Sleep Deprivation: Effects on Behavior, Thinking, Motor Performance, and Biological Energy Transfer Systems

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SLEEP DEPRIVATION has been extensively studied in terms of the phenomenology of the changes produced. In 1935, Katz and Landis[6] observed one man who remained awake for 10 days. They found no physical or physiological changes; their subject did, however, become irritable, argumentative, and slightly disoriented in time and space. Hallucinations, hypnagogic states, and a delusional system occurred, which they attributed to the precipitating effect of lack of sleep. Kleitman[7] observed generally increased irritability and a necessity for mobilizing much greater attention in order to perform tasks. He also reported that body temperature was inversely related to feelings of somnolence.[8] This was confirmed by Murray *et al.*[9] in a more controlled study.

Bliss *et al.*[2] reported a study of a group of medical students who were sleep-deprived for 72 hours. Definite psychological changes occurred, including the development of irritability, visual hallucinations, and mild intellectual deterioration. Measurement of adrenal steroid excretion reflected no change in the basic diurnal pattern, but the subjects manifested increased susceptibility to the hallucinogenic properties of lysergic acid diethylamide 25. The histories of a number of patients were also presented, with the implication that prolonged sleeplessness might have precipitated their acute schizophrenic symptoms.

Forty-three normal subjects were tested by Ax *et al.*[1] on 18 psychomotor, attention, and performance tests covering an 8-hour period following 24 hours of wakefulness. Low-motivating tasks produced a marked decrement in performance with sleep deprivation, whereas high-motivating tasks were performed without decrement. These findings were interpreted as indicating that moderate sleep deprivation lowers the internal drive state; this may be temporarily compensated for by increased external motivation.[1]

Because extended sleep deprivation produces a type of model psychosis, it was of considerable interest to study the vicissitudes of enzyme systems associated with intermediary carbohydrate metabolism in this state. In the laboratories of the Lafayette Clinic, energy transfer systems are under study, involving intracellular phosphorylation in the erythrocytes of schizo-

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Received for publication Aug. 10, 1959.

phrenic and normal subjects under basal conditions and insulin stress.[5] The most significant findings suggest a defect in chronically ill schizophrenic patients in the mobilization of energy as an adaptational response to stress. Most recent data indicate a disturbance in the control of the hexose monophosphate shunt in these patients, with an inability to shift adaptively from the synthetic cycle to the high-energy Emden-Meyerhof part of the system when stressed with insulin.[4]

Energy is ordinarily made available to the cell by the formation of adenosine triphosphate (ATP). This compound is formed from adenosine diphosphate (ADP) during the breakdown of food to CO_2 and water. The energy present in food is transferred to the bond between the second and third phosphate radicals of ATP. As ATP is broken down to ADP, this energy is released for use by the cell. In an emergency, to obtain rapid energy, ATP may be synthesized in an alternate manner. Two molecules of ADP may react to form one molecule of ATP and one of adenylic acid (AMP) in a dismutation type of reaction. The adenylic phosphates (ATP, ADP, and AMP) are broken down over extended periods to uric acid and excreted in the urine. In order to replace these compounds, adenine, ribose-1-PO_4, and phosphate combine to form AMP. This reaction occurs more slowly than the previously mentioned one and functions to replace ATP.

ADP is present in the cells in limited amounts. In order for either anaerobic glycolysis or oxidative phosphorylation to take place, ADP must be present to act as a phosphate acceptor. In other words, as can be seen in Fig. 1, ADP is a necessary starting material for the biosynthesis of ATP in the production of energy. Since the utilization of energy involves the formation of ADP, this compound then acts as a convenient regulator of energy metabolism. The expenditure of energy results in the formation of more ADP which, in turn, stimulates synthesis of ATP. Because

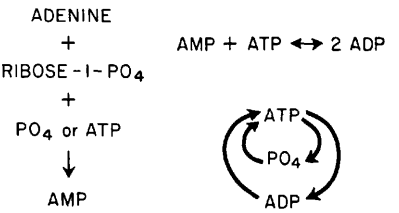

Fig. 1.

of this mechanism, the ratio of ATP to ADP (ATP/ADP steady-state ratio) remains constant under normal conditions.

These energy transfer systems were chosen as a major focus of attention in the investigation of the model psychosis occurring as a result of enforced wakefulness. Relationships between biochemical findings, behavioral observations, and results of psychological tests might be of considerable interest. The effects of prolonged sleep deprivation on these energy transfer systems, so fundamental to all cellular function, may be compared with those changes found in chronic schizophrenic patients.

Method

Our study of a single subject was made possible when a young radio announcer who planned to exceed the previous "wakeathon" record of 212 hours was referred to this clinic. The possible adverse consequences of such an undertaking were explained to him in detail in an effort to dissuade him. He was, however, determined to proceed despite these admonitions. He volunteered to be a research subject and cooperated throughout the project.

W. A., a 27-year-old married white male, was referred to us by the Muscular Dystrophy Association, for whom he was about to undertake the wakeathon. He had decided to establish a record of 220 hours of sleeplessness and to accomplish this without benefit of stimulants other than coffee. For 2 years he had been employed by a small radio station as a "disk jockey," but had recently been dismissed and was unem-

ployed at the time of the experiment. His avowed motivation for participation in such research was his desire to help "sick and powerless children." Later it became evident that he hoped the publicity would make him famous and that radio stations would then seek him out.

An adopted child, he was reportedly abandoned in a garbage can by his mother. His foster parents treated him well and he enjoyed a particularly close relationship with his father. Of importance in his early history was a period of hospitalization at age 11 in a neuropsychiatric institute, following an attempt to set fire to a barn. One year later he was apprehended for car theft and received probation. During his sixteenth year he was told that he was an adopted child and, although professing not to be disturbed by this information, soon went into the armed forces. In the army he became a staff sergeant and small-arms expert. Despite occasional fights he did well and was honorably discharged at the age of 20. Soon after discharge he married and now has three children. In the 6-year period following separation from the service he changed jobs more than 20 times, finally developing a sustained interest in radio announcing.

The mental-status examination was not remarkable. W. A. was moderately anxious, despite attempts to appear self-assured and confident. He was concerned about a potential threat to his health, but knew that he had "involved too many people to back out." There was no evidence of a thinking disorder nor a gross disturbance in affect. Physical examination also gave essentially negative results. Chest x-ray, EKG, c.b.c., and urinalysis were all within normal limits, and a base line electroencephalogram was interpreted as showing no abnormality.

The subject was seen on four occasions prior to his wakeathon for psychodynamic and diagnostic interviews. During the 10 day period of wakefulness he was seen three times each 24-hour period. More sustained observation was not possible because the wakeathon was conducted at a record shop in the Detroit suburbs. Each interview was tape-recorded and later analyzed for content. At all times at least three people were with the subject. *No drugs other than vitamins were used during the study.* His diet was observed to be adequate and he was placed on two tablets of Myadec daily.

The subject fasted for 3 hours prior to the collection of blood and urine samples which were taken daily at 7:30 A.M. Twenty-four-hour urine specimens were also collected at this time. These measurements were begun 2 days prior to the wakeathon.

Urine creatinine was measured by the method of Folin,[11] urine uric acid by the method of Benedict and Frank,[11] and blood glucose by the Anthrone method.[3] Ribose measurement was done by the method of Meijbaum.[11]

Base line determinations were done 2 days prior to the beginning of the sleep-deprived period. Urinary creatinine and uric acid were measured on days 1, 2, 4, 5, 6, and 7. Blood glucose measurement was done daily, and blood pentose levels were taken on days 2, 4, 6, and 8. Energy production was studied on the fourth and seventh days, in addition to the base line determinations. In the study of energy production, 25 cc. of whole blood were incubated for 1 hour with 0.05 mc. of P^{32}. ATP, ADP, adenosine monophosphate, and fructose-1,6-diphosphate (F-1,6-P) were then isolated by ion exchange chromatography, and their levels and specific activities measured by a method developed in the laboratory of the Lafayette Clinic.

Before W. A. began his vigil, he was given a battery of psychological tests. This included WAIS; Gorham Proverbs (Form I), a measure of conceptual thinking; the Benton Visual Retention Test (Form C), a test of visual-motor memory; the TAT; the Conceptual Thinking Examination; and Serial Sevens, a task involving goal-directed behavior. This battery afforded a base line against which to compare the results of tests given during the period of sleeplessness.

Each day during the wakeathon W. A. was given a brief battery of tests, including (1) the Benton Visual Retention Test, (2) the Gorham Proverbs, and (3) Serial Sevens. Both the Benton and Gorham tests were available in three equivalent forms, which tended to minimize practice effects of repeated administrations. No control for practice was available with Serial Sevens. The battery could be given in approximately 15 min. As nearly as possible, the tests were given at the same time of day during the vigil. Alternate forms of tests that provided them were systematically rotated from one administration to the next.

The Gorham Proverbs were scored for both abstractness and concreteness. The scoring was done by a research assistant who had no knowledge of the day of wakefulness. The Benton Visual Retention Test was scored blind by a staff psychologist. Each set of drawings was scored both for number of drawings correctly reproduced and the total number of errors per set. The Serial Sevens were scored in terms of the time per trial and the number of errors per trial.

Results

Behavioral Observations

The first 3 days produced no significant behavioral changes. Impressed with the novelty of the experience, W. A. enthusiastically played records and accepted contributions for muscular dystrophy while eagerly watching the newspaper for articles about his endeavor. The early hours of the morning, however, were agonizing as he struggled to keep his eyes open. His attendants walked him in the cold air and placed him under a needle shower. Irritability was prominent after 72 hours and, on one occasion, he impulsively grabbed an observer who had squeezed his nose in order to keep him awake. At this time, he became very angry and put his coat on while screaming, "You're all trying to make a fool out of me, and I'm quitting." This rage soon subsided and he continued with the wakeathon. After 100 hours, his mood and motor activity suddenly changed. He became expansive, hyperactive, and grandiose. There was no longer any doubt in his mind that he could complete 220 hours and he proclaimed, "Now you'll see the real W. A. I'm giving up all that artificial stuff and just behave like myself. I'm not worried about it any more. I'm sure of it now." He attributed his new-found confidence to refusal to eat a bowl of fatty soup prepared for him by a woman whom he then accused of attempting to over-protect and coddle him. He became very hostile toward women, expressing feelings of independence and self-nurturance. Finally he ate a huge dinner in the evening. In his euphoria, he threw out a challenge to all the disk jockeys in the country. He would compete with them in a gigantic wakeathon to be staged in the window of a large Detroit department store. The benefits would go to muscular dystrophy. Gradually his expansiveness and hyperactivity ebbed, and by the one hundred sixtieth hour his brow was constantly furrowed and he seemed utterly weary. Disturbance in bodily sensation occurred, described as a feeling of tightness and dryness in all his joints, associated with great heaviness of his extremities. From that time until the end of the wakeathon there were frequent visual hallucinations and hypnagogic states. In the morning, he observed a "grey mist hanging over the pool table like a spider web." Most startling was a "blue flame or luminescence" which seemed to surround a young woman who had just entered the room to serve him some coffee. This flame also "spurted from the wall," causing him to leave the room in terror. His irascibility was also prominent. While playing pool he suddenly threw down his cue and tried to choke his partner, complaining again that he was being made a fool of. His paranoid behavior also manifested itself in his great concern about the examiner's disclosing any information about him to friends or family, and he refused to allow the ex-

aminer to talk alone with them. Of interest was his sensitivity to peripheral stimuli. He had difficulty attending to whatever simple task he was doing, and was constantly distracted by music and voices which came from other rooms. During the last 3 days he alternated between sullen withdrawal and labored attempts to be polite and courteous.

The hypnagogic states were comparable to waking dreams. At the one hundred eightieth hour he felt a tight band around his head which gradually slipped down over his eyes, obstructing his vision. Then, although walking with his eyes open, he felt as though he were on a black cloud, weightlessly floating among a group of ballet dancers whose forms he could barely perceive. "Blackout" periods also occurred in which he would automatically continue certain behavior such as playing records, yet suddenly "awaken" with no memory of what he had done moments before. During one interview, when asked about his dismissal from a radio station, his voice drifted away until his name was called. He then reported feeling as though he were actually broadcasting an on-the-spot account of a fire. At the same time he was aware that he was with the examiner.

Finally, when the two hundred twentieth hour was reached, he could barely speak and had to be supported when he walked. He collapsed in the lobby of the clinic and was admitted to the hospital for 48 hours. He then slept for 14 hours, went to church, and was seemingly functioning at his premorbid level again.

Psychological Observations

The results of the Gorham Proverbs Test proved to be worthless, because the subject's performance decrements were confounded with the form of the test. All his low-abstraction scores occurred with one form of the test, independent of the day of wakefulness; this made the results uninterpretable.

The results of the Benton Visual Retention Test are shown in Fig. 2. These data

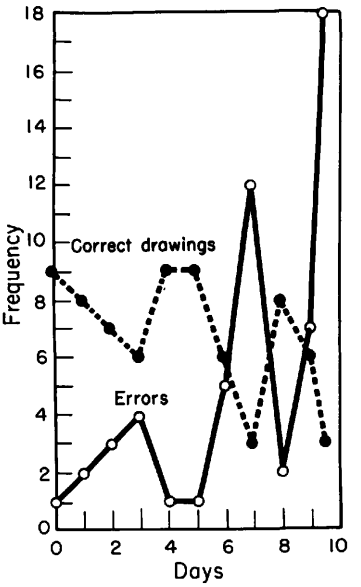

Fig. 2. Results of Benton Visual Retention Test.

suggest the presence of cyclic changes in the subject's behavior across days of wakefulness. During the first 3 days of sleeplessness there was a gradual deterioration in the subject's performance. This was reflected by an increase in the number of drawings incorrectly reproduced. During this period he made only one error per incorrect drawing. On days 4 and 5 there was an improvement in performance, the subject having only one incorrect reproduction and only one error on each of these days. On days 6 and 7 his performance again deteriorated. On day 7 his performance showed the most serious impairment. He was able to reproduce correctly only three figures, and made 12 errors in doing so. This is an average of almost two errors per drawing. On day 8 he again improved, but on day 9 his behavior deteriorated markedly. The test results on this day re-

vealed only three correct drawings out of ten, and an average of almost three errors per incorrect drawing. On the last day of the vigil his condition was so poor that he was untestable.

On the basis of these data, it would appear that the effects of prolonged sleeplessness were most dramatically reflected in the ratio of the number of errors per incorrect drawing. Initially, the ratio was 1:1, which is the normal expectancy. However, at the end of the vigil it had gone up to almost 3:1, which suggests a marked deterioration in W. A.'s ability to function in a visual-motor memory task.

The results of the Serial Sevens also tended to show cycles in performance across days of wakefulness. This is shown in Fig. 3, which shows the time in seconds required to perform the test each day. Roughly, the periods of rapid performance corresponded to the periods when W. A. was making the most errors on the Benton test, and the slowest performance to the periods when he was making the fewest errors.

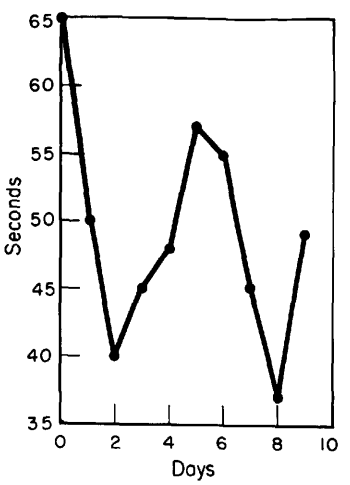

Fig. 3. Time required to complete Serial Sevens Test.

Biochemical Observations

Base line determination indicated that the specific activity of ATP* for this subject was within the range of the control participants in a previous study. On the fourth day, the specific activity of ATP rose markedly from 640,000 to 2,000,000 counts per milligram per minute (Fig. 4). On the seventh day the specific activity of ATP had dropped to 670,000 counts per milligram per minute, a possible indication of a failing system. The specific activity of ADP and F-1,6-P changed in the same direction, an anticipated finding. Most surprising were the changes in AMP specific activity. With the short incubation time used in our laboratory, no radioactive P had previously been detected in AMP. However, on both the fourth and seventh days AMP showed an appreciable specific activity; the measures being 200,000 counts per milligram per minute on the fourth day and 120,000 counts per milligram per minute on the seventh.

As shown in Fig. 5, the levels of ATP dropped from 5.6 to 3.5 mg.% on the fourth day and rose again to 4.3 mg.% by the seventh day. This drop in the ATP level represented a different ATP/ADP steady-state ratio, as shown by the increase in ADP from 1.4 to 2.9 mg.% on the fourth day. The increase in ATP between the fourth and seventh days was accompanied by a drop in ADP. At no time did the total adenylic phosphates vary significantly. During the first 4 days the level of AMP remained fairly constant, but by the seventh day it had decreased appreciably. No change was found in the levels of F-1,6-P during the entire experiment.

There were no significant changes in the

*The specific activity of ATP can be defined as the number of counts of radioactive material per milligram per minute. It represents the rate at which the erythrocyte picks up radioactive phosphorus and incorporates it into the ATP molecule and is thus an index of the amount of energy being produced over a given period. Because of the time-consuming nature of the laboratory procedure, it was performed on only 3 occasions during this project.

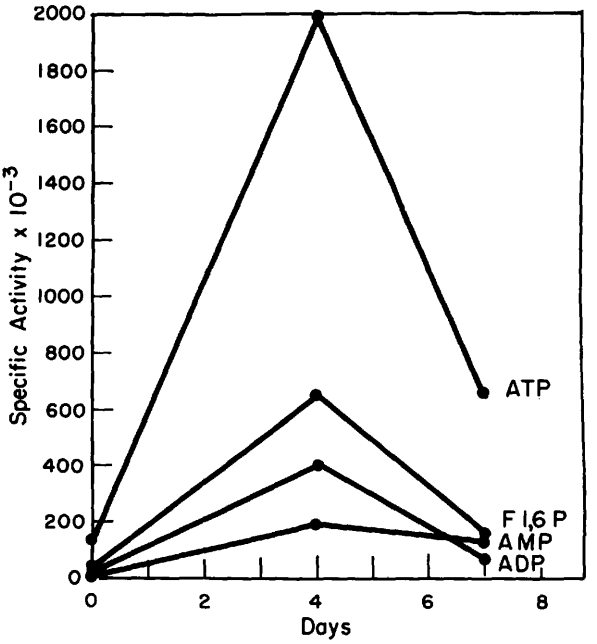

Fig. 4. Specific activity 1 hour after incubation with $P^{32}O_4^{\equiv}$.

levels of blood glucose. Blood pentose levels, however, paralleled the changes observed in ATP specific activity (Fig. 6). The urinary excretion of creatinine increased significantly during the period of sleep deprivation; uric acid decreased (Fig. 7).

Discussion

The behavior of this subject conformed to that described by other investigators in sleep deprivation studies. There was cyclic variation, but as the days of wakefulness progressed the subject grew more irritable and paranoid, found increasing difficulty in concentrating and memorizing, and finally experienced visual hallucinations, hypnagogic states, and peculiar periods of automatic behavior for which he was amnesic. These periods, not hitherto described in the literature, were almost like psychomotor seizures or sleeping while awake. Performance on psychological tests was generally correlated with clinical evaluation of his arousal, but a point was reached where alerting was no longer possible and, beyond 200 hours the subject became virtually untestable. Possibly the reticular activating system was utterly fatigued and no longer capable of producing arousal and focusing of attention. Sensitivity to peripheral stimuli might well be a part of the same phenomenon.

Changes in the specific activities and levels of the various adenylic phosphates are of considerable interest. During the first half of the study, sleep deprivation apparently acted as a stressor on the chemical

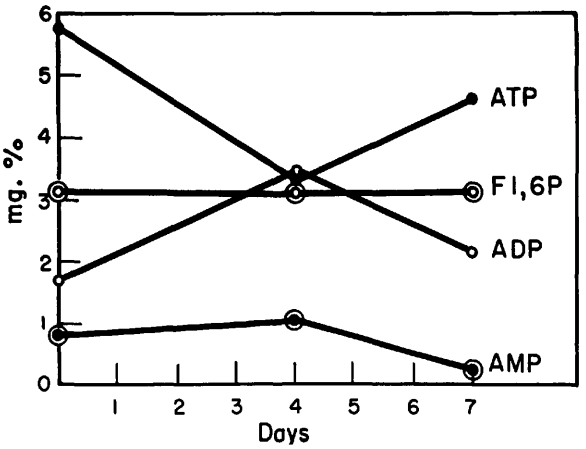

Fig. 5. Levels of ATP, ADP, AMP, and F-1,6-P in blood.

mechanisms producing energy. Energy production had increased by the fourth day, as evidenced by the change in specific activity of ATP and F-1,6-P during this period. This increase is similar to that obtained with insulin stress in the control subject. Even with a drop in the level of ATP between the base line determination and the fourth day, the specific activity of ATP almost doubled. The drop in the level of ATP could not account for the much larger increase in specific activity. This increase must have been produced by an accelerated rate of synthesis. The change in the steady-state ratio of ATP to ADP suggests that ADP was no longer the limiting factor in the production of energy, but that some other substance became the driving factor for anaerobic glycolysis, and that a mechanism not important in the other types of stress thus far studied plays a major role here. The appearance of radioactive P in AMP on the fourth day may offer a lead to the character of the reactions causing the increase in ATP specific activity as related to emergency energy mobilization. Phosphorus incorporated in ATP by means of either the Emden-Meyerhof scheme or the tricarboxylic acid cycle could never appear in AMP. To account for the presence of radioactive material in AMP, we must assume synthesis of this compound from adenine, ribose, and either inorganic phosphate or ATP. Such a reaction would increase the specific activity of ATP by incorporating labeled phosphorus in the first and second phosphate radicals, in addition to that added to the third phosphate radical during glycolysis. The increased (ATP + ADP + AMP) demonstrates the ability of the body to conserve these important materials even under severe stress. This constant level of adenylic phosphates (ATP + ADP + AMP) demonstrates the ability of the body to conserve these important materials even under severe stress. This was more evident in the drop in uric acid excretion. Since uric acid is the excretory end product of purine metabolism, one might assume that a decrease in the excretion of this material resulted from the conservation of the purines, including adenine.

Correlations between behavioral, psychological, and biochemical data are difficult to make because daily studies of energy production were not available. The trends

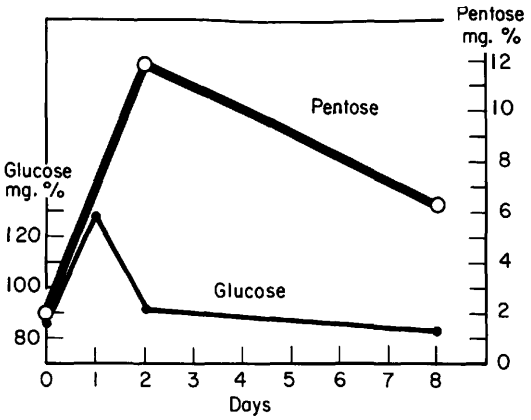

Fig. 6. Blood levels of glucose and pentose.

might indicate relationships between the greatly increased specific activity of ATP on the fourth day and the ebullient hyperactivity and grandiosity observed on the fifth day. It was at this time also that performance on psychological testing showed considerable improvement. Conceivably, the subject might have reached peak levels in energy production at this time, following which his emergency mobilization began to fail.

During the second half of the experiment the rate of synthesis of ATP fell, as manifested by the considerably lower specific activity of ATP on the seventh day. The ratio of ATP to ADP levels returned to the basal values. These results could well represent the failure of the mechanism responsible for the increased synthesis of ATP. Following the loss of this mechanism ADP presumably resumed its role as mediator of the rate of energy production, since the steady-state ratio of ATP to ADP returned to normal.

Were the more rapid synthesis of AMP responsible for the increased specific activity of ATP on the fourth day, then the decrease in both level and specific activity of AMP by the seventh day would confirm the failure of this mechanism.

Again behavioral and psychological observations apparently paralleled the biochemical findings. The subject's irritability, hallucinatory experiences, apathy, and hypnagogic states were most prominent at this time. Deterioration in psychological test performance was also concomitantly most severe.

Conceivably, the energy transfer systems respond to a stressor in a manner similar to the pituitary adrenal axis, passing through stages of alarm, resistance, and exhaustion, as described by Selye.[10] Questions concerning the function and mechanism of sleep as related to high-energy phosphorylation might well be asked. Does sleep have as its basis the restitution of these energy transfer systems, and do we sleep because of diurnal variations in their activity?

The mobilization of adaptational energy must be crucial to the organism's ability to master stress of any kind. The energy transfer systems involved in this adaptational response might be impaired either on a genetic basis or as a result of certain stressful life experiences. At a critical developmental period, overwhelming anxiety might well produce irreversible impairment of these systems. What relevance this may have to clinical phenomena is under

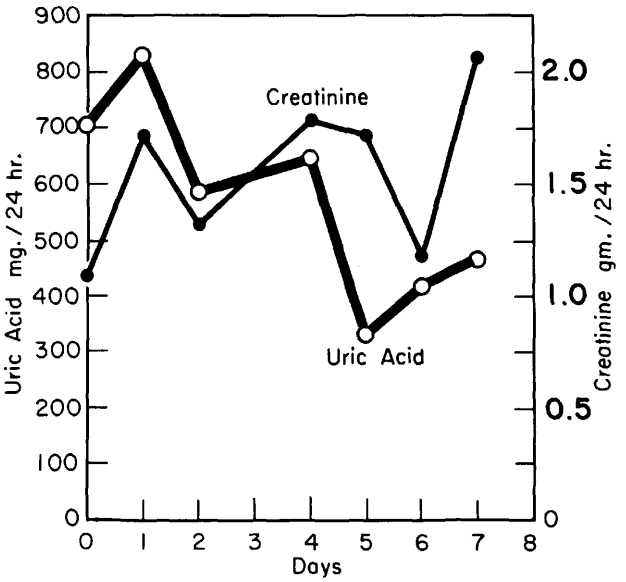

Fig. 7. Urinary excretion of uric acid and creatinine in 24 hours.

study. Present evidence suggests, in a chronic schizophrenic population, profound impairment in precisely this ability to mobilize adaptational energy.

Summary and Conclusions

The effect of sleep deprivation on behavior, thinking, motor performance, and biological energy transfer systems was studied in a single subject who remained awake without drugs for 220 hours.

Behavioral changes included irritability, paranoid thinking, expansiveness, grandiosity, hypnagogic states, visual hallucinations, and episodic rage.

Deficits in thinking and visual-motor performance occurred cyclically across days of wakefulness, with gradual deterioration finally resulting in virtual untestability on the ninth day.

Energy transfer systems responded to sleep deprivation as a stressor with a marked increase in the specific activities of ATP, AMP, and F-1,6-P; this was evident on the fourth day. For the first time in our laboratories, radioactive phosphorus was observed in AMP, a reflection of increased synthesis of this substance from adenine, ribose-1-phosphate, and phosphate. This emergency energy mobilization began to fail by the seventh day, when the specific activities of all the adenylic phosphates fell appreciably.

Conceivably the energy transfer systems respond to a stressor in a manner similar to the pituitary adrenal axis, passing through stages of alarm, resistance, and exhaustion. The relationship of disturbances in these systems (associated with the most fundamental cellular processes) to various disease mechanisms is under investigation in our laboratories.

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