Sleep
12(4):323–337, Raven Press, Ltd., New York

Sleep in Patients with Spontaneous Panic Attacks

Peter J. Hauri, *Matthew Friedman, and *Charles L. Ravaris

*Sleep Disorders Center, The Mayo Clinic, Rochester, Minnesota; and *Department of Psychiatry, Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire, U.S.A.*

Summary: Twenty-four drug-free patients with a DSM-III diagnosis of panic disorders (and their age- and sex-matched normal controls) slept in the laboratory for 3 consecutive nights. Panic patients showed a slightly longer sleep latency and a lower sleep efficiency than their normal controls. They also had more overall movement time and more body movements during stage 2 sleep. Eight panic attacks were recorded arising out of sleep. Six of them occurred in the transition phase between stage 2 and stage 3 sleep. The nocturnal panic attacks of these patients are unique, different from stage 4 sleep terrors, and different from dream anxiety attacks. **Key Words:** Panic disorder—Polysomnography—Nocturnal panic attacks—Sleep panics—Anxiety.

Although panic disorders have apparently existed for millenia, not until the publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980 (1) were they widely recognized as being separate entities, distinct from anxiety disorders or from other neurotic problems. Since that publication in 1980, panic attacks have become one of the most widely researched psychiatric entities, and much progress has been made (2,3). Nevertheless, significant aspects of panic disorders still await clarification. In particular, their etiology is much disputed. The debate primarily concerns whether panic attacks initially have a psychological or a biologic etiology.

Panic attacks can be explained psychologically both by psychodynamic theories (4) and by behavioral theories involving conditioned anxiety (5). Biologic theories, on the other hand, suggest that panic patients may suffer from abnormalities in brain neurotransmitters and/or receptor functions, from hyperventilation, from autonomic nervous system dysregulation, or from other brain dysfunctions that might precipitate spontaneous panics (6–9). Although an impressive array of research evidence currently supports the biologic theories, a psychogenic etiology cannot be ruled out. How could one ever prove that the apparently spontaneous panic attacks are not caused by some unconscious anxiety-inducing thought or by previous learning?

Accepted for publication August 1988.
Address correspondence and reprint requests to Peter J. Hauri, Ph.D., Mayo Sleep Disorders Center, The Mayo Clinic, Rochester, MN 55905, U.S.A.

A second unresolved issue concerns the diagnostic place of panic disorders, especially their relationship to depression and anxiety. DSM III-R conceptualizes panic disorders as a subtype of the anxiety disorders, mainly because anxiety and avoidance are characteristic for both panic disorders and generalized anxiety disorders. However, this nosologic fit is not perfect: The episodic, intense fright of a panic attack is not completely equivalent to the chronic and relatively stable agitation of a generalized anxiety disorder. In addition, many investigators have shown that depression occurs much more frequently in panic disorder patients than would be expected by chance, suggesting that depression and panic disorders may have a common etiology (10–14).

Because the diagnostic picture is not yet fully clear, investigators have searched for biologic markers that would clarify these diagnostic issues. Sleep may be one such marker (15). So far, investigations have focused mainly on the sleep of depression and of generalized anxiety disorders. Although specific differences vary somewhat from study to study, apparently depending on the specific subgroups of depression or anxiety disorder included, some differences seem clear. Depression may manifest itself mainly in rapid eye movement (REM) disturbances such as short REM latencies, more REM sleep early during the night, a higher REM density (more eye movements per minute of REM sleep) and, possibly, more total REM sleep during the night (16,17). However, although these REM disturbances may be quite sensitive to depression, they appear to be less specific to depression than had been hoped previously (18). Sleep in the generalized anxiety disorders is characterized by relatively normal REM measures, but by increases in stage 1 and 2 sleep and, possibly, by a decreased amount of REM sleep (19,20). Despite these differences, there are also many similarities in the sleep disturbances of depression and of anxiety: Both show difficulties with initiating and maintaining sleep (increased sleep latency, decreased sleep efficiency, and more awakenings during sleep than normal). Both also show less delta sleep than normal, possibly as a consequence of their increased sleep fragmentation.

We are aware of only three studies that compare somnographically evaluated sleep in panic patients with normal sleep. Uhde and co-workers (21) studied nine panic patients who were drug-free for 2 weeks. Each patient slept in the laboratory for 3 consecutive nights, but the first night was discarded to allow for habituation. Uhde and co-workers showed that panic patients had more movement time, a shorter REM latency, and decreased REM density as compared with matched normal subjects, but panic patients slept like normal subjects in all other respects. Dube and colleagues (22) compared the sleep of 19 patients with panic disorders with that of 52 patients with a primary major depressive disorder, that of 40 patients with a "mixed" diagnosis (both major depressive disorders and panic attacks), and that of 23 normal subjects. All patients were drug-free for 2 weeks, and each slept in the laboratory for 3–4 nights. The first night in the laboratory was again discarded to allow for habituation, and only data from night 2 were reported. According to Dube and colleagues, panic patients could not be distinguished from normal subjects on *any* sleep variable. Specifically, contrary to the findings of Uhde and co-workers, panic patients showed normal REM latencies and normal REM densities. Those with primary major depressive disorders showed the expected higher REM percentages and shorter REM latencies, and those with a mixed diagnosis (panics and depression combined) had somewhat more difficulty falling asleep (as did the depressive patients) but they then showed normal REM latency and normal REM percentage. Finally, Pecknold and colleagues (23), in a study of 44 panic patients, confirmed Dube and colleagues (22) in finding normal REM parameters but disagreed

with the other two researchers because they found poor sleep efficiency in panic patients (84 ± 12%).

Some investigators have sought other sleep-related biologic markers to distinguish psychiatric subcategories. One idea was to compare the patients' reactions to sleeping in the laboratory for the first night. Akiskal and associates (24) showed that dysthymic patients had the expected normal first night effect (sleeping poorly in the first night in the laboratory), whereas anxious patients had an exaggerated first night effect, sleeping even more poorly than expected. However, this latter finding was contradicted by Reynolds and co-workers (20) who found instead that anxious patients showed very little difference between the first and the second night in the laboratory. So far, the first night effect has not been described in panic patients because both Uhde and co-workers (21) and Dube and colleagues (22) discarded all data from that night.

Another unresolved issue in panic patients concerns the nocturnal panic attacks which reportedly awaken some of these patients from their sleep. The literature contains only a few marginal reports. Lesser and associates (25) recorded one panic attack arising directly out of delta sleep, suggesting that nocturnal panic attacks may be similar to sleep terrors. Bell and colleagues (26) found an increase in nocturnal panic attacks in patients who also suffered isolated sleep paralysis, suggesting a possible relationship between nocturnal panics and REM sleep. Mellman and Uhde (27) recorded six panic attacks during sleep, all of them arising out of either stage 2 sleep or stage 3 sleep.

In our study of 24 drug-free panic patients, we wished to evaluate whether any of the sleep abnormalities reported either by Dube and colleagues or by Uhde and co-workers could be replicated. In addition, we also were interested in the first night effect in these panic patients and hoped to document panic attacks that occurred during sleep.

METHODS

The sleep evaluation we report was part of a larger study on the diagnosis, treatment, and follow-up of patients with panic attacks. The overall study involved an initial screening of volunteers and withdrawal from all medications, followed by 3 nights of sleep in the laboratory. Patients were then given either alprazolam or propranolol in a 6-week double-blind clinical trial. Following this drug treatment, they again slept in the laboratory for 3 nights and returned for 6- and 12-month interviews. Of this larger study, this report involves only the 3 initial, drug-free nights in the Sleep Laboratory.

Entrance criteria

To be included, volunteers had to be aged between 18 and 61 years and suffering from a DSM-III diagnosable panic disorder. In the last 3 weeks before the interview, they had to have had a minimum of three panic attacks in other than life-threatening situations. These attacks had to be marked by a sudden onset of intense apprehension, fear, or terror and had to show a minimum of 4 of the 12 symptoms outlined in DSM-III. Patients with agoraphobia, social, and/or simple phobias were accepted as long as spontaneously occurring panic attacks also occurred at least once a week. Patients with affective disorders were accepted into the study only if the panic disorder clearly had preceded the development of depression. Excluded from the study were patients with bipolar illness, with other psychotic features, with obsessive compulsive disorder, and with significant alcohol or drug abuse within the last 6 months.

Medically, a physical evaluation was required within the last 12 months before en-

trance to the study. Patients with seizure disorders were excluded, as were patients with disorders that made a withdrawal from medications imprudent (e.g., high blood pressure). Similarly excluded were patients for whom treatment with either alprazolam or propranolol would have been contraindicated (e.g., patients with hypersensitivity to benzodiazepines or propranolol or patients with low blood pressure). Also excluded were patients with organic brain syndromes. Finally, female subjects had to practice an acceptable form of birth control, and none were accepted if they were either pregnant or nursing.

Subject selection

An initial subject pool was created by contacting area physicians, describing the study, and inviting referrals. To increase patient flow further, advertisements were also placed in local newspapers asking people to contact us concerning a study of sudden, unexplained panic attacks.

Screening

In all, ~150 telephone inquiries were received. After answering the callers' questions, a trained secretary administered a structured phone screen asking demographics and a description of the problem sufficiently detailed to make a preliminary DMS-III diagnosis and inquired about the callers' current and previous psychiatric and medical health.

The 38 patients who passed the phone screen were each interviewed by one of the authors for 1–2 h. The 1983 version of the Structured Clinical Interview for DSM-III-R (SCID) for affective disorders and anxiety disorders was administered (28). All criteria for inclusion or exclusion were explored and clarified. A tour through the Sleep Disorders Center explained to the patients what would be expected during their sleep in the laboratory. Alternate treatment options for panic disorders were explored. The study was then explained in detail, and patients who were interested signed a consent form. For 34 patients, this interview was done in the office; for four patients who were too agoraphobic to travel, the interviews were done in the patients' homes.

Five of the 38 patients dropped out of the study during the interview: 2 did not meet criteria for a panic disorder, 2 decided to seek clinical treatment rather than be involved in a research study, and 1 decided that she could not sleep with electrodes attached to her skull. Thus, 33 patients were accepted for washout.

Washout. The duration of the washout depended on the half-life of the patients' previous medications. For example, before being accepted to the study, patients who had chronically been taking high doses of Dalmane had to undergo a gradual reduction in dose, followed by a 3-week drug-free interval, whereas a minimum of 4 drug-free weeks were required of a patient on monoamine oxidase (MAO) inhibitors, but only a minimum of 1 drug-free week was required of a patient taking chloral hydrate. Each patient's withdrawal and washout was individually planned and supervised, and frequent contact was maintained with the patients during this difficult period. In four cases, patients had to be seen almost daily during the washout period to provide support.

Subsequent dropouts. Three additional patients dropped out of the study in its early phases: One was rejected because he was unable to abstain from diazepam during washout, 1 panicked when she could not fall asleep easily on the first night in the laboratory and one insisted on taking alprazolam again because her double-blind study

medication (later identified as propranolol) did not suppress her frequent panics but did cause unpleasant side effects.

During the first laboratory sleep night, blood was drawn from each patient to be analyzed for traces of suspected medication in the Boston laboratories of Dr. David Greenblatt. Although all patients had insisted that they were completely drug-free, the blood of six patients showed trace amounts of drugs: In four cases it was alprazolam, and in one case each it was flurazepam and diazepam. Although the drug levels were minute and clearly of no clinical significance in all six patients, they were dropped from the sleep study.

Final study sample. The final sample of patients for the study thus had 24 patients (23 women and 1 man) with a mean age of 34.8 years (SD 9.9, range 18–60 years). Seventeen patients were diagnosed with "agoraphobia with panic attacks" and 7 had "panic disorder with limited phobic avoidance." Fifteen patients had a secondary diagnosis of depression: 7 had major depression, recurrent episodes; 3 had major depression, single past episode; 3 were diagnosed as having a dysthymic disorder; and 3 had both a dysthymic disorder and recurrent major depressive episodes. Seven patients had concomitant social phobias in addition to their panic disorder, and 5 had simple phobias in addition to the panic disorder.

In sum, although the sample was quite homogeneous in that each patient experienced at least one spontaneous panic attack a week, it was heterogeneous with respect to associated psychiatric features such as depression or phobias. Of the 24 patients, 9 reported that panic attacks occasionally awakened them from sleep, whereas 15 reported only daytime panics. Six of the 24 patients remembered having had "nightmares" as children; two additional patients had been told that they had been frequent sleepwalkers. Five of the patients still experienced dream anxiety attacks as adults but described them as being different from their nocturnal panic attacks (more content, less intense fright in their dream anxiety attacks).

Procedures

Sleep was recorded in the laboratory for 3 consecutive nights according to the procedures described by Rechtschaffen and Kales (29). In addition to the four Rechtschaffen and Kales channels, each subject also had recorded, for a minimum of 1 night, one channel each of electrocardiogram (ECG), tachograph, frontalis EMG (integrated), respiratory rate, and two anterior tibialis electromyograms (EMGs). Polygraph recordings were done in the homes of four housebound patients. Patients were repeatedly told to call the technician immediately if they experienced a panic attack while being recorded.

All somnograms were reviewed by an accredited clinical polysomnographer (P.H.) who was searching for sleep apneas, periodic movements during sleep, nonrestorative sleep, or other sleep disorders. No clinically significant abnormalities were found. All records were then scored in 30-s intervals, according to the Rechtschaffen and Kales system (29), with the following exceptions.

Sleep latencies. We recorded both elapsed time from lights out until the first epoch could be scored as stage 2, and elapsed time until the first epoch of stage 2 followed by a minimum of 15 min of continuous sleep, either stage 2 or deeper.

Movement time. In the Rechtschaffen and Kales (29) system, movement time is scored when a majority of an epoch is obscured by movement artifact so that it cannot be determined whether a person is awake or asleep. In addition, the epochs immedi-

ately preceding and following movement time must be scored as sleep; otherwise, epochs obscured by movement artifact are considered wakefulness. Because movement time appeared to be an important parameter according to the data of Uhde and co-workers (21), we scored movement time in seconds rather than in the typical 30-s epochs, as was done with the other stages. Thus, movement time was any obscuring of the somnogram by movement artifact that lasted ≥15 s and was both preceded and followed by sleep.

Stage shift changes. To score stage shifts, we focused on the large changes in EEG-defined sleep, not on very small interruptions of one stage by another. For example, we scored a patient who first was in stage 2, then had numerous episodes alternating between stage 2 and 3, and finally stayed in stage 3 for a minimum of six epochs as having one stage shift. Similarly, we would not count it a stage shift if a patient's REM period was interrupted by another stage for one epoch. However, if either wakefulness or REM sleep interrupted NREM sleep even for only one epoch, we counted it as a stage shift.

Body movements. To be scored as a body movement, the chin EMG had to be elevated 2 times above baseline for 2.5–15 s. In addition, a second somnogram channel had to indicate movement artifact.

REM interruptions. Whenever a REM period was interrupted by either an epoch of wakefulness or 3 epochs of stage 1 or stage 2 sleep, a REM interruption was counted.

REM latency. Only the amount of non-REM (NREM) sleep before REM was counted. If a patient awakened before achieving REM sleep, wake time was not included in REM latency.

Sleep quality. The postsleep questionnaire asked the patients to compare, on a 7-point scale, their home sleep with their laboratory sleep. Two questions were asked: "How soundly did you sleep," and "What was the overall quality of your sleep?" Both of these questions were added, resulting in a scale ranging from 2 to 14, on which laboratory sleep equivalent to home sleep was rated as 8.

Statistics

Each panic patient was matched with a normal sleeper in sex and age (±10%). Only data from nights 2 and 3 are reported in Tables 1 and 2. Because body movements and movement time appeared to be elevated in panic patients, a more thorough analysis seemed indicated. Table 2 reports the data by size of movement and by stages from which these movements arise. The "Large body movements," section shows the stage-by-stage analysis of movement time as defined above. The "Intermediate body movements" section shows the body movements of Table 1 analyzed by sleep stage. Finally, the "Short body movements," (0.5–2.5 s) section shows new data on movements and twitches that satisfied all criteria for body movements except that they lasted <2.5 s.

RESULTS

Overall sleep

Table 1 shows that patients with panic attacks slept remarkably like normal sleepers, although they did take somewhat longer to fall asleep and they slept somewhat less efficiently than normal sleepers. However, these disturbances, although statistically

TABLE 1. *Sleep in patients with panic attacks and in normal sleepers*

Parameter	Panic patients	Normal sleepers	Matched t $p <$
Initiating and maintaining sleep			
Time in bed (min)	437.1 (41)	425.3 (27)	[a]
Time asleep (min)	397.5 (35)	400.6 (33)	[a]
Sleep efficiency (min)	90.9 (4)	94.2 (6)	0.01
Sleep latency (to stage 2) (min)	20.0 (10)	10.9 (5)	0.001
Sleep latency (to 15 min) (min)	34.1 (26)	17.9 (1)	0.01
Awake after sleep onset (min)	24.9 (16)	18.2 (22)	[a]
No. of awakenings >15 s	9.0 (4)	8.9 (6)	[a]
Sleep architecture			
Percentage of			
Stage 1 (%)	7.9 (3)	7.9 (4)	[a]
Stage 2 (%)	57.9 (7)	59.2 (8)	[a]
Delta (%)	11.5 (8)	10.5 (8)	[a]
REM (%)	22.3 (4)	22.1 (4)	[a]
Movement time (%)	0.42 (.4)	0.14 (.3)	0.02
Body movements/hour of sleep (n)	9.6 (5)	7.6 (4)	0.06
Time between stage shifts (min)	14.9 (4)	15.5 (5)	[a]
REM interruptions (n)	4.4 (3)	5.7 (4)	[a]
REM latency (min)	78.8 (30)	73.4 (23)	[a]
Sleep questionnaire			
Time asleep (total) (min)	399.1 (49)	410.4 (29)	[a]
Sleep latency (min)	32.2 (27)	10.2 (5)	0.01
Sleep quality	6.4 (2)	5.9 (2)	[a]

Numbers in parentheses are SD.
[a] $p > 0.10$.

significant, were not very great; both variables were still within the range of normal sleep for the panic patients.

Within sleep, the only abnormality that could be found in the overall somnogram was an increase in movement time and, possibly, an increased amount of body movements

TABLE 2. *Body movements during sleep*

Parameter	Panic patients	Normal sleepers	Matched t, $p <$
Large body movements (typically scored as movement time [>15 s])			
Seconds per hour			
Stage 1	30.3 (32)	10.9 (25)	0.02
Stage 2	38.3 (37)	13.2 (21)	0.01
Delta	3.8 (14)	4.5 (20)	[a]
REM	16.4 (19)	5.8 (11)	0.05
Intermediate body movements (2.5–15 s)			
No. per hour			
Stage 1	19.5 (16)	17.6 (11)	[a]
Stage 2	8.3 (5)	5.9 (4)	0.02
Delta	2.6 (2)	3.1 (3)	[a]
REM	11.5 (6)	9.4 (5)	[a]
Short body movements (0.5–2.5 s)			
No. per hour			
Stage 1	16.2 (20)	15.4 (20)	[a]
Stage 2	2.5 (3)	2.1 (2)	[a]
Delta	22.3 (36)	48.7 (99)	[a]
REM	5.4 (5)	4.0 (5)	[a]

Numbers in parentheses are SD. Definition of the different body movement types is given in text.
[a] $p > 0.05$.

during sleep. The statistical significance of these two findings has to be considered marginal in light of the 19 matched *t* tests made of this data matrix. However, an increase in movement time ($p < 0.05$) in panic patients was also reported by Uhde and co-workers (21) in a different set of patients. Combining the results from the two studies yields a $p < 0.001$. Thus, the increased movement time of panic patients is very likely a true finding, not due to chance.

In the overall somnogram, our panic patients showed no decrease in REM latency, as would be expected from depressive patients (Table 1). This differs from the findings of Uhde and co-workers (21), who reported decreased REM latencies in panic patients. However, the difference between the two studies lies not in the results from panic patients. Both the study of Uhde and co-workers and ours report a mean REM latency of ~75 min for panic patients. The difference lies in the norms obtained from our control groups. Our controls had a mean REM latency of 73.4 min, which is somewhat shorter than expected since our sample had a mean age of 35 years. The 41-year-old controls in the study by Uhde and co-workers had a mean REM latency of ~105 min, considerably longer than is expected for patients of that age. Thus, both our normative samples may be somewhat skewed. Concerning the other REM findings, we cannot comment on the report by Uhde and co-workers of decreased REM density because we did not take that measure. Nevertheless, their study and ours agree that the percentage of REM sleep was within normal limits in panic patients.

Concerning the sleep questionnaire, panic patients correctly reported that it took them somewhat longer than the normal sleepers to fall asleep. Panic attack patients were also remarkably accurate in their estimate of how long they slept. In the measure of sleep quality, a ranking of 8 would have indicated that patients believed they had slept as well in the laboratory as they typically did at home. Both panic patients and normal subjects believed that on nights 2 and 3 they had slept slightly worse in the laboratory than they typically did at home. However, no suggestion in these ratings indicates that the sleep laboratory affected panic patients worse than it did normal sleepers.

Body movement analysis

Because an increase in movement time is the only statistically significant deviation from the norms in the sleep architecture of panic patients that has now been replicated, further analysis seemed indicated. Results of this analysis are shown in Table 2. The "Large body movements" section of Table 2 is identical to the "Movement time" section of Table 1, except that data are expressed in seconds per sleep hour, rather than in percentage of total sleep.

Table 2 shows that panic patients spent about three times as much time in large body movements as normal sleepers in all stages except delta sleep. For intermediate length body movements (2.5–15 s), only the difference in stage 2 was statistically significant. Patients moved about as often as did normal sleepers in stages 1, delta, and REM. Finally, there was no difference between panic patients and normal sleepers in the frequency of short body movements. Thus, panic patients appear to have more very large body movements during all sleep stages except delta and more intermediate body movements in stage 2 sleep, but there is no difference between panic patients and normal subjects in short body movements.

Habituation to the laboratory

Panic patients suffer from many phobias. Indeed, some of them dropped out when they heard during telephone screening that they were expected to sleep in a laboratory with electrodes attached to their head. Thus, we believed that it was important to document that our findings on panic patients' sleep were not overly distorted by the panic patients' fear of sleeping in the laboratory. Table 3 reports the results from this analysis.

Both panic patients and normal sleepers showed a first night effect; i.e., they showed a longer sleep latency, longer REM latency, lower sleep efficiency and lower percentage of REM sleep to the first night in the laboratory, as expected (30,31). For sleep efficiency and REM sleep, this first night effect was more profound for panic patients than it was for normal sleepers. This indicates that panic patients indeed had more problems sleeping in the laboratory on the first night than did normal sleepers.

When we compared night 2 with night 3, we found no significant differences between panic patients and normal sleepers. Both remained relatively stable from night 2 to night 3 for sleep latency, sleep efficiency, and percentage of REM sleep. REM latency continued to decrease from night 2 to night 3 in both groups. We had previously reported on this delayed habituation effect to the laboratory in REM variables from night 2 to night 3 (32). However, for the purposes of this study, by their second night, panic patients seemed as well habituated to the laboratory as normal subjects.

Panic attacks occurring during laboratory sleep

All patients were instructed to call the technician if they experienced a panic attack while in the laboratory. They were also asked during follow-up interviews whether they had experienced any panic attacks in the laboratory. According to these follow-up interviews, 21 panic attacks were experienced during the 72 nights that the patients slept in the laboratory. However, of these 21 panic attacks reported on follow-ups, only eight were also reported to the technician at the time of their occurrence. When asked about this during a follow-up interview, many of our patients claimed that they had been so panic-stricken and confused during their sleep-related panic attacks that they simply had not remembered to call the technician.

Table 4 shows the eight panic attacks reported to the technician during the attacks. Although eight attacks is a very small sample, similarities emerged.

TABLE 3. *Differential first night effect in panic patients and normal controls*

	Panic patients			Normal sleepers			Panics vs. normals $p <$	
	Nt. 1	Nt. 2	Nt. 3	Nt. 1	Nt. 2	Nt. 3	FNE	Nt. 2 vs. Nt. 3
Sleep latency (min)	30.3	21.1	21.1	17.5	11.2	10.5	[a]	[a]
Sleep efficiency (%)	84.4	90.9	91.0	91.8	94.3	94.0	0.05	[a]
REM latency (min)	95.4	83.5	74.0	86.9	76.0	70.8	[a]	[a]
REM sleep (%)	18.1	22.5	22.1	20.7	21.3	22.8	0.05	[a]

Nt., night.

FNE, first night effect. For each patient, values of night 1 were subtracted from the mean of nights 2 and 3. These values were then compared by matched *t* between panic patients and normal sleepers.

Nt. 2 vs. Nt. 3: Values from Nt. 2 were subtracted from those of Nt. 3. These differences were then compared by matched *t* between panic patients and normal controls.

[a] $p > 0.05$.

TABLE 4. *Panic attacks occurring during laboratory sleep*

Patient	Night	Time	Stage	Notes	Sleep latency after PA
A	1	3:30	2	Three consecutive Ks, then a lightening to stage 1; a body movement 5 s later	No further sleep that night
B	3	2:18	2+	Panic attack apparently starting with a body movement	2 min
C	1	1:12	3	Panic attack apparently starting with a body movement	42 min
D	1	2:52	3	Gradual lightening of sleep for 21 s from stage 3 to 1, coupled with EMs during NREM. HR gradually speeding from 68 to 132	21 min
E	1	3:47	2	Gradual lightening of sleep for 12 s, EMs in NREM, HR speeding from 62 to 84	82 min
F	2	4:26	2+	Two short muscle twitches, then EEG lightening; a body movement 16 s later	16 min
G	1	2:19	1	Sleep onset panic after 2 min of stage 1 sleep	126 min
H	1	23:05	REM	Patient awakened after 5 min of REM, screaming, convinced it was real	28 min

Stage 2 sleep with >10% delta waves = 2+.

1. Six of the eight attacks occurred during the first night in the laboratory. Thus, the stress of sleeping in the laboratory facilitated panic attacks during sleep; it did not inhibit them as it apparently does the sleep terrors (33).
2. Six of the eight panic attacks occurred either in stage 2 or stage 3 sleep. Indeed, patients appear to be most vulnerable to these sleep-related panic attacks as they gradually descend from stage 2 to stage 3 sleep. This confirms the preliminary report by Mellman and Uhde (27).
3. Four of the eight panics clearly started and continued for a while *during* sleep (Fig. 1). Typically, some initial event such as a short muscle twitch or a flurry of Ks occurred. Sleep then gradually lightened, and a body movement occurred between 5 and 21 s later. Muscle tension appeared to be somewhat elevated during this time, and atypical events (e.g., eye movements during NREM sleep) occurred occasionally. Of the eight panic attacks, six were recorded with an ECG and a respiratory channel. Judging from this limited sample, heart rate only gradually increased during the sleep portion of the panic attack (Fig. 1) until a large body movement occurred, which finally awakened the patients. Then heart rate often evolved into tachycardia (>100 beats/min). Respiration showed no obvious changes until the patient awakened.
4. Two of the events reported as panic attacks to the technicians clearly did not fit the pattern described above. Patient G clearly had a sleep-onset panic attack. This patient also reported that many of her nocturnal panic attacks at home start with a hypnic jerk just as she is falling asleep. On the other hand, patient H had a dream anxiety attack that awakened her after 5 min of her first REM period. In the morning interview, she claimed that this event, although it led to the report of a panic attack upon awakening, was not typical for the nocturnal events she typically experienced at home because at home she never remembered dreaming when she had panic attacks.

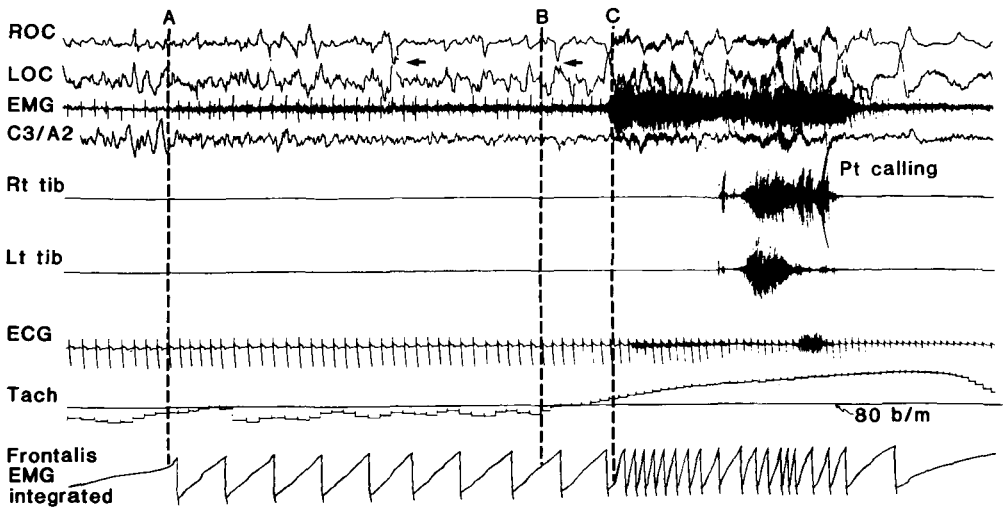

FIG. 1. After having spent ~5 min in stage 3 (not shown), patient D suddenly changed to stage 2 (A). Frontalis muscle tension was increased, and eye movements were evident during stage 2 sleep. About 25 s after the initial lightening of sleep, at point B, the patient awakened, heart rate increased dramatically; a few seconds later (C), the patient moved and then called the technician.

5. Only in the case of patient H's awakening from REM sleep could the technician elicit any mental content that might have brought on the attack. In the other seven attacks, there were not even short fragments of mentation, as would be typical for delta sleep terrors. Thus, patient H's panic attack in the laboratory in many ways appears not to have been a typical sleep-related panic attack.
6. In seven of the eight cases, patients had difficulties in returning to sleep after the panic attack and remembered the attack quite vividly the next morning. This is very different from sleep terrors from which one falls asleep quite easily and which are often forgotten in the morning.

Besides the above-described eight panic attacks, many patients showed other atypical events during sleep. Three patients frequently showed eye movements during bonafide stage 2 sleep. Four patients showed frequent, short suppressions of chin EMG, similar to those that occasionally occur during the periodic leg movements of sleep. Three other patients showed numerous short muscle twitches, either in their chin EMG or in their frontalis EMG. These twitches lasted 0.5–1.0 s and did not disturb sleep. However, although these atypical events during sleep were characteristic for individual panic patients but are rarely seen in normal sleepers, none of these events occurred in enough panic patients to be considered an overall marker for sleep in panic patients.

This study shows that spontaneous panic attacks apparently can start during sleep. We observed eye movements during NREM sleep, increased muscle twitching, increased muscle tonus, and increases in the frequency of the EEG for up to 21 s before some patients woke up with a report that they were having a panic attack. Thus, at least for some patients, panic attacks apparently awakened them from sleep and were not caused by intense startle or other events that occurred while patients awoke.

In our sample, as well as in the sample reported by Mellman and Uhde (27), panic

attacks typically occurred at the transition point between stage 2 and stage 3 sleep. In this respect, these panic attacks are different from the sleep terrors, which typically occur from stage 4 sleep, and different from dream anxiety attacks, which arise from REM periods (34). They are more similar to the "nightmares" in posttraumatic stress disorders (PTSDs) that may arise from varying sleep stages (35), although nocturnal panic attacks appear to be more concentrated at the transition between stages 2 and 3 than are PTSD nightmares. Thus, we believe that we are describing a new form of parasomnia disorder. However, because our sample is small and because two panic attacks did occur at times other than during transition between sleep stages 2 and 3, it is unclear whether the transition from stage 2 to stage 3 is only a facilitating event for panic attacks or whether it is a truly necessary precondition for development of a classic sleep-related panic attack.

As discussed in the Results section, the eight panic attacks arising from sleep did not have a specific characteristic sign by which they could be easily recognized. Sleep typically lightened during these attacks, and the patient woke up sometime later. Heart rate increased only marginally during the sleeping parts of the attack but increased dramatically after the patient woke up. Some patients showed eye movements during NREM sleep during these attacks; others showed increased frontalis muscle tension or apparently started the sleep part of the attack with a body movement. However, these signs were idiosynchratic; none could be described as typical of all attacks.

Of the eight sleep-related panic attacks reported in Table 4, six occurred during the first night in the laboratory. This is another aspect in which sleep-related panic attacks differ from sleep terrors and dream anxiety attacks, both of which seldom occur during the first laboratory night.

As discussed in the Methods section, the patients included in this study were heterogeneous with respect to associated depressions and phobias. Therefore, whether the diversity observed in the sleep-related panic attacks is inherent in this phenomenon itself or is secondary to the heterogeneity of our sample is unclear.

Our data relate to the "psychogenic versus biogenic" controversy concerning panic attacks previously discussed. The healthy human experiences no natural state that shows less thinking than NREM sleep. Although occasional fragments of mentation occur during NREM, they are typically rational and unemotional. They are unlikely to provide the intensity of conscious or unconscious thought that would appear necessary to trigger a psychogenic panic attack. Yet it is exactly this stage of relatively barren and boring thought which not only gives rise to the sleep-related panic attacks but apparently can also sustain them for some time (Fig. 1). This, we believe, deals a severe blow to the psychogenic view of panic disorders.

Similarly, sleep-related panic attacks are unlikely to be triggered by hyperventilation. Respiration during this type of sleep is quite regular and is firmly under chemical control, unlike respiration during most wakefulness and REM sleep. We found no evidence of increased respiratory drive before the panic attacks occurred. Neither did we find evidence of other disordered breathing events. Although we do not doubt that one can provoke some waking panic attacks by hyperventilation, we are confident that this is not the mechanism that causes nocturnal panic attacks. Thus, the data from nocturnal panic attacks are quite powerful in eliminating some of the etiologic hypotheses that have been proposed in recent years (8).

The diagnostic issues we have previously discussed are also clarified by the somnographic data of this study. Table 5 summarizes some of the relevant findings, suggesting

TABLE 5. *Sleep in selected psychiatric disorders*

Parameter	Endogenous depression (16, 17, 20)	General anxiety disorder (17, 19, 20)	Posttraumatic stress disorder (36–39)	Persistent psychophys. insomnia (32)	Panic disorder (5, 21, and present study)
Initiating and maintaining sleep					
Sleep latency	↑	↑	↑	↑	↑
Total sleep time	↓	↓	↓	↓	[a]
Sleep efficiency	↓	↓	↓	↓	↓
No. of awakenings	↑	↑	↑	↑	[a]
Sleep architecture					
Percentage of					
Stage 1	?	↑	↑	↑	[a]
Stage 2	?	↑	↑	[a]	[a]
Delta	↓	↓	↓	↓	[a]
REM	?	?	↓	[a]	[a]
REM latency	↓	?	↑	[a]	?
Body movements	[a]	[a]	↑	[a]	↑
Movement time	[a]	[a]	?	[a]	↑

↑, Increased; ↓, decreased; ? unknown or disputed.
[a] Same as normal sleepers.

that lengthened sleep latency and a decreased sleep efficiency are nonspecific signs of distress, common to all the disorders listed. In all other aspects, sleep in panic patients is remarkably like normal sleep, except for the now-replicated increase in movement time and, possibly, for the increase in body movements during stage 2 sleep. The sleep of panic patients differs from sleep in the other disorders listed in Table 5 in that total amounts of sleep, numbers of awakenings, and delta sleep are normal. It is specifically different from depressed sleep and PTSD sleep because REM indices are not disturbed. It differs from anxious sleep in that amounts of stage 1 and 2 are normal and from insomniac sleep in that amounts of stage 1 sleep are normal.

To our knowledge, no other disorder has yet been characterized by increased movement time. The definition of movement time involves a disruption of the EEG channels by movement artifact for more than half of a 30-s epoch, whereas neither the epoch before nor the epoch after the movement artifact can be scored as awake. In other words, panic patients show large body movements in stages 1, 2, and REM from which they do not awaken (Table 2). It would be tempting to speculate that the panic patient's inability to wake up from these large body movements might be the cause of the spontaneous, sleep-related panic attacks, but the facts do not support this idea. Only two of the eight recorded panic attacks started with a body movement.

While the goal of this study was to search for a characteristic sleep pattern in panic patients, it needs to be pointed out that not only the sleep-related panic attacks but sleep itself was not uniform among all patient panics. By a standard definition for insomnia (namely <85% sleep efficiency or >45-min sleep latency in 2 of 3 laboratory nights), 8 of the 24 panic patients could have been characterized as insomniacs. Of the remaining 16 panic patients, 12 slept well on all 3 nights and 4 had 1 poor night among the 3 spent in the laboratory.

Overall, our study suggests that panic patients sleep only slightly poorer than normal subjects. The sleep of panic patients is different from the sleep of depression, generalized anxiety disorders, insomnia, or PTSD (Table 5). Spontaneous panic attacks can

occur during sleep. They often awaken patients after they have slept at least through the beginning of these attacks.

Acknowledgment: We gratefully acknowledge Dr. David Greenblatt of Tufts University, Boston, who analyzed the blood samples, and Dr. Gregor McHugo of Dartmouth College, Hanover, New Hampshire, who performed the statistical analysis.

REFERENCES

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 3rd ed., rev. Washington, D.C., American Psychiatric Association, 1987.
2. Von Korff MR, Eaton WW, Penelope MK. The epidemiology of panic attacks and panic disorder. *Am J Epidemiol* 1985;122:970–81.
3. Shader RI, Goodman M, Gever J. Panic disorders: current perspectives. *J Clin Psychopharmacol* 1982;2:2S–25S.
4. Breuer J, Freud S. Studies in hysteria. In Strachey J, ed. *The standard edition of the complete works of Sigmund Freud.* London: Hogarth Press, 1961:81.
5. Munby M, Derek WJ, Johnston DW. Agoraphobia: the long-term follow-up of behavioral treatment. *Br J Psychiatry* 1980;137:418–27.
6. Sheehan DV, Coleman JH, Greenblatt DJ, et al. Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J Clin Psychopharmacol* 1984;4:66–75.
7. Uhde TW, Boulenger JP, Roy-Byrne PP, et al. Longitudinal course of panic disorder: clinical and biological considerations. *Prog Neuropsychopharmacol Biol Psychiatry* 1985;9:39–51.
8. Ley R. Panic disorder and agoraphobia: fear of fear or fear of the symptoms produced by hyperventilation? *J Behav Ther Exp Psychiatry* 1987;18:305–16.
9. Liebowitz MR, Fyer AJ, Gorman JM, et al. Lactate provocation of panic attacks. *Arch Gen Psychiatry* 1984;41:764–70.
10. Grunhaus L, Rabin D, Harel Y, Greden JF, Feinberg M, Hermann R. Simultaneous panic and depressive disorders: clinical and sleep EEG correlates. *Psychiatry Res* 1986;17:251–9.
11. Schapiro K, Roth M, Kerr T. The prognosis of affective disorders: the differentiation of anxiety states from depressive illness. *Br J Psychiatry* 1972;1212:175–83.
12. Leckman JF, Weissman NM, Merikangas KR, Pauls DL, Pursoff BA, Weissman MM. Panic disorder and major depression: increased risk of depression, alcohol, panic disorders in families of depressed probands with panic disorder. *Arch Gen Psychiatry* 1983;40:1055–60.
13. Uhde TW, Siever LJ, Post RM. Clonidine. acute challenge and clinical trial paradigms for the investigation and treatment of anxiety disorders, affective illness, and pain syndromes. In: Post RM, Ballenger JC, eds. *Neurobiology of mood disorders.* Baltimore: Williams & Wilkins, 1984.
14. Roy-Byrne PP, Uhde TW, Gold PW, Rubinow DR, Post RM. Neuroendocrine abnormalities in panic disorder. *Psychopharmacol Bull* 1985;3:550–4.
15. Dube S, Kumar N, Ettedgui E, Pohl R, Jones D, Sitaram N. Cholinergic REM induction response: separation of anxiety and depression. *Biol Psychiatry* 1985;20:408–18.
16. Kupfer DJ, Thase ME. The use of the sleep laboratory in the diagnosis of affective disorders. *Psychiatr Clin North Am* 1983;6:3–25.
17. Akiskal HS. Diagnosis and classification of affective disorders: new insights from clinical and laboratory approaches. *Psychiatr Dev* 1983;2:123–60.
18. Zarcone VP Jr, Benson KL, Berger PA. Abnormal rapid eye movement latencies in schizophrenia. *Arch Gen Psychiatry* 1987;44:45–8.
19. Rosa RR, Bonnett MM, Kramer M. The relationship of sleep and anxiety in anxious subjects. *Biol Psychol* 1983;16:119–26.
20. Reynolds CF, Shaw DH, Newton TF, Coble PA, Kupfer DJ. EEG sleep in outpatients with generalized anxiety: a preliminary comparison with depressed outpatients. *Psychiatry Res* 1983;8:81–9.
21. Uhde TW, Roy-Byrne P, Gillin JC, et al. The sleep of patients with panic disorder: a preliminary report. *Psychiatry Res* 1985;12:251–9.
22. Dube S, Jones DA, Bell J, Davies A, Ross E, Sitaram N. Interface of panic and depression: clinical and sleep EEG correlates. *Psychiatry Res* 1986;119:119–33.
23. Pecknold JC, Olha A, Chang H, et al. Sleep architecture in patients with panic disorders. Poster presented at the 15th meeting of the Collegium Internationale Neuro-Psychopharmacologicum, San Juan, PR, December 14–17, 1986.
24. Akiskal HS, Lemmi H, Dickson H, King D, Yerevanian BI, Van Volkenburg C. Chronic depressions: Part 2. Sleep-EEG differentiation of primary disthymic disorder from anxious depressions. *J Affective Disorders* 1984;6:287–95.

25. Lesser IM, Poland RE, Holcomb C, Rose DE. Electroencephalographic study of nighttime panic attacks. *J Nerv Ment Dis* 1985;173:744–6.
26. Bell CC, Bell DD, Thompson B. Panic attacks: relationship to isolated sleep paralysis [Letter]. *Am J Psychiatry* 1986;143:11.
27. Mellman TA, Uhde TW. Sleep-related panic. Paper presented at the 42nd Annual Convention of the Society for Biological Psychiatry, Chicago, IL, May 6–10, 1987.
28. Spitzer RL, Williams JBW, Gibbon M. Structured clinical interview for DSM-III-R—outpatient version (SCID-OP, 4/1/87). Biometrics Research Department, New York State Psychiatric Institute, 722 West 168th St., New York, NY, 10032, 1987.
29. Rechtschaffen A, Kales AA, eds. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. University of California at Los Angeles: Brain Information Service/Brain Research Institute, 1968.
30. Agnew HW Jr, Webb WB, Williams RL. The first night effect: an EEG study of sleep. *Psychophysiology* 1966;2:263–6.
31. Mendels J, Hawkins DR. Sleep laboratory adaptation in normal subjects and depressed patients ("first night effect"). *Electroencephalogr Clin Neurophysiol* 1967;22:556–8.
32. Hauri P, Fisher J. Persistent psychophysiologic (learned) insomnia. *Sleep* 1986;9:38–53.
33. Fisher C, Kahn E, Edwards A, Davis D. A psychophysiological study of nightmares and night terrors. *Psychoanalysis and contemporary science*. New York: International Universities Press, 1984.
34. Kramer M. Dream disturbances. *Psychiatr Annals* 1979;9:366–76.
35. Van der Kolk BA. Psychopharmacological issues in posttraumatic stress disorder. *Hosp Commun Psychiatry* 1983;34:683–91.
36. Friedman MJ. Towards rational pharmacotherapy for post traumatic stress disorder: an interim report. *Am J Psychiatry* 1988;145:281–5.
37. Lavie P, Hefez A, Halperin G, Enoch D. Long-term effects of traumatic war-related events on sleep. *Am J Psychiatry* 1979;136:175–8.
38. Kramer M, Kinney L, Scharf M. Sleep in delayed stress victims. In: Chase M, Webb WB, Wilder-Jones R, eds. *Sleep research,* volume 11. UCLA, Los Angeles: Brain Information Services, Brain Research Institute, 1985:39.
39. Schlosberg A, Benjamin M. Sleep patterns in three acute combat fatigue cases. *J Clin Psychiatry* 1978;39:546–9.