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EVOLVING CONCEPTS OF HUMAN STATE DISSOCIATION

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"The state of a system at a given instant is the set of numerical values which its variables have at that instant" (11).

"From a scientific point of view, we can make no distinction between the man who eats little and sees heaven and the man who drinks much and sees snakes" (182).

INTRODUCTION

In the beginning, there was one state of being – (presumably) wakefulness. Somewhere and sometime early along the evolutionary trail a second appeared – sleep. Beginning with monotremes, sleep specialized into two forms: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Each of these three states of being is extremely complex, and is comprised of numerous physiologic variables, which usually occur in concert, resulting in fully-declared states: wakefulness, NREM sleep, or REM sleep. Since the discovery of the bimodal nature of sleep in 1953, basic science research exploring the nature and pursuing the function of sleep has resulted in a virtual explosion of our knowledge of state and state control – from neuroanatomic, neurochemical, neurohumoral, neuropharmacologic, neurophysiologic, and more recently, molecular genetic aspects. Many of the lessons learned in the process of basic science exploration of state and state control can be readily extrapolated to the human condition, permitting explanation of bizarre clinical phenomena, and leading to effective therapies.

I. NORMAL STATE DETERMINATION

The states of wakefulness (W), rapid eye movement (REM) sleep, and non-rapid eye movement (NREM) sleep are very complex phenomena. State determination may be made using various criteria: behavioral (eyes open/closed, body position, movements, reactivity to the environment); electrographic (electroencephalogram [EEG], electrooculogram [EOG], electromyogram [EMG]); or neuronal state (brain neuronal activity). The state-determining properties of each state usually cycle in a predictable and uniform manner, resulting in the behavioral appearance of a single prevailing state. However, even in normal subjects, the electrographic and neuronal activity transition among states is gradual and variable, with the simultaneous occurrence or rapid oscillation of multiple state-determining markers (Fig. 1).

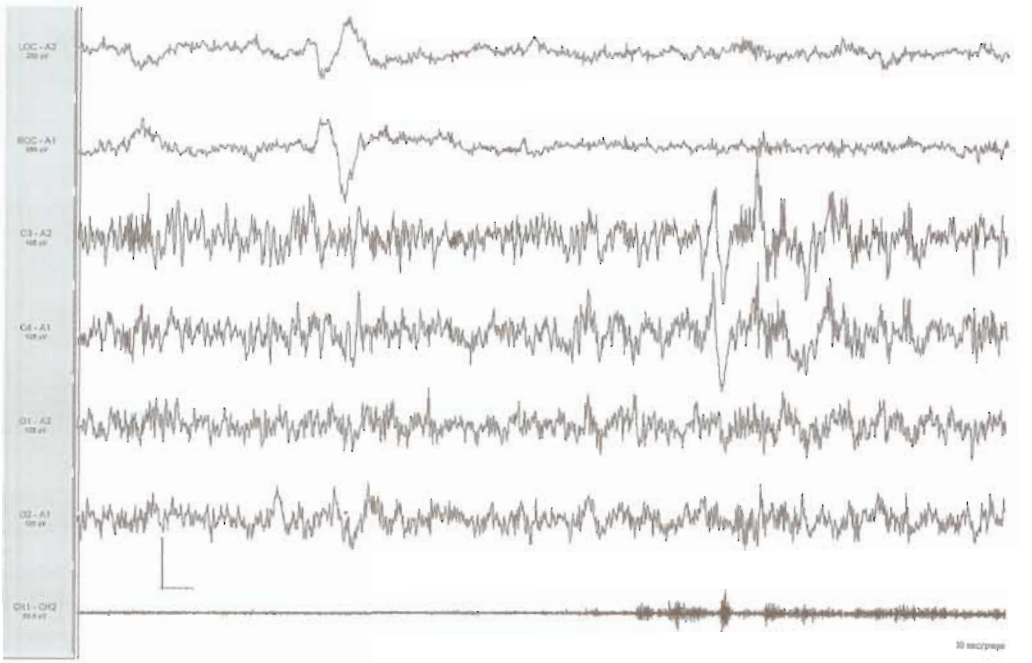

Fig. 1. - *An epoch of ambiguous sleep in a normal individual.*

Note the prominent rapid eye movement and brief period of atonia (markers of REM sleep) occurring in the midst of otherwise well-developed stage 2 NREM sleep. Legend: LOC-left outer canthus; ROC-right outer canthus; C3-left central; C4-right central; O1-left occipital; O2-right occipital; A1-left mastoid; A2-right mastoid; CH1-CH2-submental EMG.

Within each state, there is ongoing variability and fluctuation of central nervous system (CNS) activity (87, 225). Nathaniel Kleitman nicely described the concept of state admixture in his chapter "The Onset of Sleep", describing the transition from wakefulness to sleep as "a succession of intermediate states, part wakefulness and part sleep in varying proportions - what is designated in Italian as *dormiveglia*, or sleep-waking" (110).

There is compelling evidence that there is panoramic reorganization of the central nervous system activity as it moves across these three states of being. Factors involved in state generation are complex, and include a wide variety of neurotransmitters, neuromodulators, neurohormones, and a vast array of "sleep factors" which act upon the multiple neural networks, likely mediated by gene transcription factors (39, 227). These facts lead to the conclusion that sleep is a fundamental property of numerous neuronal groups, rather than a phenomenon that requires the whole brain (88, 116). Therefore, state determination is the result of a dynamic interaction among many variables, including circadian, neural network, neurotransmitter, and myriad sleep-promoting substances and effectors.

The state-determining variables of REM sleep have been the most extensively studied. REM sleep is comprised of both tonic (occurring throughout the entire REM cycle) and phasic (occurring intermittently during the REM cycle) components. Each of these elements is generated, modulated, and executed by different neuronal groups located at multiple levels of the neuraxis – from cerebral cortex to spinal cord, – orchestrated by the dorsomedial pontine region (207). Even within REM sleep, there is a stereotypical sequence of the appearance of REM physiologic markers: muscle tone reduction, saw tooth waves, and then rapid eye movements (190). Disorders of the central nervous system may alter this normal progression (206).

There are striking neurophysiological semblances between wakefulness and REM sleep. Some identical neuronal groups are extremely active in more than one state, with differing state-dependent effects, i.e.: many REM sleep phenomena are similar to the alerting response seen in wakefulness (27, 67, 149). On the other hand, there may be striking state dependent changes in function: for example, some brainstem regions effect motor suppression in REM sleep but motor facilitation in W (33, 233). The ascending brainstem reticular system potentiates thalamic and cortical responses during both states. Although the EEG is said to be "desynchronized" during wakefulness and REM sleep (in contrast to being "synchronized" during NREM sleep), there is fascinating and compelling evidence that during the two states of brain arousal (wakefulness and REM sleep), activation of the mesencephalic reticular formation facilitates oscillatory activity in the gamma frequency band (>30 Hz) which enhances synchronization of cortical responses which may play a role in the processing of sensory signals. The waking and REM sleep "desynchronized" EEG pattern is more apparent than real – it is actually highly synchronized (152, 220). This synchronization may be important for information processing by facilitating the establishment of synchrony over large distances in the cortex, linking remote neurons into functional groups (113). Perturbations (temporal, spatial, or frequency) of this synchronization may play a role in certain "psychiatric" conditions such as schizophrenia (7, 8). A recent elegant magnetoencepalographic study in a number of neurologic and psychiatric conditions firmly supports this concept (124).

II. EVOLUTION OF CONCEPT OF STATE

The clinical concept of states of being has changed dramatically over the past few decades. It was formerly thought that human existence encompassed only two states: wakefulness and sleep, with sleep being considered simply the passive absence of wakefulness. With the discovery of REM sleep in 1953, it became apparent that sleep is not a unitary phenomenon, but rather consists of two completely different states, and each state is an active, rather than a quiescent, process (95). Each state consists of a number of physiologic variables, which, under normal circumstances, tend to occur in concert, resulting in the appearance of one of the three conventional states of being: W, REM sleep, and NREM sleep (85, 87).

Animal experiments and evaluation of humans in the sleep laboratory indicate that the "three states of being" concept must be further expanded to include the observations that the physiologic event markers of one state may intrude into other states, and that the states may oscillate rapidly, resulting in the appearance of bizarre, previously difficult-to-explain and occasionally extraordinary animal and human behaviors, which can occur in diverse naturalistic and clinical settings – with important treatment implications (86, 129, 130). Recent animal experiments support the concept of state dissociation as a normal manifestation of state transition, suggesting the staggered appearance of state-determining physiologic variables: one found suppression of the cortical auditory evoked response shortly before the onset of REM sleep (156), another demonstrated that sleep develops asynchronously in different cortical areas (166).

III. STATE DISSOCIATION IN ANIMALS

The recurrent recruitment of state-determining parameters is amazingly consistent. However, multiple experimental examples of state component dissociation exist (137). These fall into three categories:

A. *Lesion/stimulation:* Hypothalamic, thalamic, and brainstem manipulation/stimulation induces state dissociation (60, 82, 96, 138, 168, 229, 231). Recent studies in molecular biology may add a fascinating new dimension to such dissociation. For example, 6-hydroxydopamine (6-OHDA) lesions of the locus ceruleus inhibit the expected immediate early gene (c-Fos) expression (normally expected during wakefulness) in the cortex and hippocampus without changing the EEG. Therefore, following such lesions, the cortex may be at least partially functionally asleep, without a sleep EEG pattern (38).

B. *Pharmacologic:* Manipulation of the cholinergic/glutamate neurotransmitter systems results in a variety of state dissociations (13, 50, 51, 55, 78, 79, 93, 118, 145, 230).

C. *Sleep deprivation:* REM sleep deprivation in cats results in the appearance of PGO spikes during NREM sleep (52).

In addition to these experimental dissociations, there is evidence in the animal kingdom for the natural occurrence of clinically wakeful behavior during physiologic sleep. Two examples which dispel the concept of "all or none" state declaration are: 1) the concurrence of swimming or flight during sleep in birds (5) and 2) the phenomenon of unihemispheric sleep in some aquatic mammals (bottle-nosed dolphin, common porpoise, and northern fur seal) guaranteeing continued respiration while "sleeping" (237). Another naturally occurring dissociated state is seen during the arousal from torpor in hibernating ground squirrels, when there is an "uncoupling between thalamic, EMG, and cortical REM correlates" (114). It is

conceivable that sleep may not be necessary in the setting of schooling of fish or flight in flocks by birds, in which case the functional process of sleep occurs during wakefulness (104).

IV. CLINICAL STATE DISSOCIATION IN HUMANS

Over the centuries, the presentations of and attitudes toward dissociated or automatic behaviors in humans have changed dramatically – ranging from demon possession, witchcraft, shamanism, hysteria, alien abductions, various psychiatric conditions, and frank malingering, to the current notion of psychobiologic phenomena. Both experimentally-induced and naturally occurring state dissociations in animals serve to predict spontaneously occurring "experiments of nature" and drug-induced state dissociation in humans, which clearly exist on a broad spectrum of expression. Such state dissociations are the consequence of timing or switching errors in the normal process of the dynamic reorganization of the CNS as it moves from one state of being to another. Elements of one state persist, or are recruited, erroneously into another state, often with fascinating and dramatic consequences.

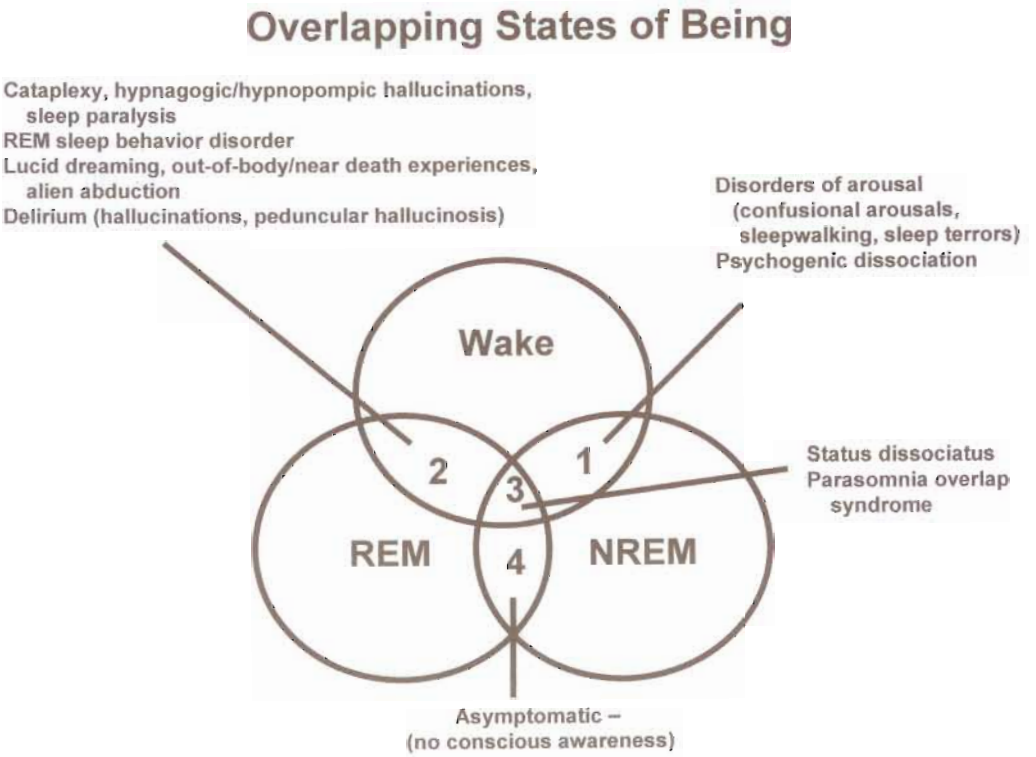

Fig. 2. - *Areas of overlap among states of being (modified from ref. 130).*

There are a number of well-documented state dissociations in humans which occur spontaneously, or as the result of neurologic dysfunction or medication administration. It is practical to assign each as a variant of the predominant or prevailing parent state (W/NREM/REM), instead of identifying each possible dissociated state as an independent entity (Fig. 2).

A. *Wakefulness variations.*

Sleepiness.

There is growing evidence that simple sleepiness may represent an admixture or rapid oscillation of wakefulness and sleep, a notion exemplified by Dinges' concept that "sleepiness = wake-state instability" (36).

Narcolepsy.

Narcolepsy is the prototypic dissociated state arising from the background of wakefulness, and may best be thought of as a disorder of "state boundary control" (28). The symptom of cataplexy (sudden loss of muscle tone, usually in response to an emotionally-laden event) simply represents the isolated "boundary-crossing" of REM sleep atonia into wakefulness. The element of surprise in triggering cataplexy supports the described similarity between the alerting response and REM sleep (67). Similarly, the symptom of sleep paralysis is the persistence of REM atonia into wakefulness. The hypnagogic (occurring at sleep onset) and hypnopompic (occurring upon awakening) hallucinations represent dream mentation occurring during wakefulness. These "hallucinations" (dreams) may be particularly frightening if accompanied by sleep paralysis (228). Narcoleptic patients may experience waking dreams – particularly during drowsiness, and be misdiagnosed and even treated as having schizophrenia (56, 203). The polygraphic occurrence of ambiguous or dissociated sleep is well-documented in the untreated narcoleptic.(49) The induction of dissociated states in narcolepsy by tricyclic antidepressant administration indicates that genetically determined and pharmacologically potentiated state-disrupting factors may act in concert (19, 30, 77). Importantly, underscoring the tendency to experience "switching errors", sleep paralysis and hypnagogic hallucinations occur frequently in the non-narcoleptic population, particularly in the setting of sleep deprivation (158, 224).

Hallucinations (wakeful dreaming).

Historically, there has been a perceived dichotomy between dreams and hallucinations. The former, although occasionally unpleasant, were held to be normal phenomena, whereas the latter were felt to be a hallmark of, if not a defining factor for, certain major psychiatric disorders. Experience in clinical sleep disorders centers, on psychiatric and internal medicine wards, and in intensive care units raises questions as to the wisdom of perpetuating this dichotomous concept.

Consciousness is now considered to be a primary function and activity of the brain itself. If so, then consciousness is simply the brain's interpretation and

integration of all information being made available to it at any given point in time. It is clear that the brain is active across all states of being: wakefulness, REM sleep, and NREM sleep. Under certain circumstances, it is likely that dreaming and hallucinations may represent variations on the same theme. In usual circumstances, during wakefulness, the brain is ignoring internally generated activity, and is attending to environmental sensory stimulation. This may reflect alterations in neuromodulation between wake and sleep (84, 97). During sleep, dreaming occurs because the brain attends to endogenously generated activity. In unusual (boundary-blurring) settings such as sleep-deprivation, sensory deprivation, or medication or drug ingestion, the brain has the opportunity to attend to exogenous and endogenous activities simultaneously, resulting in hallucinations, or wakeful dreaming. This concept is supported by numerous neurologic conditions and syndromes which are associated with "hallucinations".

Although initially felt to be a marker of rapid eye movement (REM) sleep, it has recently been established that dreaming can occur during all stages of sleep - both REM and non-REM (NREM) sleep, and may even occur during relaxed wakefulness, when alpha activity is present on the electroencephalogram (16, 26, 32, 37, 63, 178). Further support of this fact is that dreaming is frequently reported following NREM sleep occurring during multiple sleep latency test naps (16).

In contrast to dreams, hallucinations are felt to be abnormal experiences, and are often presumed to indicate the presence of underlying psychiatric conditions. The term from which "hallucination" is derived means "to wander in the mind", and refers to waking sensory experiences having no apparent external physical stimulus (222).

All theories on the nature of hallucinations share the concept of misperception and misinterpretation of endogenously generated brain activity which is occurring in the setting of relative preservation of consciousness, supporting an organic neurophysiological explanation for many hallucinatory phenomena. The concept of state dissociation permits thinking of some hallucinations as wakeful dreams (133).

For perspective, the incidence of occasional hallucinations in the non-psychiatric population is far greater than generally acknowledged (135, 171, 211). Hallucinations occur spontaneously, albeit infrequently, in the normal, presumably non-psychiatric population: between 10% and 27% of the general population report having had an hallucinatory experience (222). Furthermore, hallucinations may be readily induced in normal individuals under a number of circumstances such as: sensory deprivation, drug administration, food deprivation, and sleep deprivation (214).

Moreover, didactic dogma promulgates the myth that auditory hallucinations are indicative of psychiatric disease, whereas visual hallucinations are more suggestive of organic neurologic conditions. Closer analysis of data regarding the relationship between any specific type of hallucination and an underlying "organic" or "psychiatric" condition indicates that the overlap is extremely great, precluding use of the nature of the hallucination as a reliable predictor of neurologic vs. psychiatric disease. In fact, hallucinations are *never* pathognomonic for any given disorder (10, 70).

Under a number of different circumstances, hallucinations can readily be induced in individuals without psychiatric or neurologic disease. Examples include (for review, see 133):

a) *Sensory deprivation*
b) *Drug ingestion and medication administration*
c) *Food-deprivation*
d) *Sleep deprivation*

These hallucinatory-inducing situations have been used alone or in combination by mystics, prophets, ascetics, and religious figures to potentiate visual and/or auditory communications with the supernatural, or to receive prophecies (17, 115).

Hallucinations may be seen in a wide variety of neurological disorders - often in the setting of sensory deprivation and/or diffuse CNS dysfunction (18,31). In some (if not many) cases, the hallucinations may represent a release of REM (or NREM) dream-like mentation into wakefulness, supporting the concept of dream-hallucination isomorphism. Examples include: (for review, see 133).

a) *Charles Bonnet syndrome.*

This syndrome refers to visual hallucinations occurring in patients with reduced visual input to the CNS – at any level – usually ocular. That these hallucinatory experiences represent acquired changes or reorganization in brain function are suggested by the fact that pre-collicular blindness acquired in utero, infancy, or early childhood may result in permanent EEG changes (slowing and spike foci) in the occipital regions. It is well known that isolated cortex develops hypersensitivity (35).

b) *Brainstem lesions and musical hallucinations.*

Both formed and unformed auditory hallucinations have been well-described in a variety of peripheral and central lesions resulting in impaired auditory acuity (61, 153).

c) *Phantom limb phenomenon.*

Phantom limb hallucinations are reported in patients who have lost extremities, or who have lost sensory information coming from portions of the body (142). They have been reported to occur in up to 100% of patients following spinal cord injury (25). Interestingly, phantom limb perceptions may be present during dreaming, and may persist in dreams after resolving during wakefulness (64).

Amputation of an extremity is not necessary for the development of phantom limb sensations (i.e., the phantom limb phenomenon may follow brachial plexus injury without the loss of the arm). Subsequent surgical removal of the deafferented arm will have no effect upon the hallucinations. It is clear that these sensations must be arising from the higher levels of the CNS, as lesions of the peripheral nerves, spinal rootlets, pathways within the spinal cord, areas of the thalamus, and even extirpation of the primary sensory cortex receiving information from the "phantom" will not predictably alleviate the symptom. Therefore, the brain generates the experience of the body, and sensory information simply modulates that

experience. In support of this concept is that people born without limbs may experience phantoms (112, 142).

There is now overwhelming evidence that the nervous system is far more plastic than previously thought (106, 143). There are rapid changes in cortical organization following both deafferentation and deefferentation of peripheral structures (174). Deafferentation of an extremity by local anesthesia may result in increased excitability of cortical neurons, again indicating organic plasticity changes in the CNS as a response to absence of peripheral sensory stimulation (184). Interestingly, the magnetoencephalographic study mentioned above identified thalamocortical oscillatory abnormalities in patients with the phantom limb syndrome (124).

Visual, auditory, and phantom limb hallucinations are all excellent examples of "deafferentation" hallucinations, resulting from distortions in the normal processing of sensory information, so that abnormal perceptions occur centrally. The fact that these hallucinations can arise from peripheral pathology (ocular, auditory, limb sensory) clearly indicates that primary brain lesions are not necessary (179). Rather, the normally functioning brain is generating false information by attending to internally generated phenomena which are "released" in the absence of competing external sensory information. Recent studies suggesting that tinnitus is centrally generated support the concept of cortical plasticity resulting in the generation of a sensation which is perceived as originating peripherally (126).

d) *Peduncular hallucinosis.*

Waking hallucinations have been well-described in deep, midline lesions involving the thalamic, midbrain, hypothalamic, and third ventricular regions of the brain (59, 136, 139). That these hallucinations may represent the release of REM (or NREM) sleep dream-like mentation are supported by the fact that lesions in the same brain regions may result in symptomatic narcolepsy and cataplexy, a condition associated with the intrusion of REM sleep phenomena into the waking state (4).

e) *Neurodegenerative disorders.*

Hallucinations are often seen in a variety of neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and other related conditions such as cortico-basilar degeneration and dementia with Lewy bodies (109,121,188,201). Fatal familial insomnia, a prion disease associated with thalamic degeneration is often accompanied by hallucinatory behavior, and shares some features in common with the REM sleep behavior disorder - suggesting the admixture of states (170). The phenomenon of "sundowning" (agitation associated with darkness seen in patients with diffuse neurological dysfunction) may be related to reduced sensory input (24).

It is abundantly apparent that hallucinatory phenomena occur in a wide variety of settings: in normal individuals (particularly in the setting of sleep or sensory deprivation, or exposure to medications/drugs), in patients with psychiatric disorders, and in patients with CNS abnormalities. The nature (auditory, visual, or somesthetic) of the hallucinatory experience is not specific for any of these groups.

The unifying theme appears to be the rise (or intrusion) of internally generated brain activity into waking consciousness - the result of a mixed state of being: the waking brain attending *both* to the real environment *and* to internally generated brain activity which is usually suppressed by, or ignored due to, environmental stimulation. During all stages of sleep, attending to such internally generated brain activity is the norm, resulting in dreaming. The spectrum of dreams and hallucinations in various conditions is schematically shown in Figure 3.

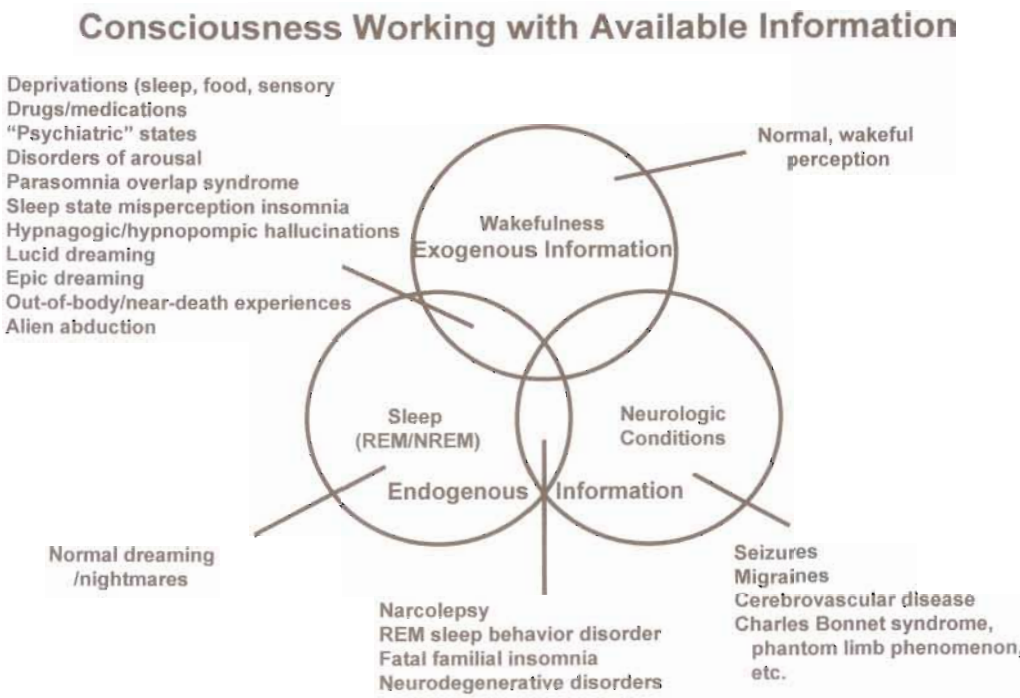

Fig. 3. - *A schematic representation of the spectrum of dreams and hallucinations across the states of being and in various neurological and psychiatric conditions (modified from ref. 133).*

B. *REM sleep variations.*

REM sleep Behavior Disorder (RBD).

RBD is the premier example of a dissociated state arising from the background of REM sleep. In retrospect, RBD was predicted in 1965 by animal experiments (96) Isolated case reports which likely described RBD preceded its formal recognition in humans in 1986 (131, 192). During normal REM sleep, there is background atonia involving all somatic musculature (sparing the diaphragm and extraocular muscles). Although this generalized atonia may be briefly interrupted by excitatory inputs resulting in muscle jerks and twitches (34), the prevailing atonia prevents

motor activity associated with dream mentation. RBD results from incomplete declaration of REM sleep: all elements of REM absent the atonia. In RBD, motor behavior attendant with dream imagery may be vigorous, occasionally with injurious results.

The acute, transient form of RBD is seen most frequently in the setting of drug intoxication or withdrawal states. There is also a chronic form of RBD, most often affecting older males. Nearly half of subjects with chronic RBD have identifiable underlying neurologic disorders (131). The fact that over half of cases are idiopathic, and tend to occur in the elderly suggests that RBD may be the reverse of sleep ontogeny (see Comment section). The absence of identifiable peri-locus ceruleus lesions in the "symptomatic" subgroup is of interest, and confirms animal experimental data which indicate that supra-pontine lesions may also affect REM sleep atonia (46). In the animal model, chloramphenicol administration can reverse the peri-locus ceruleus lesion-induced REM without atonia indicating that other structures are capable of inducing REM atonia (2). An analogous situation during W is the fact that cortical, rubral, and pontine neurons all contribute to anterior horn cell phasic excitation, indicating that motor activity may be initiated at several levels of the CNS (85).

Electrographic dissociation of REM sleep (absence of muscle atonia during REM sleep) and full-blown RBD may be induced in humans by the commonly-

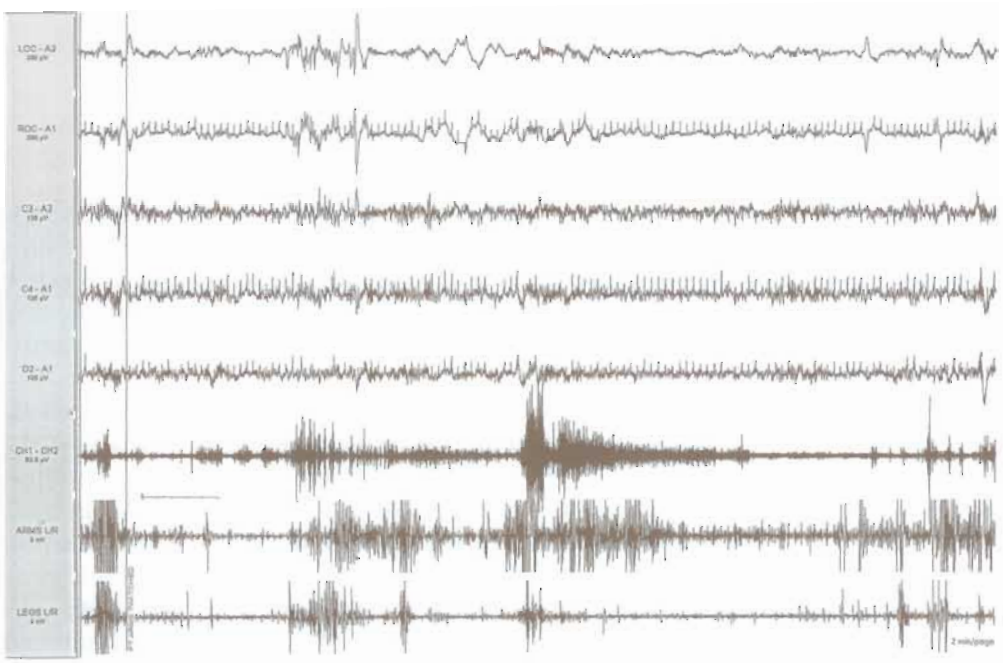

Fig. 4. - *Prominent tonic and phasic EMG activity during REM sleep in a patient with venlafaxine-induced REM without atonia and RBD.*

Legend same as Fig. 1; Arms - extensor digitorum EMG; Legs - anterior tibialis EMG.

prescribed tricyclic antidepressants, serotonin-specific reuptake inhibitors (SSRIs), and venlafaxine (Fig. 4) (21, 164, 196, 202). Spontaneously occurring RBD has also been reported in dogs and cats (81).

Other sleep-dream phenomena.

A number of other conditions have been attributed to mixed states of being, including hypnagogic/hypnopompic hallucinations in the general population and in narcolepsy, out-of body experiences, near-death experiences, and even "alien abductions" (73, 130, 160). It should be mentioned that hypnagogic and hypnopompic hallucinations occur in over one-third of the normal population (158). Lucid dreaming is another example of a mixed W/REM state, during which the dreamer is both aware of the fact that he/she is dreaming and has the ability to influence the course of the dream. REM sleep is the parent state during lucid dreaming, yet there is sufficient persisting wakefulness that subject has the facility to physically signal the presence of such a dream by means of voluntary eye and digit movements (117). Suppression of the H-reflex, a characteristic of REM sleep, persists during such dreaming (29). One recently described condition, "epic dreaming" may also represent a mixed state of being, with relative preservation of the memory systems during sleep - resulting in the remembering of the continuous sleep-mentation which occurs in all normal individuals (198, 236). It is also conceivable that some cases of "sleep-state misperception" insomnia (185) may represent an admixture of states.

C. *NREM sleep variations.*

Disorders of arousal.

Disorders of arousal are the most impressive and most frequent of the NREM sleep-state dissociation/admixture phenomena. Disorders of arousal occur on a broad spectrum ranging from confusional arousals, through somnambulism (sleep walking), to sleep terrors (also termed pavor nocturnus). Some take the form of "specialized" behaviors such as sleep-related eating and sleep-related sexual activity - without conscious awareness (177, 197).

The disorders of arousal are prevalent (and perfectly normal) in childhood (1-17%) peaking at 11-12 years of age and are far more common in adults (4-10%) than generally acknowledged (22, 69, 90, 108). Although it has been commonly felt that persistence of these behaviors beyond childhood or their development in adulthood is an indication of significant psychopathology (98, 216), numerous studies have dispelled this myth, indicating that significant psychopathology in adults with disorders of arousal is usually *not* present (75, 125, 146, 194). The clinical features, laboratory evaluation, and treatment of disorders of arousal have been extensively reviewed elsewhere (132).

The recently described cyclic alternating pattern (CAP) may play a role in the etiology of the disorders of arousal. The CAP is a physiological component of NREM sleep and is functionally correlated with long-lasting arousal oscillations.

The CAP is a measure of NREM instability with high level of arousal oscillation (238). There is no difference in the macrostructural sleep parameters between patients with disorders of arousal and controls (199). However, patients with disorders of arousal have been found to have increases in CAP rate, in number of CAP cycles, and in arousals with EEG synchronization.

Pathophysiology of disorders of arousal.

The pathophysiology of DOA is incompletely understood, however, it is certain that state dissociation plays a role, buttressed by studies of sleep inertia. It is also likely that central pattern generators are involved.

a. *Sleep inertia.*

Mention of the phenomenon of sleep inertia (also termed sleep drunkenness), which occurs normally in humans during the transition from sleep to wakefulness, is germane to the understanding state dissociation in general, and disorders of arousal in specific. Sleep inertia refers to a period of impaired performance and reduced vigilance following awakening from the regular sleep episode or from a nap. This impairment may be severe, last from minutes to hours, and be accompanied by polygraphically recorded microsleep episodes (53, 54, 181). Recent studies have clearly proven that sleep inertia is a potent phenomenon, resulting in impaired performance and vigilance, averaging *one hour, and requiring 2-4 hours to dissipate,* in normal, non-sleep-deprived individuals, and is worse following sleep deprivation, one of the known triggers for sleepwalking (1, 94, 235). Basic science support of a gradual disengagement from sleep to wakefulness comes from neurophysiologic studies in animals (89) and cerebral blood flow studies in humans (14, 111, 234). The persistent reduction, lasting minutes, of the photomyoclonic response upon awakening from NREM sleep is further confirmation of a less than immediate transition from sleep to wakefulness (141). Impaired performance during the transition from sleep to wake has important implications for rapid decision-making upon forced awakenings (such as a middle-of-the-night telephone call) and for performance following scheduled naps in the workplace (186). There appears to be great inter-individual variability in the extent and duration of sleep inertia - both following spontaneous awakening after the major sleep period, and following naps. Sleep inertia may be thought of as the "confusional arousal" potential in all of us, and it may be that disorders of arousal represent an extreme form of sleep inertia.

b. *Central pattern generators/locomotor centers.*

The fact that violent or injurious behaviors may arise in the absence of conscious wakefulness and without conscious awareness raises the crucial question of how such complex behavior can occur. Examination of extensive animal experimental studies provides preliminary answers. The widely-held concept that the brainstem and other more "primitive" neural structures primarily participate in elemental/vegetative rather than behavioral activities is inaccurate. There are overwhelming data documenting that highly complex emotional and motor behaviors can originate from these more primitive structures - without involvement of higher neural structures such as the cortex (15, 20, 40, 44, 74, 120, 204).

There are striking behavioral similarities between documented sleepwalking/sleep terror related behaviors demonstrated by humans and "sham rage" as seen in the "hypothalamic savage" syndrome (68). Although it has been assumed that the "sham rage" animal preparations are "awake", there is some suggestion that similar preparations are behaviorally awake, and yet (partially) physiologically asleep, with apparent "hallucinatory" behavior possibly representing REM sleep dreaming occurring during W, dissociated from other REM state markers (107). The neural bases of aggression and rage in the cat also support an anatomic basis for some forms of violent behavior (20, 205). In humans, confusional arousals which can result in confusion or aggression, there is clear electroencephalographic evidence of rapid oscillations between W and sleep (76, 180). It is likely that such behaviors occurring in states other than W are the expression of motor/affective activity generated by lower structures - unmonitored and unmodified by the cortex. This accounts for the fact that decorticate experimental and barnyard animals are capable of performing very complex, integrated motor acts. These animal studies provide insights to sleep-related violent behaviors in humans: structural lesions at multiple levels of the nervous system have been implicated in wakeful violence (23, 58, 72, 232).

Keeping in mind that not only is sleep a very active process, but that the generators or effectors of many components of both REM and NREM sleep reside in the brainstem and other "lower" centers proximate to LMCs, it is hardly surprising that, during sleep, prominent motoric and affective behaviors do occur.

A common thread linking RBD and the disorders of arousal is the appearance of motor activity which is dissociated from waking consciousness. In RBD, the motor behavior closely correlates with dream imagery, and in disorders of arousal, it often occurs in the absence of (remembered) mentation. This dissociation of behavior from consciousness may be explained by the presence of LMCs, from the mesencephalon to the medulla, which are capable of generating complex behaviors without cortical input. It is likely that during NREM sleep, the LMCs are not activated. The thesis that LMCs are actively inhibited during REM sleep is supported by the observations that in cats, smaller peri-locus ceruleus lesions result in REM sleep without atonia - without any behavioral manifestations, but larger lesions are necessary to produce active motor movements. Clearly, the isolated loss of REM atonia is insufficient to explain complex REM sleep motor activity in the experimental animal (150), suggesting a release of LMCs during the parent state, just as is seen in the loss of REM atonia. Dissociation of the LMCs from the parent state of REM or NREM sleep would explain the presence of complex motor behavior seen in both RBD and disorders of arousal. It is possible that the complex motor activity associated with amnesia characteristic of alcohol-induced "black-outs" (239) and with "unconscious" behavior occurring during partial complex seizures represents dissociation between LMCs and waking consciousness and/or memory (165). Such dissociation between behavior and consciousness may be related to inactivation of attentional or memory systems (88).

c. *Parasomnia overlap syndrome.*

The recently described "parasomnia overlap" syndrome, further linking RBD with disorders of arousal may serve to expand the concept of state-dependent motor dyscontrol. In this syndrome, the patients have both clinical and PSG evidence of both disorders of arousal and RBD, suggesting the possibility that motor dyscontrol during sleep is the primary abnormality. If this motor dyscontrol occurs during NREM, the result is disorders of arousal; if during REM, the result is RBD (191).

d. *Status dissociatus.*

A condition termed "status dissociatus" is the most extreme form of RBD, and appears to represent a complete breakdown of state-determining boundaries. Clinically, these patients, by behavioral observation, appear to be either awake or "asleep;" however, clinically, their behavioral "sleep" is very atypical, characterized by frequent muscle twitching, vocalization, and reports of dream-like mentation upon spontaneous or forced awakening. Polygraphically, there are few, if any, features of either conventional REM or NREM sleep; rather, there is the simultaneous admixture of elements of wakefulness, REM sleep and NREM sleep. Conditions associated with status dissociatus include protracted withdrawal from alcohol abuse, narcolepsy, olivopontocerebellar degeneration, and prior open heart surgery. Clonazepam may be effective in treating the sleep-related motor and verbal behaviors (129, 130). The clinical features of fatal familial insomnia, a prion disease closely related to Creutzfeldt-Jakob disease are highly reminiscent of "status dissociatus" (66, 128).

D. *"Psychogenic" dissociations.*

It is now apparent that psychogenic dissociative disorders may arise exclusively or predominately from the sleep period (62, 200). Virtually all patients with nocturnal dissociative disorders evaluated at our center were victims of repeated physical and/or sexual abuse – which is often un- or incompletely- remembered, beginning in childhood (200). There is now overwhelming neurophysiologic evidence in animal models that such physical or psychic trauma may lead to permanent alterations in functioning of the central nervous system (129, 130), – predisposing to clinical dissociative disorders. This would suggest that these disorders also have a neuro(psycho)biological basis, and may not be "functional" in the psychiatric sense. These conditions include psychogenic dissociative disorder and multiple personality disorder, and have been reviewed elsewhere (200).

V. COMMENTS

Review of the ontogeny of state appearance facilitates the analysis of observed experimental and clinical state dissociations. During embryogenesis, there are no

clear-cut states, but rather the simultaneous admixture of all states, which gradually coalesce to form the three recognizable states of W/REM/NREM (41-45). This ontogeny of state development is supported by phylogenetic studies (208, 209). The mechanisms of complex synchronization/recruitment of the state-specific variables are unknown. Basic science neurophysiologists have long known that state dissociation in animals occurs frequently, under many circumstances (221). The inability of animals to report or indicate mentation and consciousness (i.e. waking hallucinations, mental imagery with disorders of arousal, dream-mentation associated motor behavior in RBD) has been a significant limitation upon the evaluation of animal state dissociation and its application to the human clinical experience.

Many endogenous and exogenous factors can affect state cycling/synchronization. These include (6, 80, 91):

1. age
2. sleep deprivation
3. shift-work/rapid travel across time zones
4. endogenous humoral factors (hormonal)
5. drugs/medication
6. affective disorders
7. environmental stress.

With the multiplicity of state markers, and the relatively rapid normal cycling of states requiring recruitment of these numerous physiologic markers, there are innumerable theoretically possible state combinations. It is likely that major psychic or neural insults can result in acquired functional restructuring of the CNS which then may interfere with conventional state determination (57). There is strong evidence that environmentally-mediated events can and do affect the structure and function of the CNS (71, 80, 140, 161) and that the CNS displays learning of new neural behaviors (92, 99, 172) (i.e. the development of secondary epileptogenesis ["mirror foci"] (148), or acquired sensory synesthesia (47, 175)). Such dissociated states may play a role in the appearance of psychogenic dissociative states. Indeed, given the genetic variability of CNS development and its plasticity (9, 57, 122, 215), the relentless cycling, and the ever-present multiplicity of endogenous and environmental influences upon both CNS plasticity and cycling, it is actually surprising that state-component timing errors do not occur more frequently. Truly, the drive for complete state determination must be very powerful. Striking sleep abnormalities have been reported in a wide variety of degenerative (3, 128, 144, 151, 162, 187, 189) and acquired (12, 48, 83, 123) neurologic conditions. This patient population should serve as a rich source of "high risk for state-dissociation" subjects.

VI. PRACTICAL CAVEAT

The multiple component concept of state determination is a most important notion to consider when pharmacologic or lesion studies are employed to "sup-

press" one or another state. Such manipulation may suppress some of the commonly used markers for that state (i.e. polygraphic) - without affecting other variables of that state. The naturally occurring (119) and drug-induced dissociation between REM sleep-related penile tumescence and conventional polygraphic features of REM sleep attest to this fact (100, 217-219). Recent molecular biologic studies mentioned above underscore the complexity of state determination (38). Nielsen's concept of "covert REM" to explain the confusion of REM sleep vs. NREM sleep dreaming lends clinical relevance to the concept of part of one state manifesting itself during polygraphic trappings of another state (154, 155), as does the phenomenon of sleep inertia (discussed above). This concept is supported by the fact that cortical activity of REM sleep may precede commonly used polygraphic physiologic markers of REM sleep (157).

VII. PERSPECTIVES

We, as clinicians, are in no position to add to the basic science bench research aspect of these most important studies. What clinicians can contribute is the application of the basic science findings to the human clinical condition, to see if there is relevance, and if there is, communicate back to the basic scientists to encourage additional studies, and ask for specific answers for other related clinical phenomena. Indeed, these studies all have a high degree of relevance to the human condition, and have served to explain previously enigmatic clinical complaints, symptoms, and findings.

The question: "What is the minimal component of the brain that is capable of sleep?" – when viewed in the context of the above-mentioned basic science research – lends itself to fascinating extrapolation of basic science animal research to the human clinical condition. All of these studies contribute to the "state dissociation" concept of many human behaviors, and, in fact, many of these state dissociations can be explained by the fact that certain parts of the brain "fall asleep" or "wake up" out of sequence with the parent state of the individual. Two clear examples are: 1) cataplexy (and sleep paralysis) – the REM-atonia generating portion of the brain (presumably the pontomeduallary region) "sleeps" in isolation (during wakefulness) and 2) REM sleep behavior disorder – the REM-atonia generating portion of the brain "wakes up" during REM sleep. These phenomena simply represent "switching errors." Although these may seem to be relatively minor glitches from a neurophysiologic standpoint, the clinical consequences are impressive, and occasionally serious (129, 130).

The concept that sleep is a synchronous phenomenon for the entire brain, or one hemisphere (as in the case of birds and dolphins) for that matter, is not the case, but rather, sleep may occur in small parts of the brain. Extrapolation from these simple examples of small portions of the brain waking or sleeping inappropriately or in isolation to more complex situations likely explains myriad sleep/wake complaints or symptoms discussed above. The animal studies of state generation

and control, and the increasing numbers of human conditions which may be explained on the basis of state dissociation will become important in the growing debate as to whether sleep is a local or global phenomenon (the "top down" vs. the "bottom up" theory).

VIII. FUTURE DIRECTIONS

It is conceivable that human state dissociations may shed light upon the function of sleep. Recently, Kavanau has proposed that fatal familial insomnia (FFI), a prion disease, may be the result of lack of dynamic stabilization of the central nervous system which normally occurs during sleep (105).

Kavanau's theory of dynamic stabilization also raises the ostensibly egregious question: "Is the development of Parkinson's disease in the setting of RBD due to the interference of dynamic stabilization during REM sleep in these individuals" (193)?

He contends that in FFI, the progressive loss of sleep interferes with the suspension of sensory processing, and progressively reduces non-sensory dynamic stabilization. The end result is the lack of maintenance of neuronal network integrity. Therefore, the symptoms of FFI, other than insomnia, are due to widespread insufficiencies of dynamic stabilization. Support for this hypothesis is that these symptoms are not seen in other prion diseases (unaccompanied by insomnia), and therefore may be a direct consequence of the insomnia (failed dynamic stabilization) per se. The absence of sensory symptoms in FFI may would be explained by the fact that the sensory systems are operating nearly continuously, being maintained by "supranormal" functional dynamic stabilization.

If the FFI/failed dynamic stabilization model may serve as an explanation for *what happens if* processing of sensory information is not suspended, then it would be encouraging to find another model which could address the consequences of absence of the dynamic stabilization resulting from the lack of motor inhibition during REM sleep. Understanding this concept requires a review of the motor dynamic stabilization theory of the function of REM sleep.

Kavanau's motor stabilization theory states that in more primitive animals, the skeletal muscle hypotonia (not atonia) was sufficient to permit motor non-utilitarian dynamic stabilization to persist without interrupting sleep. As endothermy evolved, the skeletal muscle hypotonia of primitive sleep may have become insufficient to prevent sleep-disrupting skeletal muscle contractions during non-utilitarian dynamic stabilization. This may have led to the development of inhibition of skeletal muscle tone (actual atonia) during a portion of primitive (NREM) sleep. REM sleep may have evolved through modifications of this fraction of NREM sleep, driven primarily for suppression of disruptive movements in sleeping endotherms during reinforcement of motor circuits by dynamic stabilization. Support for this theory is that constantly-swimming marine animals engage only in unihemispheric NREM sleep. They do not require REM sleep and its non-utilitarian dynamic stabilization, as the circuitry is in virtually continuous use (101-103).

There is evidence to support the concept that REM sleep developed from NREM sleep in the works of Siegel (210), and that in humans, REM and NREM sleep in utero develop from a common precursor (65). The pioneering work by Roffwarg and his group suggests that REM sleep plays an important role in the development of the CNS. The overwhelming state of being in utero in mammals is REM sleep (173), and REM sleep deprivation in utero results in abnormal brain development (134, 159, 176). These facts support Kavanau's motor circuitry dynamic stabilization theory for the development of REM sleep from a more primordial sleep in endotherms.

Returning to the human condition, it is possible that the REM sleep behavior disorder (RBD) may shed some light on the consequences of the absence of motor dynamic stabilization during REM sleep. As mentioned above, RBD is a condition characterized by the absence of the anticipated atonia during REM sleep, permitting patients with RBD to "act out" their dreams, occasionally with violent or injurious consequences. This condition is seen most commonly in older (> 50 years of age) males (88% male) (195). In one series of older men initially felt to have "idiopathic" RBD, 38% went on to develop clear-cut Parkinson's disease (PD) (193). Although subtle signs and symptoms of PD may antedate the fully-developed clinical PD by some time, the average interval between the onset of the symptoms of RBD and the development of PD in this group of patients was 12 years. This extraordinary interval allows us to at least ask: "Is the development of PD in patients with RBD, in fact, the consequence of failed motor dynamic stabilization during REM sleep?"

Interestingly, there also appears to be a relationship between FFI and RBD-like symptoms (dream-enacting behaviors during both wakefulness and sleep). These RBD-like symptoms in FFI may reflect the appearance of REM sleep dynamic stabilization intruding into wakefulness and NREM sleep.

These two uncommon clinical neurological syndromes, FFI and RBD, do, in fact provide tantalizing, but imperfect, support to buttress the dynamic stabilization theory of sleep - one involving sensory (FFI), the other, motor (RBD) consequences of failure of dynamic stabilization, with dramatic clinical consequences

In his thoughtful and elegant discussion of the search for the function(s) of sleep, Rechtschaffen urges us to be cautious in our selecting any currently proposed theories of the function of sleep, as many exist, and although each has its merits, likewise, each has serious unanswered questions and unexplained loose ends. Numerous studies of sleep deprivation in animals (inevitably fatal if of sufficient extent) have shown the biological importance of sleep, but have provided little information regarding its function (169). Rechtschaffen has pointed out flaws in the Krueger and Kavanau theories, including: the lack of specification of sensitive sensors which direct neuronal activity during sleep preferentially to the synapses needing strengthening, and the fact that these theories require the operation of elaborate processes to direct the neural activity to those synapses which are worth preserving (169). Furthermore, Kavanau's dynamic stabilization theory of the function of sleep does not explain the fact that either total sleep (NREM and REM) or selective REM sleep deprivation is fatal in rats. The cause of death in

sleep-deprived rats remains unknown, but it does not appear to be due primarily to brain dysfunction, which should be the case if one were to extrapolate from the FFI/failed dynamic stabilization model. Our highly speculative proposal of the relationship between RBD and the subsequent development of PD must also be considered with great skepticism, in view if fact that an extraordinarily high percentage of patients with PD and similar conditions such as multiple system atrophy may develop RBD coincidental or subsequent to the onset of the extrapyramidal symptoms (147, 163, 167, 183, 212, 213, 223, 226).

An overview of all the literature on the function of sleep suggests that sleep is a biological necessity in its own right - but why (169)? Kavanau has proposed a highly conjectural answer, and, for the first time, has used human clinical observations to support his theory. It is important to offer such theories for scrutiny, criticism, and refinement by the scientific community. His theory flawed or not, this approach could lead to very important discoveries, and encourages the continued close collaboration between basic neuroscientists and clinicians. Neurologic conditions such as FFI and RBD may serve to expand our knowledge, and confirm or refute important theories of the function of sleep. Sensitive new tools such as functional neuroimaging may add invaluable new perspectives (127). Such experiments of nature undoubtedly exist in many forms, and will be identified, if only we look closely enough.

SUMMARY

The concept of state dissociation in humans was made possible only by applying information obtained from basic science animal research studies to the human condition - without which these often dramatic, and treatable conditions would have remained in the mystical, supra-natural, or psychiatric arenas, without appropriate or effective treatment options. Sleep or wakefulness occurring asynchronously in bits and pieces of the brain is a most useful concept. From our standpoint, the basic science work in the function and mechanism of sleep is pertinent, not only adding to our knowledge in these important areas for the sake of knowledge, but also in providing clinicians with important information that is of immense clinical importance. The payoff of such research has been great, and demands that it should be ongoing. The field of sleep research and sleep medicine is in a unique position to foster close interactions between basic scientists and clinicians, the result being basic science answers to clinical questions, and unanswered clinical questions guiding the direction of and reinforcing the basic science research. The clinical conditions discussed above underscore the value of close cooperation among those working at all levels: molecular, cellular, multi-cellular, and clinical. Continued study of state dissociation by both basic scientists and clinicians will undoubtedly identify and explain even more of these fascinating conditions, with important therapeutic implications. The reciprocal benefits of close collaboration between basic scientists and clinicians will continue to be realized.

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