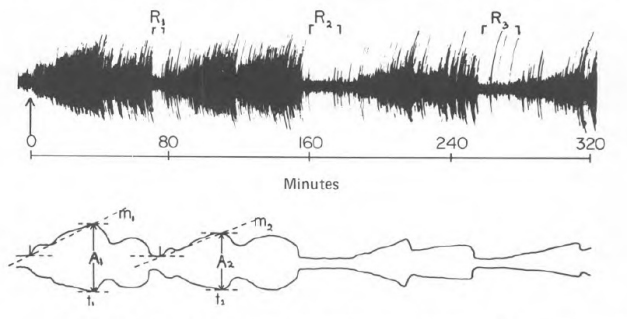

Figure 8.20.
(Top) Cortical EEG of a male subject, age twenty-four, recorded on a compressed time scale during a night's sleep.

(Bottom) Diagramatic representation of sleep-EEG. $m_2, \ldots,$ are midpoints of the maximum amplitude plateau in that particular cycle.

Second, many advances should be made in the next few years in the general area of experimental design and statistical analysis of data from sleep experiments. Early work on sleep was difficult enough without being concerned with such factors as seasonal change between the beginning and

the end of the data-gathering period, the statistically appropriate number of variables to be analyzed from one set of subjects, and the best combination of measures to use in asking experimental questions.

Today, however, since most sleep recording routines are firmly established and most investigators have automated data reduction capabilities, more attention can be given to design and statistics. For example, it is now quite possible to do a two-or-three-condition study lasting as long as five or six weeks with humans. The study could involve recording over fifty variates per night, and the study could be designed to make all nights comparable by, for example, letting the subjects sleep at home on weekends, allowing Monday to serve as a laboratory adaptation night, and having Tuesday and Thursday be study nights. Seasonal change could be assessed by doing two or more comparable runs at different times of the year. As Lubin (personal communication) has suggested, experimental conditions can easily be differentiated by using the statistical technique of discriminant analysis and then assessing the significance of any differences by another technique called multivariate analysis of variance. The dividends of such statistical treatment should far outweigh the costs of conducting the long and elaborately designed study. First, if the data are organized so that nights are comparable and seasonal factors are assessable, then the investigator need not guess as to what variates to look at: discriminant analysis will tell him precisely. Further, the investigator need not worry about performing many

independent statistical tests on different but nonindependent variates from the same subjects: multivariate analysis of variance automatically accounts for nonindependence. Thus, very precise answers may be obtained from large and complicated data matrices if the data is simply organized appropriately. Such new design and analysis procedures should improve all aspects of sleep research from patient evaluation to determining hypnotic effectiveness.

Conclusion

In the early part of this century, while sleep may well have been a pressing concern to many, laboratory research was extremely meager and almost totally uninvolved with human problems. The discovery of REM sleep, coming as it did at what retrospectively seems like the zenith of the psychoanalytic movement (with its insistence on the practical and theoretical importance of the dream) was to inaugurate an explosive increase in sleep research much of which was carried out by psychiatrists or in psychiatry departments and generously supported by the National Institute of Mental Health. However, other specialists were soon attracted into the sleep research field and over the past decade they have accomplished a great deal in a wide variety of highly sophisticated areas. There is a great deal of work that is directly relevant to traditional psychiatric problems. However, there is now a great deal of knowledge that is directly and almost exclusively relevant to sleep and sleep pathologies, and, by implication, to whoever is primarily

responsible for these areas. It is our feeling that basic and clinical sleep research need to be presented in a unified manner. We do not feel that the sleepy person belongs to a neurologist and a sleepless person to a psychiatrist. We feel that one of these disciplines should either assume overall responsibility at least for the sleep pathologies or that the biochemistry, physiology, and pathology of sleep should be a discipline unto itself. In his preface to Volume III of the first edition of the *Handbook,* Silvano Arieti remarked: "Perhaps no other field of human endeavor is so encompassing and difficult to define as that of psychiatry." Within such nebulous and fuzzy boundaries, surely the field of sleep research can be easily and fully accommodated.

The area continues to grow and new information is accumulating at a frightening rate. However, the old problems are still with us. Do we really need to sleep? Why does REM sleep exist? What is insomnia? Why do we dream (exactly) what we do? These are fascinating and frustrating problems. We can safely estimate that a young sleep researcher will be well-occupied throughout his entire career. However, we must be aware of the concrete solutions that have been achieved. The anatomical localization of sleep mechanisms, an enormous increase in physiological understanding, a rational approach to pharmacology, a great clarification of pathophysiology in a variety of sleep disorders, and, finally, a number of promising leads in unraveling the role of sleep processes in mental illness.

All of this should be taught by someone in an integrated fashion. Here again, who will assume the responsibility? There is at least a hint in the very fact that so much space is devoted to the topic in this *Handbook.* It should be said that the foregoing material has only touched the highlights, and not all of those either. Reviews or overviews with similar goals will have more difficult problems in the future. Further, it is clear that many of the areas we touched upon are just beginning, and will soon be epicenters of intense scientific activity. If there were any surprises in this chapter, there will surely be many more in the future. This is the kernel of a final thought. It is hoped that each section will have been viewed as a guidepost of the present, pointing out future trends in research and clinical application, and that the interested student will see more clearly how sleep and dream research may be interwoven with his own career.

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Notes

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2 Since this chapter has begun its editorial processing, the first of an excellent review series has appeared which deserves special mention here: E. D. Weitzman (Ed.), *Advances in Sleep Research* Vol. 1, New York: Spectrum Publications, 424 pages.

3 These data have now begun to appear since our first writing. Lubin A., Moses, J., Johnson, L., and Naitoh, P. The recuperative effects of REM sleep and stage 4 sleep on human performance after complete sleep loss: Experiment l. Psychophysiology, 11(2): 133-146, 1974. And Johnson, L., Naitoh, P., Moses, J., and Lubin, A. Interaction of REM deprivation and stage 4 deprivation with total sleep loss: Experiment 2. Psychophysiol. 11(2): 147-159, 1974.

4 Since our first writing, we have begun studies on dogs apparently afflicted with narcolepsy-cataplexy.

Such efforts may disclose much concerning the neurological deficit underlying the syndrome. See Mitler, M., Boysen, B., Campbell, L. and Dement, W. Narcolepsy-cataplexy in a female dog. *Exp. Neurol.* (in press) for an account of this work.

5 A discussion of these findings can be found in: McGinty, D., Harper, R., and Fairbanks, M., "Neuronal unit activity and the control of sleep states," *Adv. Sleep Res.* 1, (1974), 173-216.

6 These data are now published: Jacobs, B., Asher, R., and Dement, W. "Electophysiological and behavioral effects of electrical stimulation of the raphe nuclei in cats," *Physiol. Behav.* 11, (1973), 243-252.