# Studies of Sleep Deprivation—Relationship to Schizophrenia

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## Introduction

There were several reasons for investigating the effects of sleep deprivation in man. One was simply a curiosity about the unusual consequences of prolonged insomnia described by earlier investigators. Kleitman [1] and Tyler [2] cited in detail the hallucinations and "psychotic-like" symptoms that occur under these circumstances and also described subjects who developed short-lived "schizophrenic" psychoses. Psychological alterations, such as inattention, apathy, illusions, and hallucinations, which commonly appear after 36 to 50 hours of wakefulness, have been noted to coincide with an increase in high-frequency, low-amplitude waves on the electroencephalogram.[3-5] In contrast to such spontaneous psychological disturbances, sleep-deprived subjects have been able to perform normally on specific tests designed to measure work capacity, psychomotor performance, intellectual acumen, and personality structure.[1,8] Measurements of the basal metabolic rate, blood sugar, alkaline reserve, blood and urinary adrenal steroids, etc., have not been found to change significantly with sleep deprivation.[1,6]

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A more pertinent reason for our interest was the hypothesis that sleep deprivation had greater clinical significance in the precipitation of a *few* schizophrenic reactions than had previously been suspected. It is common knowledge that fatigued children and adults tend to be irritable and unreasonable. It is less commonly emphasized that many agitated persons on the brink of a psychotic break suffer from severe insomnia and that a few pass through a prolonged period of wakefulness as the schizophrenic process unfolds. Two such patients have been studied and will be reported. They have prompted us to inquire whether a prolonged loss of sleep might have a deleterious effect upon the personality of an individual already on the verge of a psychosis. It was hoped that these studies might clarify the importance of this possibility.

## Experimental Design, Subjects, and Methods of Observation

In designing the studies, major emphasis was placed upon the measurement of the psychological effects of sleep deprivation. The tests employed were not entirely satisfactory, despite their numbers, since precise psychological tools to appraise the highest and most refined cortical functions are not available. As a reflection of our interest in psychoendocrinology, studies were made also of the concentrations and the diurnal pattern of the blood and urinary adrenal steroids. In a second series of experiments, the effect of *d*-lysergic acid diethylamide (LSD-25) on sleep-deprived subjects was studied to determine the influence of prolonged wakefulness on sensitivity to this

hallucinogenic agent. Finally, one subject was studied on a metabolic ward to determine the effect of sleep deprivation on protein and electrolyte metabolism.

Seven medical students, motivated by a progressive pay scale, remained without sleep for 72 consecutive hours. During this time, they stayed in rooms on an open psychiatric ward, took their meals in the hospital cafeteria, and were free to stimulate wakefulness by whatever diversions they might choose. To ensure wakefulness, the subjects were constantly attended by relays of monitors, who were also responsible for carrying out behavioral observations and administering the various psychological tests. In terms of interpersonal relationships between subjects and investigators, the experimental setting was permissive and anxiety-sparing. No efforts were made to irritate, challenge, or otherwise deliberately stress the subjects. The various observations and tests carried out and their timing during the 72-hour experimental period are summarized in Table 1.

The effects of LSD-25 were studied in four subjects who remained awake for 48 hours before receiving the drug. The one subject who was carefully studied metabolically was placed on a constant diet, and, after seven days, when he was in nitrogen, sodium, potassium, phosphate, chloride, and

TABLE 1.—*Observations and Tests During Seventy-Two Hour Experimental Period*

| Procedure | Description | Time Administered Daily |
|---|---|---|
| **Behavioral ratings by observers** | | |
| Estimates of behavior * | 25 descriptive items were rated on 4-point scale; these were clustered into 15 categories | 12 m., 6 p.m., 1 a.m., 6 a.m. |
| Estimates of degree of sleepiness | Subjects were rated on a 10-point wakefulness-sleepiness scale | Every 2 hr., 8 a.m. to 12 a.m.<br>Every hour, 12 a.m. to 8 a.m. |
| **Psychological tests** | | |
| Estimate of time | Subjects estimated ½- and 2-min. intervals | 9 p.m., 3 a.m. |
| Introspective questionnaire * | A 57-item questionnaire was administered, modified from that developed by Jarvik et al.[7] for study of LSD-25 effects; this was clustered into 9 categories | 12 m., 6 p.m., 1 a.m., 6 a.m. |
| Adjective check list * | The list was composed of 106 adjectives descriptive of mental states; these were clustered into 7 categories | 12 m., 6 p.m., 1 a.m., 6 a.m. |
| Drive preference * | Drive preference tests sampled desire for food, sleep, activity, sex, intellectual and hostile behavior: One test was self-rating procedure on a 4-point scale; the other was a forced-choice questionnaire | 8 a.m., 4 p.m., 1 a.m., 6 a.m. |
| Rorschach test | This was a modification of the test designed to identify "psychotic" thinking | 2 a.m. (1st and 3d days) |
| Subjects' estimate of degree of sleepiness | Subjects rated themselves on a 10-point wakefulness-sleepiness scale | Every 2 hr. 8 a.m. to 12 a.m.; every hr. 12 a.m. to 8 a.m. |
| Fantasy formation | (a) Subjects visualized scenes on blank white cards<br>(b) Subjects remained alone facing wall for 5 min. and then related their thoughts | 8 p.m.<br>4 a.m. (1st and 3d days) |
| Rate of association to graded nonsense syllables * | Subjects associated to nonsense syllables; speed and ability to perform were measured; the 3 lists were equivalent, but the syllables were different | 12 p.m. |
| Perception of mutilated words (Thurstone's Test) | The capacity to perceive fragmented words was measured | 11 p.m. (1st and 3d days) |
| Learning test-spatial concept formation test[10] | This was a test designed to measure the capacity to organize symbols | 3 a.m. (3d day) |
| Introspective description of experience by subjects | Subjects described retrospectively, after the experiment was terminated, their recollection of the experience | |
| **Endocrinology** | | |
| Plasma 17-hydroxycorticosteroids | 20 ml. of blood was drawn and analyzed by a modification [12] of Nelson and Samuels' technique [11] | 8 a.m., 10 p.m., 4 a.m. |
| Urinary 17-hydroxycorticosteroids | Urines were analyzed by a modification [13] of technique of Reddy et al. [14] | Every 6 hr. |
| Urinary 17-ketosteroids | Urines were analyzed by the technique of Callow et al. [15] | Every 6 hr. |

* The results of these tests are expressed numerically in Tables 2, 4, 5, and 6. A scoring system based upon aggregate mean responses for the group of subjects was devised for each procedure. These were inexact measurements but did offer a rough quantitative estimate of the variations in psychological state that occurred during the period of sleep deprivation.

calcium balance, was deprived of sleep for 72 hours and then kept on the same dietary regimen for another five days.

## Clinical Observation

Although many patients suffer some degree of insomnia prior to and during an acute psychotic attack, only a few seem to experience prolonged sleep deprivation. The two patients who are briefly described appear to have been cases of this situation. Neither had experienced a previous schizophrenic episode; both were in their middle years, and each had a short-lived psychotic episode that responded rapidly to treatment.

The first patient was a 44-year-old woman who decompensated after the accidental death of her 16-year-old son. While driving the family car, he struck a cow and was fatally injured. For the next 27 hours he lingered in coma and then died. During this time his mother stayed at his side. She cried, remained sleepless, and complained of pains in the region of all her son's injuries. Thereafter she became emotionally more controlled but could not sleep. By Tuesday her insomnia had lasted almost three days, and at that time further evidences of irrationality were present. The next day, after close to 90 hours of sleep deprivation, self-recriminations, and excruciating psychic distress, she became grossly psychotic. She railed against the atomic bomb, expressed religious delusions, refused to wear clothing, screamed, and lapsed into an incomprehensible gibberish. She was taken to the hospital and seven days later, after three electroshock treatments, reverted to normal behavior. Thereafter she received two more electroshock treatments, her behavior remained rational, and she was discharged.

Eight months later, at the time her son would have graduated from high school, a series of events reactivated her psychotic grief reaction. Again she became depressed, ruminative, and intensely miserable; failed to sleep for three days, and relapsed into a psychotic state. She was rehospitalized, was treated with chlorpromazine (Thorazine) and perphenazine (Trilafon) and in six days recovered.

The second patient was a 51-year-old man, a successful cattle and dairy rancher, who had a schizophrenic sister, two years his senior. The previous year he had been elected to the local school board and found himself deeply involved in a dispute as to where a new school should be placed. He represented a minority position and, very much a neophyte to politics, found himself battling the board unsuccessfully. Under the stress of this bitter conflict, he began to smoke and drink coffee excessively and was so disturbed that he slept no more than two or three hours a night. Finally, after three weeks of turmoil, culminating in four days of total sleeplessness, he became psychotic. He felt that he was being watched, that his telephone was monitored, and became convinced that God had given him special powers. Acting on his newly acquired divine authority, he descended upon the local school and abruptly dismissed the school clerk, superintendent, and janitor. His physician made the diagnosis of schizophrenia and referred him to the hospital. He was placed on a regimen of chlorpromazine, began to sleep again, reduced his consumption of cigarettes and coffee, resolved to leave politics to more skilled and experienced neighbors, and within a few days recovered.

Since patients often unwittingly exaggerate the extent of their insomnia, every effort was made to verify the history in both cases. In the first instance the patient's husband was able to confirm the accuracy of the story, and there seemed little doubt that she had experienced total or near-total prolonged sleep deprivation on both occasions. The second patient had been sleeping in a room by himself, and his wife could not contribute any useful information about disturbances in his pattern of sleep, since she was not present to observe it. There was no way to check his story, except to note that he was an impeccably honest and factual person, ordinarily a good observer, who was convinced that his insomnia had been prolonged and severe.

## Experimental Observations on Sleep-Deprived Subjects

*1. Psychological and Behavioral Observations.*—A. Intellectual Function: 1. At 2:00 a. m. on the morning of the first and third sleepless days, all subjects were given a modification of the Rorschach Test,[8] designed to distinguish psychotic from nonpsychotic states. It was assumed that if prolonged sleep deprivation caused a thinking disorder, this would be evident on such a test. All seven subjects scored within the normal range, and variations from the first to the third day were insignificant, indicating that no formal thinking disorder as meas-

ured by the tests was evident during the testing procedure.

2. On the early morning of the third day, four subjects were given a complex learning test (Spatial Concept Formation Test) that lasted three-fourths of an hour. It called for considerable concentration, the capacity to order symbols, and the ability to integrate and solve moderately difficult problems. As a test, it was the most complex one administered, and intellectually the most difficult we could provide. Nevertheless, at 3:00 a. m., when all were glassy-eyed with fatigue, each subject was able to mobilize his addled senses and concentrate sufficiently to solve the problems. When these scores were compared with those of 53 students who acted as controls, there were no significant differences between the two groups. All four sleep-deprived subjects scored within the normal range.

3. Each day subjects were asked to associate to a list of graded nonsense syllables. This proved to be much too simple a task, and it was accomplished rapidly and efficiently on every occasion. No differences in performance from the first to the third day could be demonstrated.

4. Subjects were given a "mutilated" word test on the first and third days. Again, they performed as capably on the last day as they did on the first.

It was concluded from these studies that subjects deprived of sleep had the capacity to mobilize their intellectual facilities when confronted with these formal tests of relactively short duration. They could perform in a normal fashion under these conditions, despite evidences of disorganization under informal circumstances.

B. Drive States: Subjects were asked to grade their preference for items involving sex, food, sleep, exercise, intellectual activity, and hostile behavior. They were required on a second questionnaire to make a forced choice of these items. Although imperfect procedures, these tests revealed some interesting trends. As might be expected with prolonged sleeplessness, a desire for sleep became prominent, as an interest in exercise and intellectual pursuits waned. Less expected was the persistent and sustained interest in food and sex despite the uninterrupted insomnia, suggesting either that medical students are a hardy breed or that these interests are strong and not easily diminished. Feelings of hostility underwent little change under the conditions of the experiment (Table 2).

TABLE 2.—*Drive States*

| | 1st Day P.M. | 3d Day P.M. | 1st Day A.M. | 3d Day A.M. | |
|---|---|---|---|---|---|
| Sex | 12 | 21 | 20 | 21 | Self rating (7 subjects) |
| Food | 14 | 14 | 14 | 14 | |
| Sleep | 7 | 21 | 6 | 21 | |
| Exercise | 17 | 5 | 14 | 3 | |
| Intellectual activity | 20 | 2 | 15 | 4 | |
| Sex | 7 | 8 | 9 | 7 | Forced choice (4 subjects) |
| Food | 9 | 6 | 10 | 7 | |
| Sleep | 4 | 12 | 6 | 12 | |
| Exercise | 6 | 3 | 5 | 3 | |
| Intellectual activity | 5 | 2 | 7 | 1 | |
| Hostility | 2 | 3 | 3 | 1 | |

C. Estimate of Time: Twice a day subjects were asked to estimate the passage of one-half and two minutes. They were not told at any time how accurately they performed and were asked not to practice. An unexpected observation was the tendency of the subjects to reduce their estimates as sleeplessness progressed. Although one-half- and two-minute intervals were usually judged to be longer periods than those early in the experiment, by the third day most subjects estimated that one-half and two minutes had elasped before that amount of time had passed. This may have been due to the tendency of subjects on the second and third days to doze, then to awake suddenly and feel more time had elasped during the "blank" period than really had passed (Table 3).

D. Fantasy Formation: On each experimental day subjects were instructed to stare at a large, white blank card and to visualize a scene. They described the picture, and their comments were recorded verbatim.

TABLE 3.—*Estimation of Time* *

| | Overestimation | | Underestimation | |
|---|---|---|---|---|
| | P. M. | A. M. | P. M. | A. M. |
| 1st day | 13 | 20 | 13 | 8 |
| 2d day | 8 | 7 | 17 | 21 |
| 3d day | 6 | 3 | 12 | 24 |

* One-half and two minutes.

The same procedure was repeated a second time, with the suggestion that they visualize another scene. It was noteworthy that these projections remained pleasant throughout the three days. Preoccupations with sleep did not become prominent; scenes did not become closer or more distant; fantasies remained specific and well organized; the number of items stayed virtually constant, and the ratio of human to nonhuman content did not significantly fluctuate from day to day.

In contrast, subjects were asked on the first and third days to sit alone, facing the wall, without conversation for five minutes. Afterward they recorded the thoughts that crossed their minds. This proved to be a much less structured situation. On the first day fantasies were quite specific. They related to thoughts of jobs, girl friends, plans for parties, fishing, and the like. In every case fantasies were well organized and had no obvious reference to the experiment. By the third day the content appeared to have changed. Fantasies frequently pertained to such topics as "cessation of the experiment and sleep" and "How much energy must be expended on keeping awake even for this five minutes of reverie?," "What do all these tests mean?," "Why doesn't Russia conquer Finland?," "the cycles of sleepiness," and similar preoccupations. Many fantasies dealt with the immediate dilemma of sleeplessness and the problems it provided. Several subjects noted that their thoughts were jumbled, and that they "couldn't think of anything for more than 10 seconds," or that they "had difficulty concentrating." The two techniques indicated the dichotomy between performance on a specific test and mentation during periods of informal behavior. On the first test responses were logical and organized; on the second procedure, after prolonged wakefulness, thinking tended to be loose and at times befuddled.

E. Periodicity of Sleepiness: A characteristic of prolonged wakefulness which has been noted by others, and that was clearly demonstrated, as well as reported, by our subjects, was the rhythm of sleepiness. There were two general patterns. One was the usual diurnal pattern of alertness during the day and early evening, followed by somnolence at night. The other involved short periods of an hour or two, usually during the earlier hours of the morning, when fatigue became virtually intolerable.

The broad pattern is illustrated in Figure 1, where the consolidated estimates by subjects of the depth of sleepiness during the vigil are plotted. Estimates by the observers followed the same general pattern. Generally, subjects tended to be less sleepy during the hours they were accustomed to be awake and more somnolent late in the evening and

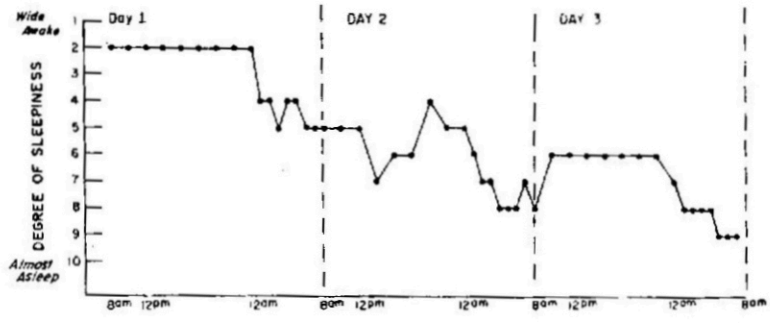


Fig. 1.—Average degree of somnolence as estimated by the six subjects during the three days of wakefulness.

early in the morning, when they habitually slept. Although they were quite alert during the first day, with each succeeding day, as well as night, there was increasing fatigue, so that on the third day they were sleepier than on the second day. Most had little trouble during the first 24 hours. It was only the last two days that vigilance and activity were necessary to forestall sleep.

Interpolated throughout were waves of sleepiness. One subject described them as lasting for one and one-half to two hours at a time. Between them he would feel fairly normal. His worst periods would occur at 5:00 or 6:00 o'clock in the early morning. Another subject experienced his first wave at 10 p. m. on the second day. This lasted only 45 minutes, and he remained alert until 4 a. m. that morning, when he was overwhelmed by a period of painful somnolence, which lasted two and one-half hours. At 10 p. m. on the evening of the third day, and also from 2 to 7 a. m. the same day, he had similar experiences. A third subject felt a little sleepy around his usual bedtime at midnight the first day. At 4 a. m. to 5 a. m. the first morning he had his first strong wave of sleepiness, which lasted two hours. He then became awake and felt almost as though he had had a night's sleep. From 2 to 6 a. m. the second day he again found it difficult to remain awake, but by 7 a. m. he was again alert. At 2 a. m. on the third day his drowsiness became severe. He stated: "I was very tired—this was not the tired feeling after a long day's work at physical labor, but the tired, nagging, feverish feeling of being just all run down. I was very drowsy, and nothing but very active play or moving about kept me from nodding away." The state of extreme drowsiness persisted until 7:30 a. m., when it began to lift.

The other subjects had similar experiences. It was surprising to observe how the psychobiological pattern of the sleep-wakefulness cycle persisted despite the unremitting, abnormal 72 hours of sleep deprivation. During the early hours of the morning, when sleep was habitual, sleepiness was most intense and the difficulty of remaining awake was severest. By 8 or 9 a. m., when all were accustomed to being awake, all felt considerably more alert, and there was a marked diminution in somnolence, even after three days of sustained wakefulness.

F. Visual Changes: All subjects experienced some visual distortions, ranging from minor disturbances to hallucinations. During the early morning of the third day, one subject felt that the men's room seemed larger and the floor higher. The dark squares of the floor tile seemed to pulsate and would become darker, as well as larger, with every pulsation. A little later, he reported that the floor of the laboratory "seemed to be covered by a layer of shimmering water. I knew the hallway doors should be familiar but they looked strange." It looked as though the room were on a second story, and it appeared to him that it was necessary to climb a step to get to it from the hall. He commented that late the second evening "as I walked down the hall, I thought I saw an old lady sticking her head out from the room. She seemed to have gray hair, which was rather 'frizzy.' I stopped to look again. She still had her head showing, and it did not move. It wasn't until about 10 yards from her that I realized it was a fire alarm box." He also saw a fine smoke coming from the linoleum floor cover as he was finishing his breakfast. The smoke then began to rise from the floor in a very fine stream. This became misty and faded into a fine spray of water, so that as he stared at the floor more closely, fine jets of water appeared to be rising.

One subject occasionally had the sensation of tunnel vision, and another one saw things shimmering and oscillating. He perceived the "coke" machine as moving up and down. Another subject on the second night spent considerable time pacing the hall. Momentarily, he saw a roll of luminous

chicken wire on the floor, and, as he walked through it, the wire disappeared and did not return. For a period, the base of the shuffleboard stick seemed to follow an undulating, twisting motion, although it was well lighted and only a few yards away. The legs of a table also occasionally quivered. One subject reported that during the third night the "coke" machine became distorted, as though he were looking at it through a piece of glass with flaws in it. He also saw black spots in the periphery of his visual fields.

G. Auditory Changes: Subjects reported that loud sounds seemed harsh and disrupting or that people's voices seemed distant. One noticed that he could watch his companions' mouths as they talked next to him, yet feel their voices were coming from the next room. Another described it as though "their voices seemed to come from somewhere else." During periods of somnolence, all found it difficult to concentrate on conversations and to listen intelligently. They might talk or listen and then be unable to remember the content of the conversation. None experienced frank auditory hallucinations. One commented that the radio was on nearly all the time; yet occasionally, he would notice that he had not heard the music for an hour or more.

H. Paresthesias: All subjects reported some variety of altered sensation. Like so many other experiences during the procedure, these sensations also were usually transient. One felt his body was numb and insulated; his eyes smarted, and his muscles felt stiff and sluggish. He compared the sensation of numbness and feeling of insulation with that of a mild alcoholic intoxication. Another was walking down the hall when his left heel seemed to raise by itself, and a "funny," electrical, cold sensation shot up the back of his leg. He experienced, also, a peculiar numb feeling in his knee, a fleeting flush over his skin, and peculiar feelings in his hands.

Another subject felt a tight sensation over his face, similar to those he had experienced previously with alcohol and lysergic acid diethylamide. One reported that his hands seemed to be larger, and another had a warm, tired feeling in his arms and legs. Only one subject had persistent sensory disturbances. He had a "creepy" hypersensitivity all over his skin, except for his palms and soles, that was constant and lasted throughout the final 48 hours of sleep deprivation.

I. Mood Changes: The setting of the experiment was uncritical and friendly. Everything was done to minimize anxiety and reduce irritations. The investigators were casual and amicable, and the entire procedure was an informal one. In this *specific* setting disturbances in mood, particularly unpleasant reactions, were infrequent. Two subjects reported periods of anxiety—one because he was concerned about his ability to stay awake during the second day, and the other, due to his concern about feelings of depersonalization and a progressive sense of loss of self-control. Several passed through periods of giddiness and silly laughter, like addled drunks, when their behavior became uninhibited. One moved through several stages. Until 45 hours had elapsed, he was happy and silly. Thereafter he felt rather depressed, enough so that a slight irritation could have provoked an argument or fight.

J. Impaired Cerebration: Although the subjects could mobilize their befuddled faculties for specific, formal psychological tests and perform normally under pressure, their informal behavior reflected intellectual deterioration. They behaved and felt impaired, particularly during the later portion of the experiment.

One expressed it: "There was extreme difficulty keeping my thoughts coherent. On one occasion I remember writing out a profound statement and ending the statement with the irrelevant comment, 'owes $8.00.'" Some had difficulty in forming their thoughts, in finding the proper words, or in composing a sentence. They forgot their fellow-participants' names, and one

had the nagging conviction that Ronald's (another subject) name was really not Ronald but Robert. There was confusion as to what they had said in casual conversation and what others had said to them. One recalled that they had played Scrabble and said: that "An 8-year-old boy could have doubled my score. Most of the words I put down were two letters, such as 'at, do, it.'" Most periodically felt confused. Thoughts were often jumbled, and certainly during the last evening, thinking was fragmented during periods of inactivity. One subject recalled trying to discuss women with a fellow subject. It must have been a fascinating conversation, since neither was able to follow the thread of the discussion.

K. Miscellaneous Observations: One subject who had a mild cold noticed it

TABLE 4.—*Adjective Check List*

| Categories | First Day P. M. | Third Day P. M. | First Day A. M. | Third Day A. M. |
|---|---|---|---|---|
| Alertness | 53 | 10 | 20 | 5 |
| Feeling of well-being | 78 | 24 | 35 | 15 |
| Emotional distress | 1 | 7 | 2 | 10 |
| Hostility and irritability | 0 | 8 | 3 | 3 |
| Disorganization in function | 2 | 1 | 5 | 27 |
| Sleepiness and fatigue | | | | |
| Mild | 5 | 40 | 35 | 40 |
| Severe | 1 | 10 | 7 | 15 |
| Increased motor activity | 10 | 30 | 30 | 20 |

became worse during the period of sleep deprivation. Two others developed colds during the experimental period. In all three cases the upper respiratory difficulties cleared after the subjects finished the marathon and had ample sleep.

Two subjects noticed some motor incoordination, unsteadiness, and ataxia, comparable to the feeling of being intoxicated. Several reported "waking" dreams, when they might stand or sit with eyes open and yet be completely out of contact, experiencing sensations like hypnogogic reveries.

Time seemed to several to be a "hodgepodge." One felt the hours passed rapidly

TABLE 5.—*Introspective Questionnaire*

| Categories | First Day P. M. | Third Day P. M. | First Day A. M. | Third Day A. M. |
|---|---|---|---|---|
| Motor incoordination | 0 | 10 | 0 | 60 |
| Feeling of weakness | 3 | 60 | 23 | 87 |
| Sleepiness | 20 | 100 | 90 | 130 |
| Blurring of vision | 0 | 45 | 0 | 70 |
| Illusions & hallucinations | 0 | 15 | 0 | 10 |
| Paresthesias | 0 | 20 | 5 | 20 |
| Emotional lability | 0 | 7 | 10 | 30 |
| Impaired concentration | 10 | 110 | 20 | 110 |
| Feelings of estrangement | 0 | 20 | 0 | 50 |

but that the days were interminable. Another stated that between activities time seemed to stand still.

A variety of sensations that could be subsumed under the heading of depersonalized and derealistic states were reported. There were reports of feeling "separated from others." One subject stated that for about five minutes he pondered whether the whole experiment were a dream. Most felt moments of estrangement, distance from others, and disturbances in their habitual concept of their person.

Much of the preceding descriptive material is summarized in Tables 4, 5, and 6. These represent quantitative estimates of behavior, affect and thinking during the three days of the experiment and are analyses of the adjective check list, introspective questionnaire, and the observations by the monitors.

TABLE 6.—*Observations by Monitor*

| Description of Subjects | First Day 1 A. M. | Second Day 1 A. M. | Third Day 1 A. M. |
|---|---|---|---|
| Sad | 0 | 0 | 0 |
| Asocial | 0 | 0 | 0 |
| Emotionally disturbed | 0 | 0 | 0 |
| Withdrawn | 0 | 0 | 0 |
| Angry | 0 | 0 | 2 |
| Happy & friendly | 8 | 7 | 7 |
| Anxious | 0 | 0 | 2 |
| Apathetic | 0 | 0 | 7 |
| Alert | 9 | 7 | 2 |
| Social | 10 | 7 | 5 |
| Sleepy | 1 | 5 | 9 |
| Restless & moving | 2 | 4 | 6 |
| Thinking clearly | 9 | 8 | 2 |
| Thinking "fuzzily" | 0 | 2 | 9 |
| Acting drugged | 0 | 5 | 12 |

TABLE 7.—*Plasma Adrenal Steroids—Hydrocortisone* *

| | 8 A. M. | | 10 P. M. | | 4 A. M. | |
|---|---|---|---|---|---|---|
| | 13 | 15.1 | 0.5 | 2.2 | 0.3 | 4.6 |
| | 11.8 | 17.8 | 3.0 | 0.8 | 9.2 | 6.4 |
| Day 1 | 12.4 | 12.4 | 1.2 | 3.0 | 1.1 | 4.2 |
| | 16.4 | | 1.7 | | 7.0 | |
| | Average=14.1 | | Average=1.8 | | Average=4.7 | |
| | 9.6 | 10.3 | 1.4 | 2.2 | 6.4 | 5.2 |
| | 11.3 | 21.4 | 2.8 | 1.8 | 8.6 | 5.2 |
| Day 2 | 10.6 | 18.8 | 1.8 | 2.4 | 4.4 | 3.2 |
| | 10.8 | | 4.0 | | 7.8 | |
| | Average=13.3 | | Average=2.3 | | Average=5.6 | |
| | 9.3 | 15.8 | 1.2 | 2.3 | 4.6 | 7.8 |
| | 11.8 | 14.2 | 3.1 | 2.2 | 11.0 | 4.0 |
| Day 3 | 10.0 | 18.3 | 1.8 | 3.6 | 1.0 | 8.6 |
| | 11.4 | | 4.3 | | 9.0 | |
| | Average=13.0 | | Average=2.6 | | Average=6.6 | |
| | 10.3 | 13.9 | | | | |
| | | 17.0 | | | | |
| Day 4 | 9.2 | 16.0 | | | | |
| | 11.2 | | | | | |
| | Average=12.9 | | | | | |

* Micrograms per 100 ml. of plasma.

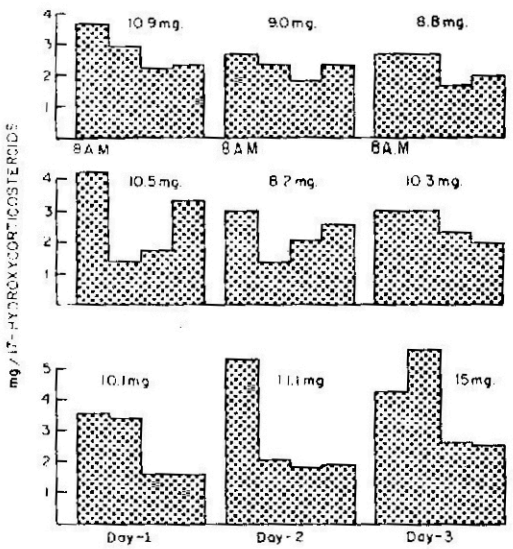


Fig. 2.—Urinary excretion of 17-hydrocorticosteroids. In all subjects, during the period of sleep deprivation, urinary collections were made every six hours. These aliquots were analyzed, in three subjects, for 17-hydroxycorticosteroids, and demonstrated the persistence of a normal diurnal rhythm.

*II. Adrenal Steroid Studies.*—In agreement with the observations of previous investigators,[15,16] we found no significant alterations in adrenocortical activity despite 72 hours of wakefulness. Both the concentrations and the diurnal rhythm of hydrocortisone (17-hydroxycorticosterone) in the blood remained remarkably stable and normal from day to day (Table 7).

Similarly, the 24-hour urinary excretion of the 17-hydroxycorticosteroids and the 17-ketosteroids remained relatively constant from day to day, and the normal urinary diurnal rhythm of the 17-hydroxycorticosteroids persisted (Fig. 2). This constancy appeared to be a tribute to the body's capacity to maintain its normal biological patterns despite a radical departure from accustomed routines.

*III. LSD-25 Experiment.*—Four subjects were chosen for this experiment. All had received lysergic acid diethylamide (LSD-25) without sleep deprivation on at least four previous occasions, so that their responses to the drug and tolerance for it were well known. Each had taken 0.5μg. of LSD-25 per kilogram of body weight

TABLE 8.—*Dosage*

| Subject | 1μg/Kg. LSD-25 | 1μg/Kg. LSD-25 with Other Drugs | 0.5μg/Kg. LSD-25 | 0.5μg/Kg. LSD-25 with Other Drugs | 0.5μg/Kg. LSD-25 with 48 hr. Sleep Deprivation |
|---|---|---|---|---|---|
| B | Hallucinations | Hallucinations (mescaline 0.1 gm.) | No hallucinations | No hallucinations (amobarbital sodium 0.3 gm.) | Hallucinations |
| S | | Hallucinations (amobarbital 0.3 gm.) | No hallucinations | No hallucinations (atropine 1.2 mg.) | Hallucinations |
| M | | Hallucinations (BOL 2 mg.) | No hallucinations | Hallucinations (mescaline 0.1 gm.) | Hallucinations |
| R | Hallucinations | | No hallucinations | No hallucinations (BOL * 2 mg.) | Hallucinations |

* BOL 148 is 2-bromo-d-lysergic acid diethylamide.

alone or in combination with another compound on two or three previous occasions and had not developed perceptual disturbances (LSD-25 hallucinations) except in one instance, when 0.5μg. of LSD-25 had been combined with 0.1 gm. of mescaline. In contrast, all subjects had hallucinations after taking 1μg. of LSD-25 per kilogram of body weight [17] (Table 8).

After being deprived of sleep for 48 hours, each subject received 0.5μg. of LSD-25 per kilogram of body weight. In striking contrast to previous responses, all four under the combined influence of sleeplessness and drug, developed hallucinations. It should be reemphasized that this amount of drug had not previously been hallucinogenic. Furthermore, the total response to 0.5μg. of LSD-25 per kilogram combined with sleep deprivation was in other particulars as severe as or severer than the reaction to 1μg. of drug per kilogram in the rested state.

It would appear from these observations that sleep deprivation enhances the disruptive effects of LSD-25 upon ego function. Presumably, this may have been due to an alteration in cerebral metabolism consequent to prolonged sleeplessness, which made the brain more susceptible to the "psychotomimetic" effects of LSD-25.

*IV. Metabolic Study.*—The one subject who was studied on a metabolic ward showed no significant changes in the urinary excretion of chloride, sodium, potassium, calcium, phosphate, or nitrogen during the 72 hours he remained awake, as compared with the seven-day control period preceding the sleep deprivation and the five-day control period which followed. The only unusual observation was a polyuria of 5000 to 6000 ml. during the test period. It seemed unlikely that this might have been due to a posterior pituitary inhibition, since our other subjects did not have high 24-hour urinary volumes. The study did indicate that sleep deprivation of this magnitude neither increased protein catabolism nor disturbed electrolyte metabolism, and the results were consistent with our observation of a lack of variation in adrenocortical activity.

## Comment

It has long been recognized by experienced inquisitors in "police" states that sleep deprivation can induce personality disorganization. They have been well aware that enforced wakefulness, when combined with emotional turmoil and physical isolation, may lead to psychotic behavior in susceptible subjects.[18] These are observations that have generally been overlooked by the psychiatrist.

It is our impression that these unconscionable techniques are unwittingly reduplicated by certain psychiatric patients who experience intolerable psychological distress and then suffer emotional isolation and prolonged sleeplessness. In a few susceptible persons the combination of these forces may precipitate some schizophrenic illnesses. Two examples were cited of patients who illustrated this situation. Both were racked with intense psychological pain and overwhelmed by seemingly insoluble problems. Both failed to sleep for several days, emotionally isolated themselves, and became psychotic. In each case the schizophrenic episode was brief and rapidly reversible. Either might have become schizophrenic without the additional insult of sleep deprivation, but it seems plausible that the insomnia may have been a critical factor in the process. Since these clinical situations combined a variety of noxious influences and did not allow an accurate estimate of the impact or importance of the individual factors, one of the disturbances—the loss of sleep—was isolated and investigated in experimental subjects. The setting of the experiment was a social one, in which communication was free and congenial. This eliminated in part the factor of isolation. Furthermore, every effort was made to create and maintain an anxiety-free situation so that emotional disturbances could be minimized or excluded. This left a relatively controlled situation, where the prin-

cipal variable was prolonged wakefulness. In this setting subjects remained awake for 72 hours, and series of observations and studies were performed.

After prolonged sleeplessness subjects were able to handle relatively brief psychological tests adequately, but developed a variety of ego disturbances during the intervening periods. These disturbances included feelings of depersonalization, confusion, hallucinations, paresthesias, motor incoordination, and other subtle psychological changes. All of these characteristically were inconstant and came in waves, coinciding with periods of intense somnolence. They probably represented hypnogogic states when the subjects were "asleep on their feet." No subject became psychotic. One can only infer that if these changes were to occur in someone who was also profoundly anxious and deprived of group support, more serious psychopathological sequelae might result.

A second series of observations in which LSD-25 was combined with sleep deprivation had further interesting implications. The hallucinogenic properties of the drug were considerably enhanced by sleeplessness. Amounts of the drug which ordinarily produced mild changes induced extensive perceptual disturbances in subjects who had been awake for 48 hours. This suggested that the loss of sleep may have altered cerebral metabolism so as to make the cortex more susceptible to the hallucinogenic properties of the drug.

Another general observation was the stability of deeply entrenched biological rhythms. Despite continuous wakefulness, both the diurnal sleep-wakefulness pattern and the adrenal steroidal pattern followed their normal fluctuations, and protein and electrolyte metabolism remained unaltered. None were significantly altered by the extraordinary circumstances of the experiment.

Unfortunately, the observations to this point are suggestive but not conclusive. The facts suggest, however, that prolonged sleep deprivation may have a pathogenic potential, especially when combined with other disruptive psychological processes, and that prolonged wakefulness may be a critical factor in the precipitation of a *few* schizophrenic illnesses.

## Summary

The clinical observation that a *few* schizophrenic episodes are preceded by prolonged insomnia led us to postulate that sleep deprivation, although a consequence of the emotional turmoil, might play a critical role in the precipitation of some psychoses. Therefore, studies were made of normal subjects who were kept awake for 72 hours. The setting was a social one, where anxiety was kept minimal. Changes on psychological tests were insignificant, but behavioral and subjective alterations were considerable. Feelings of depersonalization, illusions, hallucinations, disturbances in time perception, and auditory changes were common. Despite the long period of wakefulness, adrenocortical activity remained normal.

In another study subjects were kept awake for 48 hours and then given small amounts of LSD-25. Sleep deprivation markedly enhanced the ego-disruptive effects of the drug. It is suggested that sleep deprivation, when combined with isolation and incapacitating anxiety, may have a pathogenic potential that has not been adequately appreciated.

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