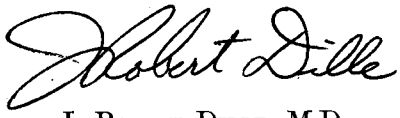
# PHYSIOLOGICAL RESPONSES OF MEN DURING SLEEP DEPRIVATION

**Vincent Fiorica, Ph.D.**
**E. Arnold Higgins, Ph.D.**
**M. T. Lategola, Ph.D.**
**Audie W. Davis, Jr., M.D.**
**P. F. Iampietro, Ph.D.**

*Approved by*



J. Robert Dille, M.D.
Chief, Civil Aeromedical Institute

*Released by*

P. V. Siegel, M.D.
Federal Air Surgeon

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**Department of Transportation**
**FEDERAL AVIATION ADMINISTRATION**
**Office of Aviation Medicine**

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# PHYSIOLOGICAL RESPONSES OF MEN DURING SLEEP DEPRIVATION

## I. Introduction.

Human fatigue as a problem of concept, of personal health, and of efficiency and productivity has long been given general and continuing attention.[1 2 3 4 5] In the specific area of aviation activities, concern with the problem of fatigue is also well documented[6] and the importance of further investigations in the area has been emphasized.[7] The present report describes the results of studies concerned with the physiological, biochemical, and psychomotor responses of men experiencing fatigue induced by the loss of sleep.

Sleep loss as a means of generating fatigue or as a nonspecific stressor for laboratory study has been frequently suggested.[8 9 10 11 12] Although considerable efforts have been made in the past toward defining the physiological consequences of extended sleeplessness, little success has been realized. The accounts of Kleitman,[13] Oswald,[14] and Wilkinson[15] review many of the earlier studies and present some current thinking on the problem. Clearly positive physiological findings have been achieved only in the area of electroencephalography with the consistent observation of a decrease in the alpha rhythm of the brain as sleep loss progresses.[16 17 18] The significance of this finding, however, remains controversial.[19 20 21]

Biochemical findings during prolonged sleep loss have been generally negative[22 23], or conflicting.[11] Luby et al.,[24 25] have reported a decrease in the specific activity of erythrocyte ATP in men between the 48th and 96th hour of sleep loss, but this finding has not yet been confirmed in other laboratories. The excretion of an indolic substance during sleep deprivation was reported by Mandell[12] and was believed to indicate a stress response to the condition. The excretion of the indole, however, could not be demonstrated in a later study.[26]

Apparently greater success in characterizing the consequences of sleep loss has resulted from a psychological approach, particularly in those studies concerned with behavioral changes and performance decrements.[27 28 29 30] The sensitivity of psychological testing and of psychophysiological measurements to even moderate levels of sleep deprivation immediately suggest that the greatest changes occur in those systems requiring a high degree of cerebral involvement. However, physiological and biochemical mechanisms with little cerebral interaction appear unresponsive to the sleepless condition.

The emphasis in the present study was directed toward examining specific physilogical responses to standard stress conditions superimposed on the sleep deprivation episode. In this respect the current study departs from the classic approach to the problem. Primary attention in the present report is focused on the physiological responses of the sleep-deprived man to the stresses generated by acute whole body cold exposure. Additional attempts were made during this study to distinguish the sleep-deprived individual on the basis of psychomotor performance and the urinary excretion of stress and sleep-related substances.

## II. General Procedures.

*Subjects:* Subjects were paid volunteers. Twelve young men divided into two groups, sleep-deprived (SD) and control (SC), were studied in six separate trials, each lasting 84 hours. Physical characteristics of the subjects are given in Table 1. Each of the subjects was given a medical examination at the time of selection and again immediately prior to beginning the test. All subjects were considered normal and in good health.

*Subject Routines:* Subjects were studied in pairs, one SD and one SC, throughout the 84-hour trial. Subjects reported to the laboratory at 0800 Monday without breakfast and, until released on Friday evening, were constantly monitored by laboratory personnel. The first day at the laboratory was primarily devoted to orienting the subjects to the conditions of the test. Practice sessions for the psychomotor, hypoxia, and

TABLE 1.—Physical characteristics of experimental subjects.

| Subject (No.) | Age (Yrs.) | Height (cm.) | Weight (kgm.) | Surface Area ($m.^2$) |
|---|---|---|---|---|
| | | Sleep-deprived (SD) | | |
| 01 | 26 | 172.7 | 74.40 | 1.88 |
| 03 | 25 | 172.7 | 59.04 | 1.70 |
| 05 | 20 | 171.4 | 79.09 | 1.92 |
| 07 | 25 | 170.8 | 71.66 | 1.83 |
| 09 | 25 | 178.4 | 75.94 | 1.94 |
| 11 | 22 | 181.6 | 79.22 | 1.99 |
| Mean(SE) | 24(1) | 174.6(1.8) | 73.22(3.07) | 1.88(0.04) |
| | | Control (SC) | | |
| 02 | 26 | 175.9 | 62.74 | 1.76 |
| 04 | 21 | 182.9 | 75.98 | 1.98 |
| 06 | 24 | 185.4 | 85.79 | 2.10 |
| 08 | 23 | 181.0 | 65.48 | 1.84 |
| 10 | 25 | 175.9 | 68.86 | 1.85 |
| 12 | 23 | 170.2 | 61.17 | 1.69 |
| Mean(SE) | 24(1) | 178.6(2.3) | 70.00(3.82) | 1.87(0.06) |

hypercapnia tests were completed during the day and baseline data for other standard tests (orthostatic tolerance and maximum work capacity) were also collected on this day. Sleeping facilities were provided at the laboratory. Both subjects retired on the first night at 2230 hours. On Tuesday morning both subjects (SD and SC) were awakened at 0545 for body weight, resting oxygen consumption, and rectal temperature measurements. Thereafter, the routine for the remainder of the test was followed as shown in Table 2.

Subject dietary intake was not controlled, but was approximately similar between the two subjects. Breakfast was eaten at the laboratory and was the same each day: toast, eggs, bacon, and orange juice. Lunch was taken at a local cafeteria and dinner, in the form of "TV dinners," was also taken at the laboratory. Vending machines were available and some subjects, notably of the SD group, purchased candy bars and soft drinks, particularly during the nighttime hours. Coffee was available to both SD and SC subjects at all times, but unknown to either group, it was a commercial, decaffeinated preparation. Several forms of diversion were available to keep SD subjects occupied during the study. Pocket billiards, machine bowling, and "pin-ball" were the primary devices used. Other activities, at the choice of the subject, included painting, model-building, or walking out of doors. Reading was effective only during the first sleepless night and was not permitted thereafter. Television was viewed occasionally, but its use was restricted to a brightly lit room.

TABLE 2.—Testing schedule and routine.

| Time | Test or Activity | |
|---|---|---|
| | SD | SC |
| 0545–0600 | Body wt. | Waken, Body wt |
| 0600–0615 | $T_r$; $\dot{V}O_2$ (26.7° C) | $T_r$; $\dot{V}O_2$ (26.7° C) |
| 0615–0630 | Psychm | Open |
| 0630–0645 | Open | Psychm |
| 0645–0830 | Orthost.; Work Cap. (1) | Orthost.; Work Cap. (2) |
| 0830–0930 | Bkfst.; Cleanup | Bkfst; cleanup |
| 0930–1000 | Open | Open |
| 1000–1015 | Psychm | Open |
| 1015–1030 | Open | Psychm |
| 1030–1100 | Open | Open |
| 1100–1130 | Hypoxia | Open |
| 1130–1200 | Open | Hypoxia |
| 1200–1300 | Lunch | Lunch |
| 1300–1330 | Hypercapnia | Open |
| 1330–1400 | Open | Hypercapnia |
| 1400–1415 | Psychm | Open |
| 1415–1430 | Open | Psychm |
| 1430–1500 | Cold Test Prep. | Cold Test Prep. |
| 1500–1530 | Control (26.7° C) | Control (26.7° C) |
| 1530–1630 | Cold Test (10° C) | Cold Test (10° C) |
| 1630–1730 | Cleanup | Cleanup |
| 1730–1800 | Open | Open |
| 1800–1815 | Psychm | Open |
| 1815–1830 | Open | Psychm |
| 1830–1930 | Dinner | Dinner |
| 1930–2200 | Open | Open |
| 2200–2215 | Psychm | Open |
| 2215–2230 | Open | Psychm |
| 2230–0200 | Open | Sleep |
| 0200–0215 | Psychm | Sleep |
| 0215–0545 | Open | Sleep |

All data were statistically evaluated by analysis of variance assuming independency over days. The 5% level of probability was used to assess the significance of F ratios.

## III. Psychomotor Performance.

*Procedure:* A single task, given at regular intervals, was used in these studies to evaluate psychomotor performance as the trials progressed. The device used was the "Kugelmaschine" (Fig. 1). A description of the instrument and the theory of its operation and validity are given elsewhere.[31] Psychomotor performance data are

given in terms of the percentage change in performance from the first (control) day.

*Results:* Performance data on the psychomotor task (Kugelmaschine) are given in Fig. 2. SC subjects improved their performance in the task with successive trials through the first and second days. Thereafter, during the third and fourth days of the trial, performance scores became relatively stabilized at a level between 20 and 25% above beginning scores for the group. SD subjects, however, demonstrated a marked difference ($P<0.05$) in achievement on the task. After the loss of only one night of sleep, the SD group increased performance on the second day of the trial only by about 8 to 10%, whereas the SC group increased by 12 to 20% over the same period of time. During the third and fourth day of the trial, performance by the SD subjects was erratic and without trend. Statistical analysis of the data indicated a difference in performance

FIGURE 1. Kugelmaschine apparatus showing operator's control panel. The device records the number of correct responses during a standard test program.

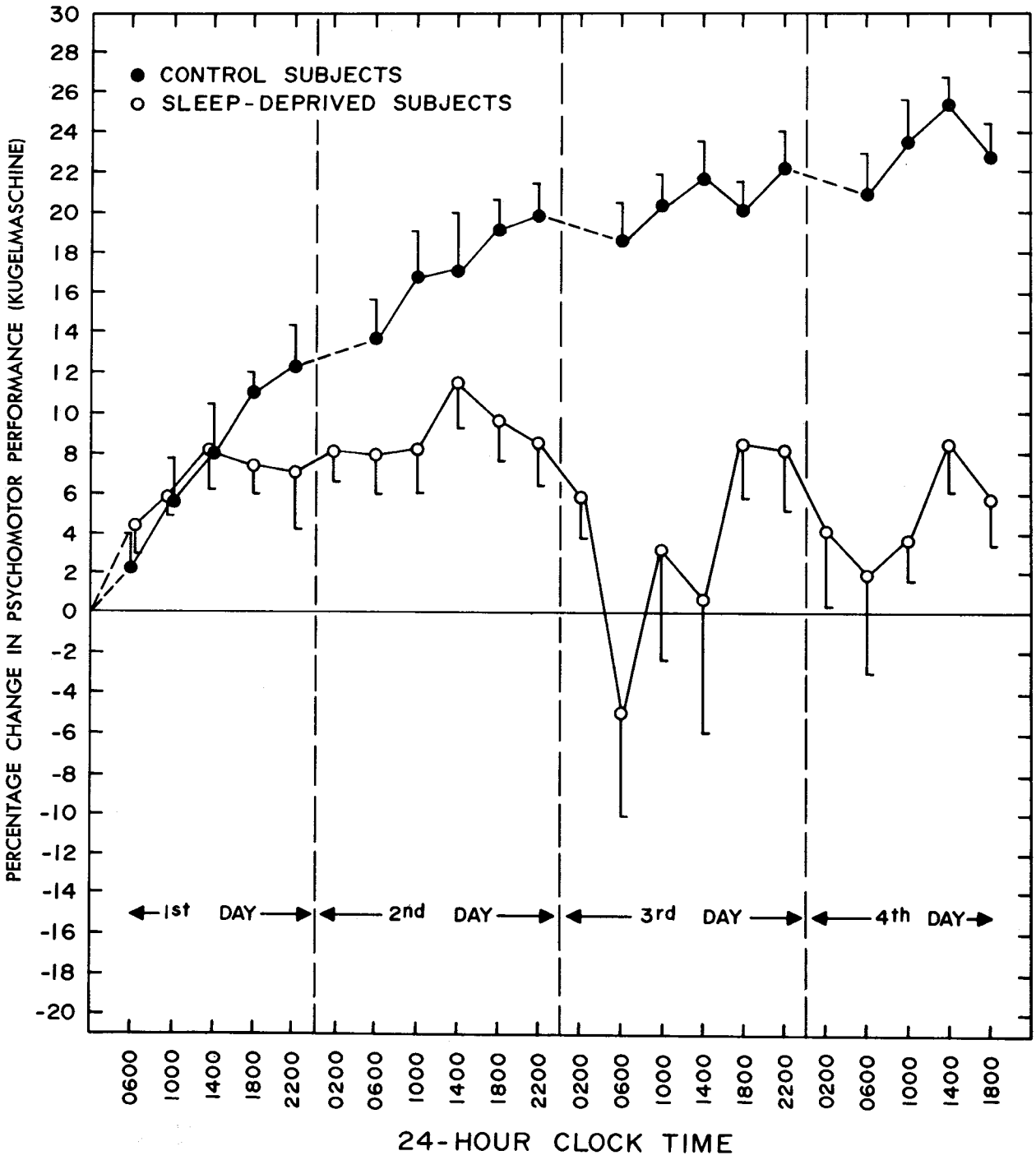


FIGURE 2. Psychomotor performance changes measured at 4-hour intervals for 84 hours. Measurements were not made at 0200 in the control subjects. Vertical lines represent the S.E.

($P<0.05$) between SC and SD on the second, third and fourth days but no significant difference on the first day.

*Comment:* The results of the present study demonstrate that loss of sleep unequivocally impaired performance on the test presented in these studies. Although this conclusion seems apparent from the data presented here, it should be recognized that the effects of sleep loss on psychomotor performance are not invariate. Among other factors which can affect psychomotor performance in the sleep-deprived state, the stimulating

effect on the task itself and structure of the testing situation have been emphasized.[20 32] The impairment in performance that occurs during sleep deprivation is viewed by some workers[33 34] as resulting from the increased incidence of short lapses in attention as the sleep-loss episode progresses. In the present experiments the results of the psychomotor task were used to provide a convenient reference point, i.e., to demonstrate that the lack of sleep was indeed affecting some aspect of the subject's performance.

## IV. Regulation of Body Temperature during Acute Cold Exposure.

*Procedure:* Cold exposure tests were preceded by a 30-minute period of stabilization in the environmental chamber (26.7° C.; 80° F.). Subjects wore only light cotton athletic shorts and were seated in a plastic-webbed lawn chair. $T_r$ was monitored with a calibrated thermistor probe (10 cm. insertion) and bridge circuit. A pneumograph and pressure transducer system was used to record respiratory frequency (f). The electrocardiogram was recorded to measure heart rate (HR). $T_r$, f, and HR were displayed continuously on a Grass Polygraph and readings of these parameters were made every five minutes. Skin temperatures ($T_s$) were recorded at five points; index finger, large toe, chest, lateral upper arm, and medial upper leg. Skin temperatures were measured with copper-constantan thermocouples at these points and recorded on a Leeds-Northrup Speedomax G multipoint recorder. $T_s$ readings were made every 5 minutes. Mean weighted skin temperatures ($T_{sav}$ were calculated using the following weighting factors: index finger, 0.06; large toe, 0.06; chest, 0.40; lateral upper arm, 0.18; medial upper leg, 0.30; $\dot{V}_{O_2}$ was measured over a 5-minute period at 15-minute intervals. Expired air collected was analyzed for oxygen with a Beckman F-3 oxygen analyzer. $\dot{V}_{O_2}$ data have been corrected to STPD and unit body surface area.

At the end of the 30-minute stabilization period ambient temperature was quickly lowered (5 min) to 10° C. (50° F.) and maintained at that temperature for 60 minutes. $T_r$, f, HR, and $T_s$ were recorded at 5-minute intervals; $\dot{V}_{O_2}$ was measured at 15-minute intervals.

Venous blood samples (15 ml.) were taken just before lowering the ambient temperature and at the end of the cold exposure. Blood was analyzed for total catecholamines,[35] and the red cell volume was estimated by micro-hematocrit.[36]

*Results:* Changes in $T_r$, $T_s$, or $\dot{V}_{O_2}$ during cold exposure are given in Fig. 3. The most prominent difference in the response to cold between SC and SD groups is in the pattern of the $T_r$ change. Although the SD group had a slightly lower initial (zero time) $T_r$ at the beginning of each cold exposure, internal temperature stabilized rapidly, albeit at somewhat lower levels as the trials progressed. In this group, $T_r$ stabilized around 37.3° C. during the first cold test; on the last day $T_r$ was maintained around 37.0°

TABLE 3.—Changes in total body heat (TBH) and caloric density (CD) during acute cold exposure

| Exposure No. | TBH kcal. | TBH kcal. | Δ TBH kcal. | $CD_i$ kcal./kg. | $CD_f$ kcal./kg. | Δ CD kcal./kg. |
|---|---|---|---|---|---|---|
| | Sleep-deprived (SD) | | | | | |
| 1 | 2191(94) | 2050(86) | 141(11) | 29.9(0.1) | 28.0(0.1) | 1.9(0.1) |
| 2 | 2206(90) | 2036(78) | 170(16) | 30.0(0.1) | 27.7(0.2) | 2.3(0.2) |
| 3 | 2211(92) | 2042(79) | 169(21) | 29.9(0.1) | 27.6(0.2) | 2.3(0.2) |
| 4 | 2198(95) | 2049(82) | 149(15) | 29.8(0.1) | 27.9(0.2) | 1.9(0.2) |
| | Control (SC) | | | | | |
| 1 | 2103(119) | 1967(105) | 136(16) | 30.0(0.1) | 28.1(0.1) | 1.9(0.1) |
| 2 | 2112(119) | 1957(107) | 155(17) | 30.1(0.1) | 27.9(0.1) | 2.2(0.2) |
| 3 | 2124(118) | 1969(109) | 156(15) | 30.2(0.1) | 27.9(0.1) | 2.2(0.2) |
| 4 | 2132(120) | 1989(110) | 142(14) | 30.2(0.1) | 28.2(0.1) | 2.0(0.1) |

Numbers in parentheses are standard errors. i=initial, f=final; Δ is the change over 1 hour.

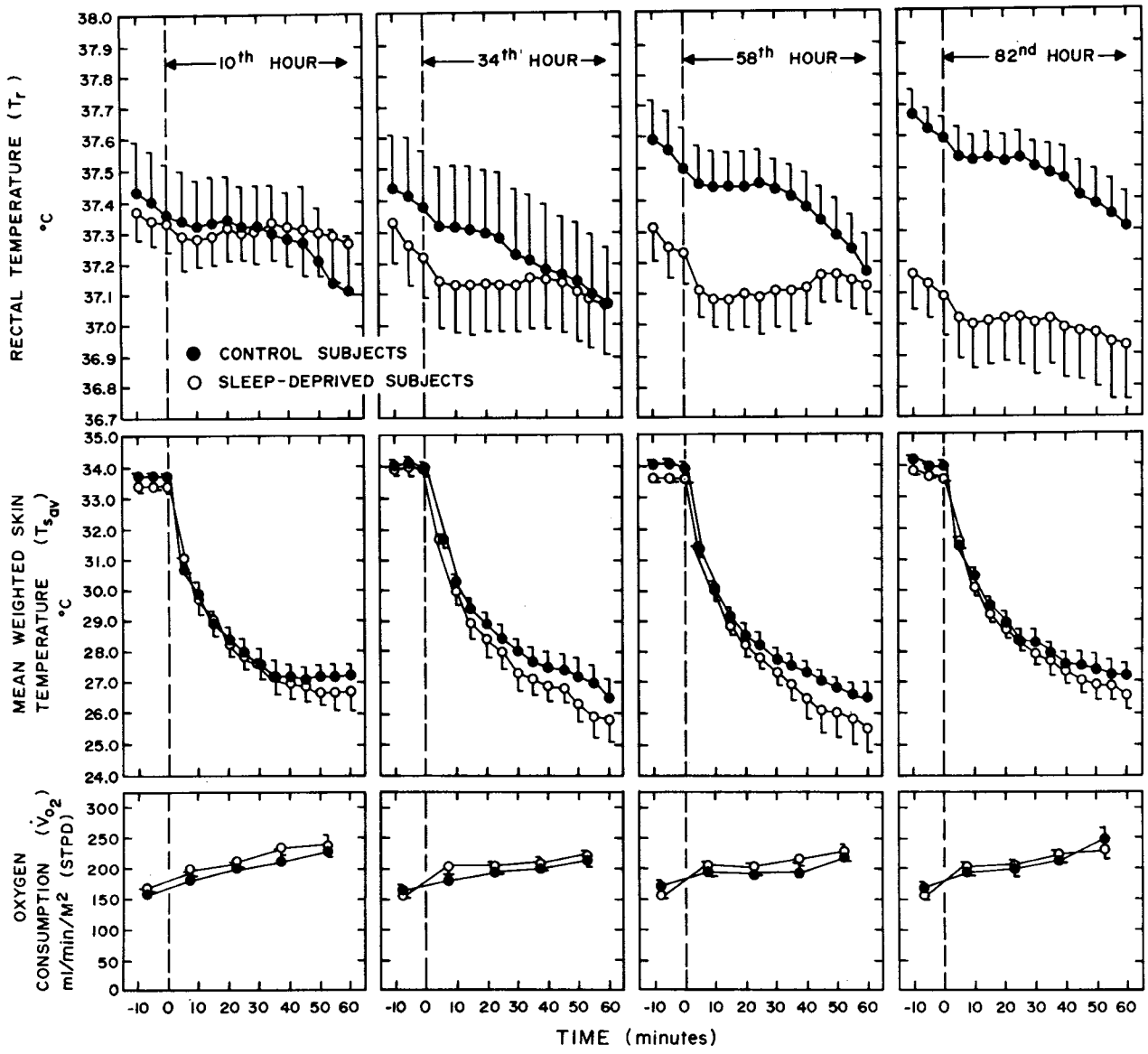


FIGURE 3. Rectal temperature, mean weighted skin temperature, and oxygen consumption during a standard cold exposure given once a day for 4 consecutive days. Hour designations in the top panel indicate the time without sleep for deprived subjects. Ambient temperature changed from 26.7° C. to 10.0° C. at zero time. Vertical lines represent the S.E.

C. SC subjects had an altogether different response to the acute cold test after the first day. Initial (zero time) $T_r$ in this group was appreciably higher at each succesive test. Also, $T_r$ in this group did not stabilize during exposure beyond the first day. This was probably a result of the higher initial temperatures; during the last cold exposure of the trial, final temperature in the SC group averaged 37.3° C., 0.2° C. higher than the average initial temperature for the SD group. Because of the tendency of the SC group to begin and end each cold exposure at a higher internal body temperature than the SD group, the difference in the response of $T_r$ in the two groups was statistically significant ($P<0.05$) during the cold exposure on the third and fourth days (58th and 82nd hour of the sleepless period). Measurements of $T_s$ revealed the rapid decrease in $T_{sav}$ (Fig. 3, middle panel) characteristic of abrupt exposure to a cold environment. The difference in response between SC and SD subjects was not significant. In both groups initial temperatures were equivalent (approximately 33° to 34° C.), as were final temperatures at the end of

the cold exposure. $\dot{V}_{O_2}$ measurements before and during the cold exposure indicated a significant increase during the cold in both groups, but no difference between groups. Initial values for $\dot{V}_{O_2}$ in both groups were approximately 150 ml./min./m.$^2$ $\dot{V}_{O_2}$ increased uniformly in both groups to a final value of around 250 ml./min./m.$^2$ (Fig. 3, lower panel). Neither the responses in $T_{sav}$ nor $\dot{V}_{O_2}$ adequately account for the difference detected between groups in internal body temperature during acute cold exposure.

Measurements of HR and f before and during the cold exposure showed that the response of these parameters to the testing situation was extremely variable (Fig. 4). In general HR decreased during the cold exposure, but this response appeared largely a function of the elevated initial values. In all tests except one, HR was above 80 beats/min. at zero time and decreased during the cold exposure to approximately 75 beats/min. In the last cold exposure of the trial (82nd hour) initial values for the SC groups were typical (80/min.), whereas SD subjects had a depressed initial rate relative to previous cold exposures. During this exposure the difference in

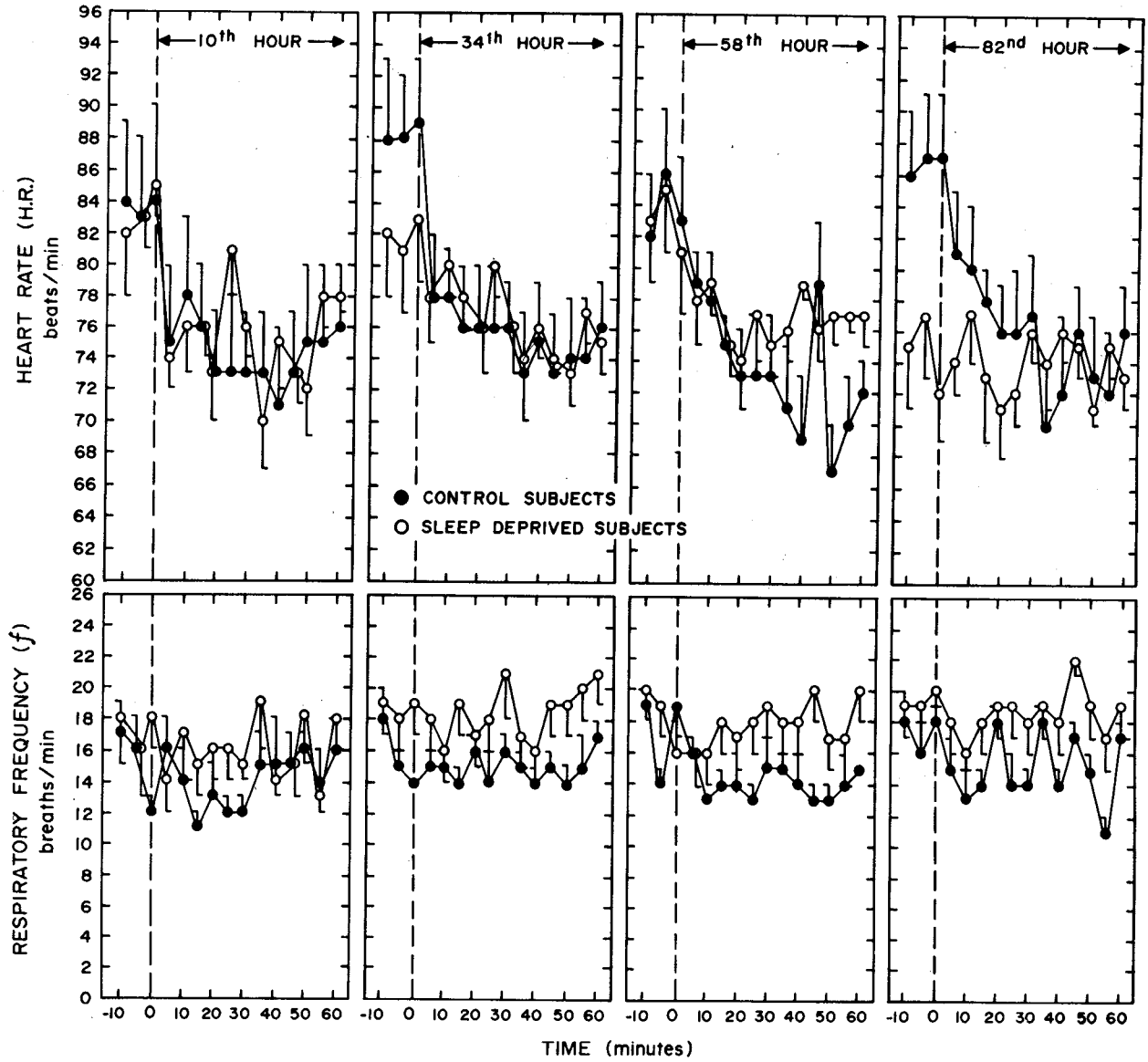


FIGURE 4. Heart rate and respiratory frequency during a standard cold exposure given once a day for 4 consecutive days. Hour designations in the upper panel indicate the time without sleep for deprived subjects. Ambient temperature changed from 26.7° C. to 10.0° C. at zero time. Vertical lines represent the S.E.

HR between groups was found to be statistically significant. Measurements of f also showed (Fig. 4, lower panel) a clear and significant difference between SC and SD groups. In general, SD subjects responded to the cold test with a higher f than did the SC group. Initial frequencies of approximately 16 to 18 breaths/min. were maintained by the SD subjects whereas the frequencies of SC subjects decrease from similar initial values to approximately 12 to 14 breaths/min.

Significant elevations in plasma catecholamine levels as a result of the cold exposure were found in both SC and SD groups to a similar degree (Fig. 5). Initial levels of approximately 1.6 $\mu$g./l. were increased to 2.0 $\mu$g./l. at the end of the 1-hour cold exposure. No significant differences between SC and SD groups were detected. Characteristic increases in hematocrit as a function of cold stress were also observed in both groups (Fig. 6), but with no significant differences between groups. Hematocrit in both groups increased 2 to 4%.

*Comment:* In contrast to the impaired psychomotor performance, the physiological response of the SD subject to acute cold exposure was adequate to maintain thermal equilibrium at the lowered environmental temperature (10° C). No essential differences between SD and SC subjects were noted in the response of mean weighted skin temperature and oxygen consumption during the cold exposure periods. This suggests that heat conserving mechanisms (vasoconstriction) and heat generating mechanisms (shivering) were not affected by the loss of sleep. However, despite the uniformity of response between groups in $\dot{V}_{O_2}$ and $T_{sav}$, the pattern of change in internal body temperature was significantly different between SD and SC subjects. The SC group began each cold exposure test with a progressively elevated initial $T_r$. Consequently, the disparity of the internal body temperature response became greater throughout the trial and most pronounced during the fourth cold exposure. To provide a more adequate comparison of the two groups with respect to thermal regulation, the total body heat (TBH, kcal.) and caloric density (CD, kcal./kg.) were computed for each of the subjects and the rate of change in CD (kcal./kg./-hour) compared for each cold exposure. These data are given in Table 3. No significant difference was detected between SC and SD groups or within days (cold exposures); the interaction between groups and days was also not significant. This anlaysis suggests that despite the higher thermal state of the SC group at the beginning of each cold exposure test, heat loss characteristics of the two groups were equivalent. This further suggests that the heat production and heat conserving mechanisms of the SD group during cold exposure were relatively unimpaired by the simple loss of sleep.

No explanation is apparent for the progressively higher thermal state of the SC group at the beginning of each successive cold exposure test. The activity of both groups immediately prior to the cold test preparation was the psychomotor test (the SC group approximately 15 minutes after the SD group). It may have been that the intense involvement with the psychomotor task exhibited by the SC group, particularly on the latter 2 days when SC scores approached near perfection (approximately 85 to 90% of maximum), was sufficient to affect the thermal state of the subjects. The increased muscular tension and activity displayed by the SC subjects in their desire to "beat the machine" may have been responsible for an increased heat production and the elevated initial internal body temperatures measured on the third and fourth days.

Experiences with HR changes during whole body cooling have been varied. Decreases in HR during cold exposure have been reported by Arnett and Watts[37] and by Budd and Warhaft,[38] in the latter study to the point of bradycardia. On the other hand, Wood et al.,[39] and Iampietro et al.,[40] observed an increased rate with whole body cooling. Reasons for the observed differences in response are not clear, but may be related, from study to study, to differences in position of the subject (seated, standing, supine), metabolic status (post-absorptive, post-prandial), or time of day. In the present study the HR of SC subjects always decreased during cold exposure. An equivalent response was measured in SD subjects except for the fourth cold test when no change from control was observed. In general, both groups maintained the same HR after 30 minutes of exposure (70 to 80 beats/-min.).

The higher respiratory rates of the SD subjects are not readily explained on a physiological basis. The higher rates of this group however,

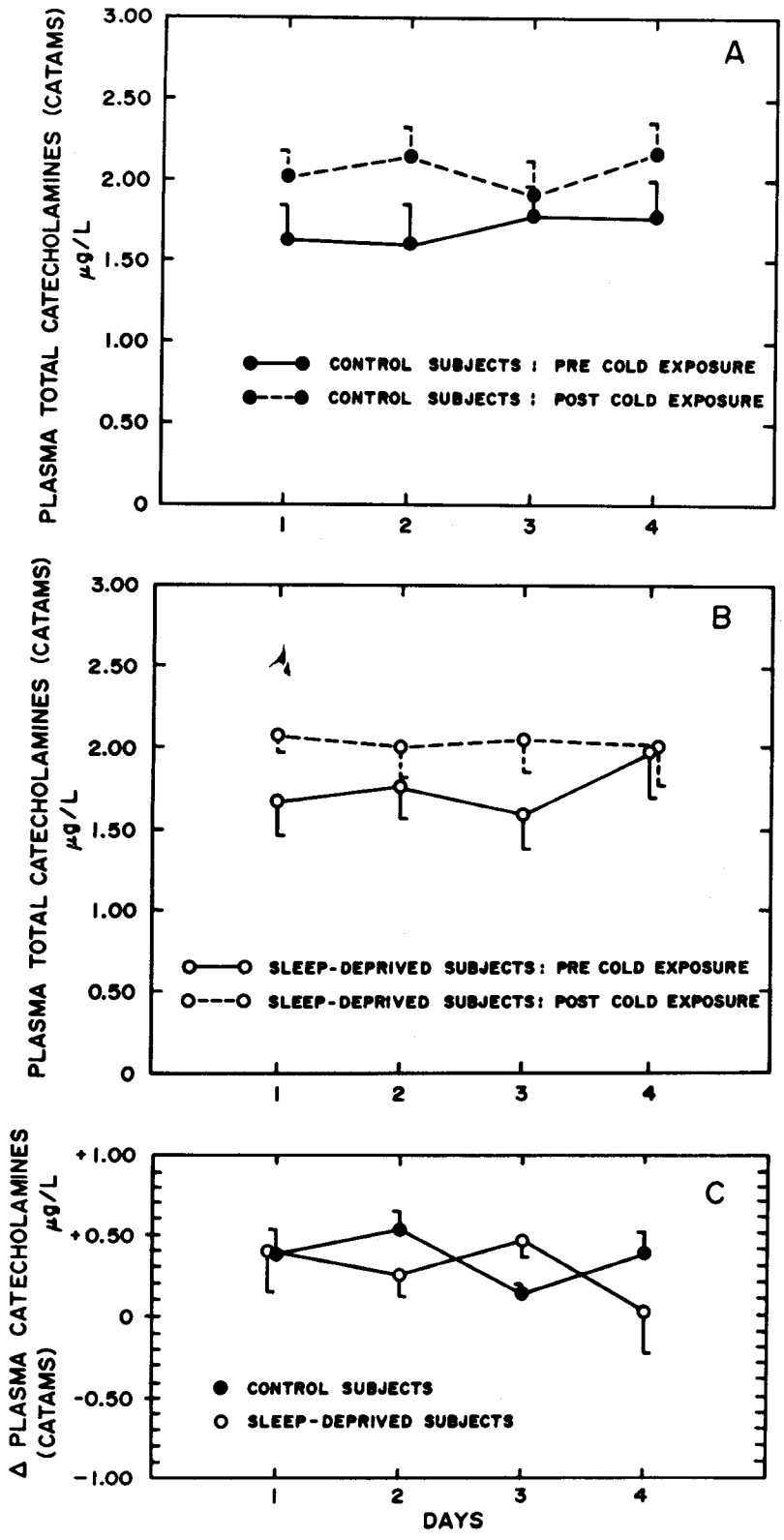


FIGURE 5. Plasma catecholamines and change in catecholamine level during four standardized cold tests conducted at daily intervals. Vertical lines represent the S.E.

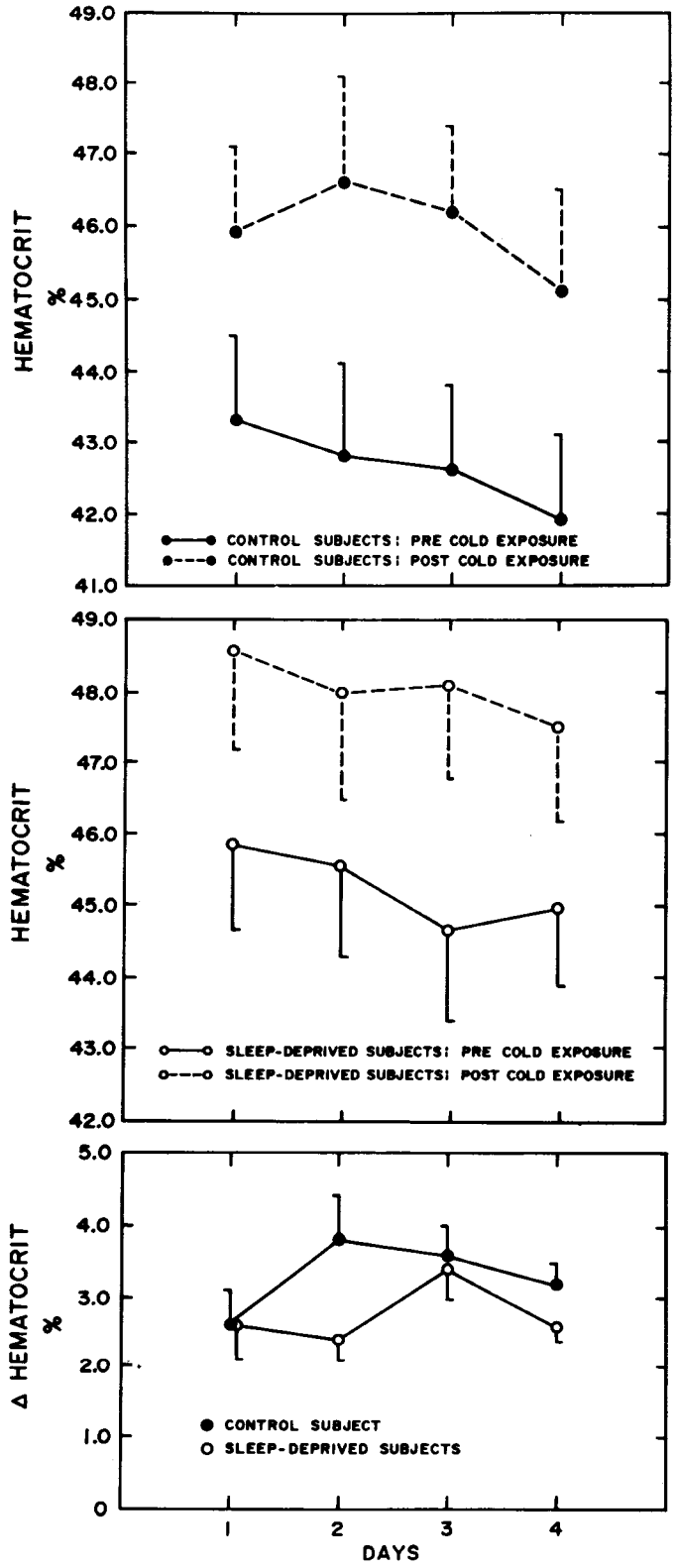


FIGURE 6. Hematocrit and change in hematocrit during four standardized cold tests conducted at daily intervals. Vertical lines represent the S.E.

may reflect the greater "effort" necessary to maintain "arousal" in the resting condition.[21]

Considering the total response to cold, it appears that continued loss of sleep, up to the point examined in these studies (84 hours), has little measurable effect on the ability to adjust to a cold stress. Unfortunately, the present data do not permit extrapolation to environments colder than 10° C. or exposure times longer than 1 hour. Evaluation of the more severe cold environments will be necessary before a generalized statement can be proposed.

## V. Other Physiological and Biochemical Responses.

### A. MORNING RESTING MEASUREMENTS

*Procedure:* Nude body weight (BW), rectal temperature ($T_r$), and oxygen consumption ($\dot{V}_{O_2}$) were measured each morning during the test and were made within 30 minutes of the awakening of the control subject. BW was taken to the nearest 5 gm. after the subjects had voided and defecated. $T_r$ was measured with a thermistor probe inserted 10 cm. into the rectum and read on a YSI Tele-Thermometer. $\dot{V}_{O_2}$ was measured with the subjects seated and resting in an environmental chamber (26.7° C.; 80° F.). The subjects were clad only in light cotton athletic shorts. Expired air was collected in a Collins spirometer for a 5-minute interval and the expired gas analyzed for oxygen with a Beckman F-3 oxygen analyzer. Values for oxygen uptake were corrected to STPD and are reported per unit body surface area.

*Results and Comment:* The data for $\dot{V}_{O_2}$ and $T_r$ are given in Figure 7. Both SC and SD groups had equivalent resting $\dot{V}_{O_2}$ on the first day (following a night of sleep by both groups) of approximately 140 ml./min./m.$^2$. Thereafter, $\dot{V}_{O_2}$ in SC subjects remained at the same level for the following 3 days, whereas, as anticipated, resting $\dot{V}_{O_2}$ for SD subjects increased slightly as a function of sustained activity throughout the night. In the SD group resting $\dot{V}_{O_2}$ increased to approximately 150 ml./min./m.$^2$ on both the second and third days, but fell to control (SC) levels of 140 ml./min./m.$^2$ on the fourth testing day. This may reflect a greater degree of relaxation during the testing sessions in the latter phase of the sleepless period. Despite the physiological rationale for the difference in resting $\dot{V}_{O_2}$ in SC and SD subjects, no statistically significant differences between groups were evident at the 5% level.

Resting morning $T_r$ was elevated in SD subjects after the first day (Fig. 7). The SC group maintained a uniform $T_r$ for this time of day throughout the 4-day test (36.7° to 36.8° C.). The higher morning $T_r$ in the SD group is probably related to the level of activity during sleepless nights, however, no explanation is apparent for the abrupt decrease on the third day. The differences between SC and SD morning temperatures were significant at the 5% level.

### B. URINARY EXCRETION PATTERNS

*Procedure:* Urine samples were taken every 4 hours over the course of the study. Total urine voided during each 4-hour period was measured and acidified with 1 ml. of 25% $H_2SO_4$. Urines were refrigerated during the collection periods. At the end of the collection interval an aliquot was taken and frozen (−20° C.) until analyzed. Total catecholamines in urine were measured fluorometrically.[35] Magnesium was measured by the automated method of Hill[41] and creatinine by a modified Pino procedure.[42] Values for catecholamine and magnesium excretion are expressed per unit excretion of creatinine.

*Results:* A significant increase in urine flow was observed in SD subjects as compared to their SC counterparts (Fig. 8). This difference may have been due, in part, to the increased intake of fluid by the SD group, particularly during the nighttime hours. Fluid intake, however, was not measured and the observation of increased drinking is a subjective one. Urine flow in SC subjects appears to follow a pattern according to the sleep-wake cycle. Trough values of about 0.5 ml./min. were recorded in this group and coincided with the sleeping hours. Peak values in the SC group reached 1.0 to 1.5 ml./min. No regular pattern of excretion was noted in the SD subjects who maintained levels of 1.5 to 2.0 ml./min. throughout the trial.

Creatinine excretion was variable in both groups and ranged between 1.0 and 1.5 mg./min. No significant differences in the excretion of this compound were detected. Magnesium excretion likewise fluctuated widely with no difference be-

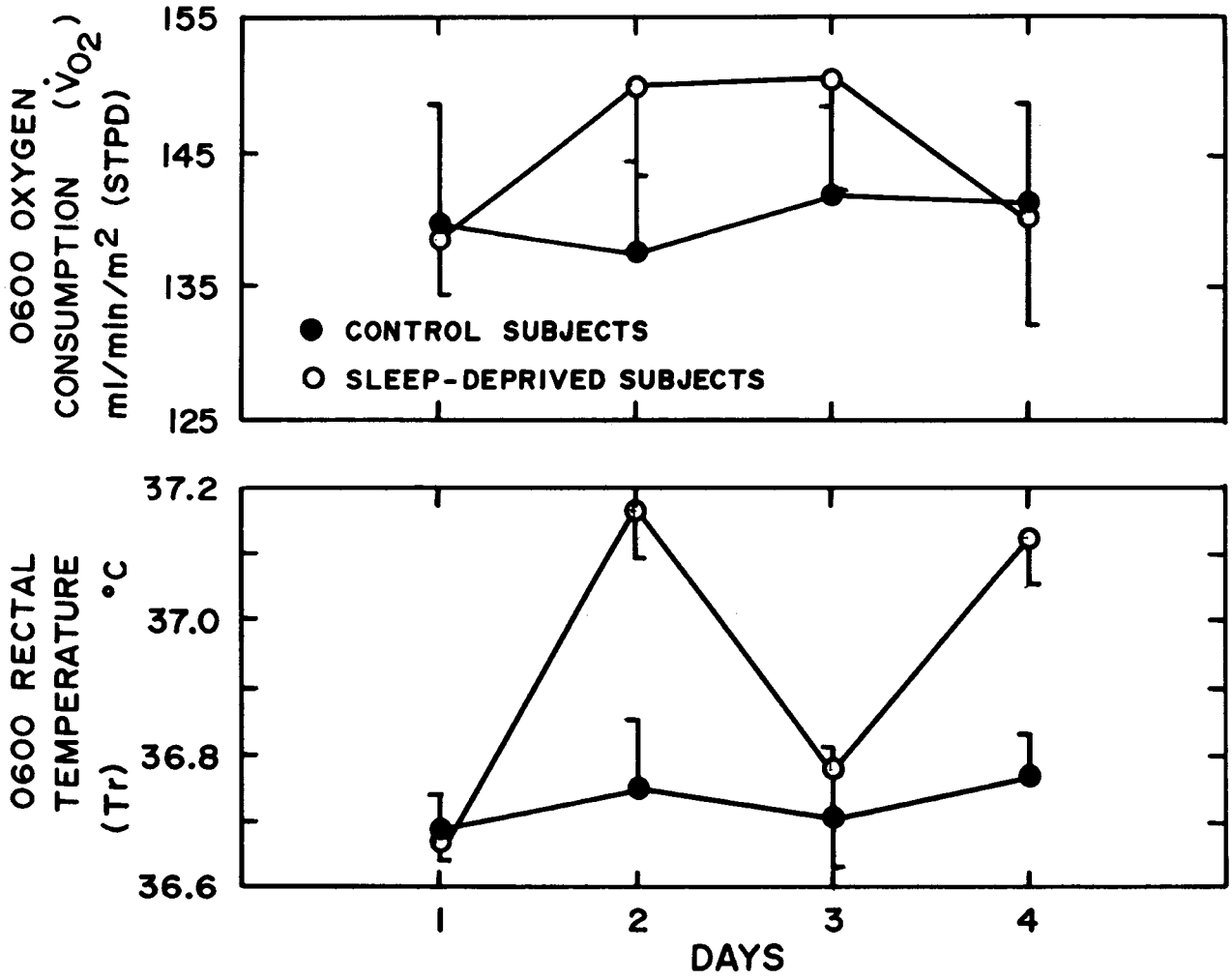


FIGURE 7. Resting oxygen consumption and rectal temperature measured at 0600. Values on day 1 followed a night of sleep by both groups; values for days 2, 3, and 4 represent 24, 48, and 72 hours without sleep for SD subjects. Vertical lines represent the S.E.

tween groups in the urinary excretion of this ion. Magnesium excretion varied in both groups between 3.50 and 6.75 meq./gm. creatinine with most values around 4.50 meq./gm. creatinine.

Measurements of the urinary excretion of the catecholamines revealed clear differences between SC and SD groups which reflected, primarily, the activity levels of the subjects (Fig. 8). The excretion pattern of catecholamines in the SC group was reproducible from day-to-day and reflected the activities associated with (1) the sleeping period 2200–0600, (2) the work period 0600–1000, (3) the hypoxia-hypercapnia testing period, 1000–1400, (4) the cold exposure period, 1400–1800, and (5) the evening post-test period, 1800–2200. Peak activity catecholamine excretion levels for SC subjects were consistently around 35 to 40 nanogm./mg. creatinine and trough (resting, sleeping) levels were on the order of 10 to 15 nanogm./mg. creatinine. The catecholamine excretion values for the SD group superimpose the SC values on the first day to the point of the SC sleep period. Thereafter, catecholamine excretion in the SD group follows the excretion levels of SC subjects during the testing periods 0600–2200, but maintains an intermediate level (approximately 30 nanogm./mg. creatinine) during the nighttime hours (2200–0600). Two points (third day, 1000–1400, 1400–1800) of the SD excretion pattern deviated from the general pattern for the group. These points reflect an unexplained but inordinately high excretion of catecholamines during those periods by a single SD subject. Beyond those periods the excretion levels of that subject were decreased to levels consistent with those of the group.

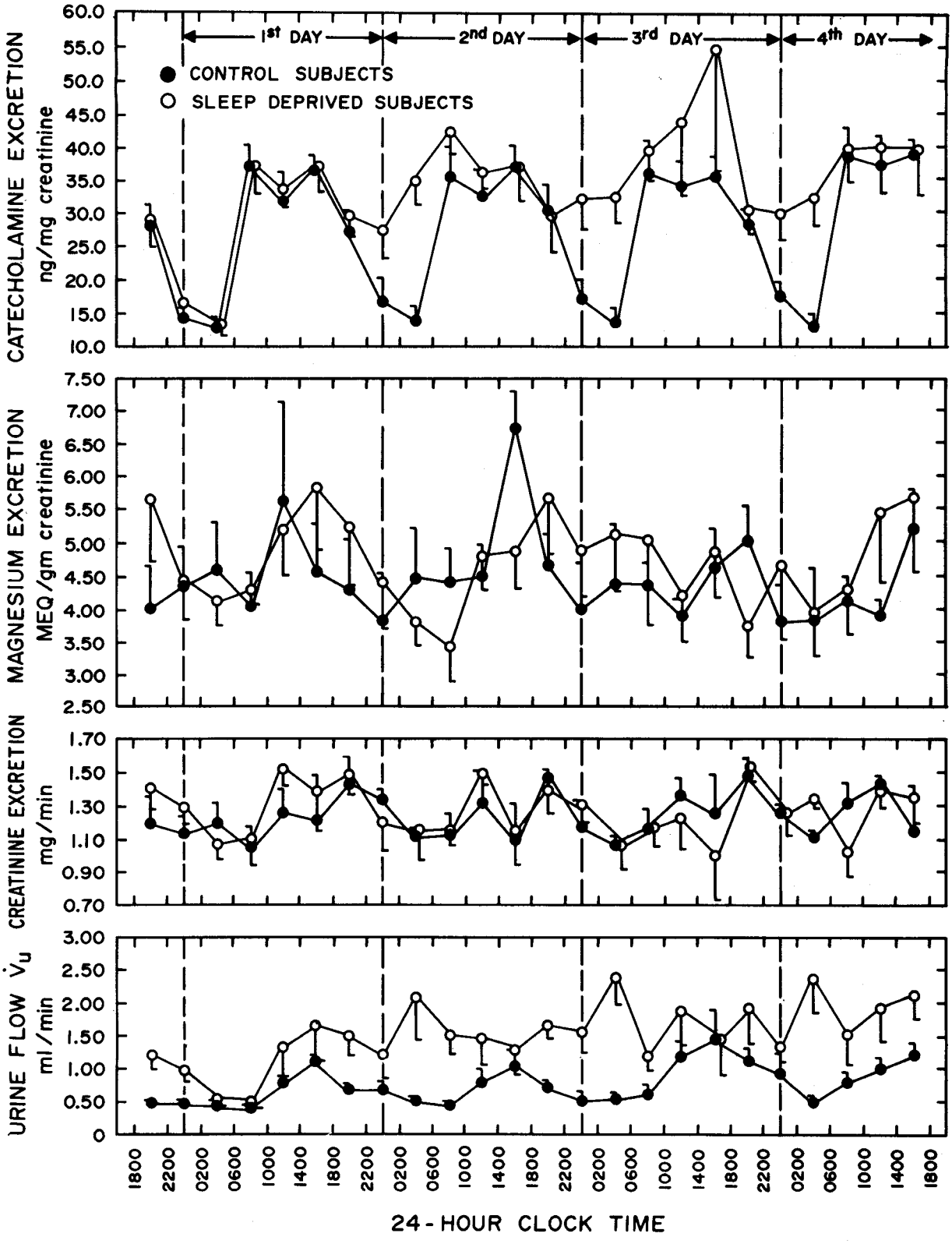


FIGURE 8. Patterns of urine flow and excretion of catecholamines, magnesium and creatinine. Values represent consecutive 4-hour urine samples. Vertical lines represent the S.E.

*Comment:* The results obtained on the excretion patterns of creatinine, magnesium and catecholamines further support the contention that it is difficult to distinguish the sleep-deprived individual solely on a physiological or biochemical basis. The present data do not confirm the findings of Luby et al.,[24] who reported an increase in the excretion of creatinine (gm./24 hrs.) in a single subject deprived of sleep for 220 hours. Rather, the present data indicate no difference between SD and SC subjects in terms of the excretion of creatinine and support the earlier observations of Kleitman[22] and of Tyler.[8] The examination of the excretion patterns of magnesium in our study was prompted by two reports,[43 44] which implicate magnesium in the genesis of sleep. According to those studies it was suggested that the inreased urinary excretion which occurs at night is associated with the onset of sleep. It was postulated in the present studies that if the magnesium excretion increases at night prior to sleep, and if magnesium is indeed associated with the onset of sleep, then excretion should be observed in SD subjects at a continuously high level. This idea was not supported by the present findings. Magnesium excretion, though variable, was not different between SD and SC subjects. The conclusion that magnesium excretion is unrelated to sleep is, however, not an appropriate one. Other studies from this laboratory have demonstrated that the excretion of magnesium is subject to a well-defined, 24-hour periodicity (peak excretion between 2200 and 0600), but only when diet is rigidly controlled and food intake is regulated.[45] This tends to support previous reports.[43 44] When diet is not controlled or regulated, the excretion of magnesium is erratic and the diurnal periodicity is masked. Additional studies further suggest that the excretion of magnesium is inversely related to the level of activity;[45] the periodicity in excretion seems, therefore, to be a function of the sleep-wake cycle. The failure in the present study to detect a difference between SD and SC groups (with obvious activity differences) may simply reside with the fact that diet was not controlled. This point deserves further study and clarification.

Differences in the excretion of catecholamines betwen groups were most well-defined during the hours 2200 and 0600. During the daytime hours when activity levels were equivalent, the excretion levels of the catecholamines were similar. These data suggest that the difference in the catecholamine excretion between SD and SC subjects is primarily a function of level of activity and not the loss of sleep per se. Elmadjian et al.,[46] observed significant increases in the excretion of both adrenaline and noradrenaline during daytime hours as compared to nighttime (sleeping) levels. Those findings are readily confirmed in the present study. The excretion of catecholamines by SC subjects follows a regular pattern with peaks occurring during the day and troughs at night. This pattern closely corresponds to the major activities involved during the 24-hour period: 0600–1000, treadmill walking; 1000–1400, hypoxia, hypercapnia testing; 1400–1800, cold stress test (shivering); 1800–2200, light recreation; 2200–0200, sleep; 0200–0600, sleep. With the exception of the elevated excretion by SD subjects between the hours 2200–0600, data for this group followed closely the pattern established by the SC group. The present data are not in accord with those presented by Hasselman et al.,[47] on the interaction of work (activity) and sleep deprivation. In those studies elevations in catecholamine excretion during a period of activity were greater when the work period followed a sleepless night than when work followed an adequate night of sleep. In view of the uniformity of the response we have obtained in catecholamine excretion during work following three sleepless nights, the data of Hasselman are difficult to explain. Perhaps the greater response in catecholamine excretion in his studies was the result of the prolonged period (8 hours) over which the work was performed. A quantitative relationship between rate of excretion of the catecholamines and the level of work (activity) with and without adequate sleep remains to be established.

## VI. General Conclusions.

Considering the results of this study together with those of other reports employing direct measures of stress[11 26 48] lack of sleep in itself does not elicit the expected increases in adrenocortical and sympathicoadrenomedullary activity characteristic of physiological stress. Nor does the condition of sleeplessness affect the usual physiological responses to a stressful environment (cold). Yet, the behavioral deficits and psychomotor per-

formance decrements readily and consistently observed during prolonged sleep loss clearly demonstrate the pronounced effects of the experience.[15] It seems apparent that those integrative functions requiring a high degree of cerebral input are most readily and most seriously affected by sleep loss, whereas biochemical and physiological functions operating under a lesser degree of cerebral control are more resistant to the effects of sleeplessness. It seems likely at this time that further progress in clarifying the mechanisms responsible for impairment due to sleep loss must come from neurophysiological and neurobiochemical studies of the central nervous system.

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