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RESEARCH REPORT

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During the period of the contract, 17½ months, the following studies were performed and the results described.

(1) Effect of a prolonged 3 hour sleep-wake cycle (ultradian) on Sleep Stages, Plasma Cortisol and Growth (GH) Secretion.

Seven subjects underwent the following 3½ week (24 day) scheduled sleep-wake cycle changes, while living on a hospital (Clinical Research Center) unit. Following 1 week of baseline nocturnal sleep polygraphic recording (11 P.M. to 7 A.M.), the subjects assumed a schedule for 10 days of 2 hours waking followed by 1 hour sleep for each 24 hour period. This was then followed by 1 recovery week of nocturnal sleep (11 P.M. to 7 A.M.). Rectal temperature and urine samples were obtained every 3 hours for the entire 24 day period except for the nocturnal sleep periods. On days 5-6 and 13-14 an intravenous catheter was used to obtain plasma samples every 20 minutes for a 24 hour period. Cortisol was determined by the competitive protein binding method and human growth hormone by the radio-immunoassay technique.

When average sleep time was obtained for 6 subjects, a partial ultradian sleep-wake cycle was established. However a prominent superimposed circadian sleep-wake cycle persisted throughout the entire 10 day experimental period. During this period, total sleep time was consistently reduced by approximately one third compared to baseline. Most sleep was obtained during the 4 hours of 3 A.M. -4 A.M., 6 A.M. -7 A.M., 9 A.M. -10 A.M. and noon to 1 P.M. Therefore, a phase shift of peak sleep time of approximately 5 hours (from approximately 3 A.M. to 8 A.M.) was established during the first 3 days and then maintained throughout the experimental period. The amount of time utilized for sleep was dramatically reduced from approximately 90% at 9 to 10 A.M. to approximately 25% at 9 to 10 P.M. Therefore in spite of significant chronic sleep deprivation, the subjects were generally less able to utilize the 3 hourly periods between 6 P.M. to 1 A.M., consistently sleeping less than one third of each hour. The 24 hour distribution of REM sleep closely paralleled that of total sleep with the maximum occurrence between 3 A.M. and 1 P.M., and virtually no REM sleep present between 9 P.M. and 1 A.M. However, stage 3-4 sleep was more evenly distributed throughout the 24 hour period with a slight tendency for circadian periodicity.

Analysis of the pattern of cortisol secretory activity for both baseline and ultradian 24 hour periods revealed no significant differences in average 24 hour cortisol output, number of secretory episodes and total secretory time. However, in the ultradian experimental condition the secretory episodes appeared to be entrained to the 3 hour sleep-wake cycle. In this 3 hour cycle cortisol output and secretory time were maximal for the first hour after awakening, was less for the second hour of awakening and was minimal for the third hour, i.e., the hour of the next available sleep period. Despite the establishment of this 3 hour pattern, a clear circadian rhythm was

also present with maximal secretory activity occurring between 4 A.M. and 4 P.M. coinciding with that of the baseline rhythm and with the time of maximal sleep. However the usual maximal secretory phase seen in baseline, between 4 A.M. and 8 A.M., was not prominent on the ultradian 24 hour curves.

Analysis of Human Growth Hormone in 5 subjects during the ultradian period revealed that GH was released in 19 of 28 periods of sleep. There were an additional 17 episodes of hormonal release not associated with sleep. Several of these were clearly associated with venipuncture or other stressful events. The temporal organization of the 24 hour GH release pattern was altered by the establishment of a 3 hour sleep-wake cycle although the previously demonstrated relationship of GH release to sleep persisted under these experimental conditions.

As part of this study several subjects were studied during the course of the experimental period with special psychological performance tests. This aspect of our research efforts was performed by Dr. Louis Costa and Dr. Steven Mattis.

Two lines of investigation have been pursued with the subjects run on sleep cycle alteration experiments. Dr. Louis Costa has initiated a study of choice reaction time performance and Dr. Steven Mattis has developed an apparatus to study vigilance behavior in the manner reported by Wilkinson. Both experiments were carried out on three subjects during the course of the larger study involving electrophysiological and biochemical measurement.

To date three subjects have completed the choice reaction time experiment originally projected. This study involved 320 trials of 8 choice reaction time per hour, 4 hours per day, during baseline, altered sleep cycle and recovery periods. Half the trials required the subject to match a number appearing at the center of a circle by touching the same number at the periphery. Half the trials involved adding 3 to the center number and then touching the sum of the addition at the periphery. Subjects were run at 7:30 A.M., 11:30 A.M., 3:30 P.M. and 7:30 P.M. during baseline and recovery conditions and 7:30 A.M., 1:30 P.M., 7:30 P.M. and 1:30 A.M. during alteration of sleep cycle.

Response accuracy remained high (.005 to .02 errors) throughout the entire experiment so results were expressed in terms of reaction time (RT) alone. RT latencies for each trial were recorded on punch tape and tabulated and analyzed by computer. Median RT's for blocks of 40 trials were averaged to produce means for each condition on each hour. For both the matching and addition conditions grand mean RTs for the baseline period were determined; all RT results were expressed as a percentage of this baseline value. Grand mean RT values ranged from 720 to 1300 msec.

During the baseline period itself consistant variation in RT occurred as a consequence of hour of testing with latencies being one hundred msec. or more longer at 7:30 A.M. than 11:30 A.M. in all subjects.

Under normal conditions (a repeated daily trail without alteration of sleep cycle) RT's on this apparatus show a slow consisent decrease reflective of learning. During the altered sleep cycle aspect of the present experiment however, instead of decreasing, RT's increased to as much as 121% of RT during baseline conditions. RT during the later part of the sleep alteration period tended to be longer than RT early in sleep alteration. Recovery of RT to baseline levels was rapid, by the second day of the recovery period RT latencies were at baseline levels or lower and continued to improve. The observation that 7:30 A.M. RTs were longer in latency than the next daily period was true through sleep alteration and recovery for all subjects. No interaction of task (matching or adding) with either time of day or period in the experiment was observed.

These preliminary results with three subjects are felt to demonstrate the sensitivity of the RT task to alteration of sleep cycle as well as a consistent trend, for the subjects tested, to longer latencies in RT early in the morning. This held true irrespective of the segment of the experiment from which the data were produced.

Further observations on experimental and control (non-altered sleep cycle) subjects are needed to enable the investigators to generalize regarding the extent and severity of behavioral disruption and the speed of recovery of function as well as the ultradian aspects of RT performance. Changes in RT latency shortly after awakening perhaps associated with concurrent monitoring of EEG and recording of average event related EEG potentials could be pursued to provide a more molecular picture of physiological and behavioral events during the waking process.

The auditory vigilance experiment is derived from R.T. Wilkinson's studies which indicated that the most sensitive measure to date, of the effects of sleep deprivation on cognition can be obtained by observing subjects engaged in a continuous performance essentially uninteresting vigilance task. In our study Ss are presented with a 1000 Hz, 60 d.b. tone every 2 seconds for one hour. The tones are embedded in white noise. Forty stimuli randomly distributed throughout each hour are of 600 msec. duration. The remaining 1760 stimuli are of 800 msec. duration. The subject's task is to detect the shorter stimulus, pressing a recognition button as quickly as possible. Reaction time, and the number of hits and false alarms (incorrect response to long duration stimuli) are recorded. The system for stimuli delivery and automated response recorded was constructed to our specifications by BRS Foringer, Inc., Beltsville, Md. Dr. Wilkinson who visited our laboratory felt that although we used different delivery systems, the resultant discriminability of our stimuli were essentially similar to his own. This judgment, he felt, was supported by the congruence with his data of the hit and false alarm rates we obtain.

During 2 days of both the baseline and recovery periods, Ss were tested 9:30 A.M., 1:30 P.M., 5:30 P.M. and 9:30 P.M. During the altered sleep cycle phase testing was conducted at 10:30 A.M., 4:30 P.M., 10:30 P.M., and 4:30 A.M. the following morning. The major statistical analysis entailed converting the hit and false alarms rate to a measure of the efficiency of information processing, independent of motivational factors (d') developed by Swets et al. (Swets, J.A. (ed) Signal detection and recognition New York: Wiley, 1964). Wilkinson found a significant decrement in d' in Ss who incurred only 3 hours of sleep deprivation.

Observations: During the baseline period, the range of percent hits (45% to 70%) false alarms (.02% to .03%) and d' (2.00 to 2.65) were well within the limits reported to be maximally effective in gauging effects of sleep deprivation. In all subjects information processing as measured by d' was poorest at 9:30 A.M. and maximal at 9:30 P.M. with d' at 1:30 falling midway between. All Ss demonstrated a marked decrement in d' at 5:30 P.M. which fell below the 1:30 P.M. efficiency level and approached the 9:30 A.M. low d'. In reviewing these data Dr. Wilkinson commented that he found a similar pattern when sampling vigilance at 8:00 A.M., 12:00 P.M., 4:00 P.M., and 8:00 P.M.

During the altered sleep cycle phase, d' fell well below the range obtained during baseline, varying widely (.05 to 2.00) with no apparent trend. In the recovery period, efficiency did not rapidly return to baseline levels. On the first recovery day, after a full 8 hours sleep, absolute levels of d' were below baseline levels although the pattern of d' during the 4 time periods was similar to that obtained at baseline. On the second testing day, the 3rd recovery day, d' approached baseline levels.

The data suggest that some significant phenomena were being observed that warrant further study. Dr. Wilkinson's studies and ours, sampling behavior at different 4 one hour periods, suggests that this auditory vigilance task is sensitive to (1) a circadian rhythm in the efficiency of information processing such that efficiency is poorest in the morning and maximal in the mid evening, and (2) is capable of measuring a possible ultradian rhythmicity in d'. If one can demonstrate stable ultradian variation embedded in circadian rhythm of cognitive efficiency, then future research must take into account the high probability of an interaction effect between duration of sleep deprivation and time of day in which performance is tested.

The sluggishness of return to baseline values during the recovery periods suggests more frequent observation on successive days is necessary, the data to be correlated with the differing recovery rates of other parameters explored in the parent study.

(2) Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects.

The following is a brief summary of the results of this study. Since the full report was recently published (July, 1971 - J. Clin. Endocr., 33:14, 1971 - Ref. # 4   ). Copies are enclosed as part of this report.

Plasma cortisol was measured for seven 24-hour periods using the frequent sampling technique (every 20 minutes) in 6 normal acclimated subjects. A defined sleep-wake schedule was established over 3-5 consecutive nights with polygraphic definition of their sleep patterns. A mean of 9 secretory episodes (range 7-13) occurred over the 24 hour sampling time, the subjects spending an average of 24% of the time in active secretion. It was estimated that on the average, 16 mg. of cortisol was secreted over the 24 hours with a mean of 66 min. half-life of cortisol decay. Although great variability was found in both the amount of cortisol secreted and the time spent in secretory activity per hour, the secretory rate was quite constant at approximately .05 mg/min. A temporal pattern of episodic secretion was recognized, and the 24 hour sleep-wake cycle could be divided into 4 unequal temporal phases: Phase 1 - a 6 hour period of "minimal secretory activity" (4 hours before and 2 hours after lights out); Phase 2 - a 3 hour period called "preliminary nocturnal secretory episode" (3rd to 5th hour of sleep); Phase 3 - A 4 hour period, the "main secretory phase" (6,7,8 hours of sleep and 1st hour after awakening); and Phase 4 - the 11th hour of "intermittent waking secretory activity." No evidence for a "basal level" or "steady state" of cortisol concentration was found. Changes in cortisol output during the 24 hour day appear to be due to differences in frequency and duration of secretory episodes and not to major changes in secretory rate.

(3) Telemetry recording of 72 continuous hours of electroencephalography, electromyography and electro-oculography analyzing for the presence of ultradian rhythmicity.

This aspect of our laboratories research efforts were performed by Dr. Daniel Kripke.

Techniques were developed for continuous EEG eye movement and muscle recording on subjects ambulating about a clinical research ward and sleeping in the special research laboratory. The biosentry SM-FM telemetry system was fixed to the vertex of the head with collodian, and electrodes were applied using NASA Apollo electrode jelly, double adhesive discs and a collodian overseal. This technique provided excellent continuous recordings of physiologic data on both polygraphic paper and FM analog tape. This data was then reduced using an analog filter system, integration, and a manual write-out. Reliable measures of EEG amplitude for each 5 minute epoch for delta, theta and alpha frequency bands were obtained, as well as measures of eye movements, muscle tone and gross body activity. Although data analysis is not complete, variance spectrum analysis of continuous and complete 72 hour data from one subject indicated a clear about 90 minute ultradian rhythm during sleep and suggestive similar ultradian rhythms during unrestricted waking activity, including ambulation. These results must be confirmed with further analyses of data of the four remaining subjects. An interesting incidental finding of the polygraphic EEG monitoring was that two normal subjects had clear sleep episodes during the day which

Average time from sleep onset, defined as beginning of first epoch of Stage 2, to earliest sample showing HGH increase was 14 minutes (2.5 - 23). There was no increase in HGH during several extended periods of Stage 1 preceding sleep onset (Stage 2). When sleep stages were scored in 30 second epochs, no consistent relationship between Stage 3 and HGH rise was found. When 10 second epochs were considered, Stage 3 occurred from simultaneously with initial HGH elevation to 15 minutes before, longer latencies to Stage 3 being associated with longer time to initial HGH elevation. Scoring records in 10 second epochs resulted in little difference in percentages of sleep stage from those seen using 30 second epochs, with only a 1 - 2% increase in Stages 3 and 4 demonstrated at the expense of Stage 2.

These data indicate that Stage 1 is apparently not sufficient for sleep-related HGH release but that this release occurs more rapidly (14 minutes) after sleep onset (Stage 2) than could be determined in previous studies using 20 - 30 minute sampling intervals. Since average time was 14 minutes, it would appear that 4 minute sampling was adequate to demonstrate this temporal relationship. Stage 3 sleep occurred prior to initial HGH elevation only with 10 second epoch scoring, indicating that if slow electrocortical activity must precede initiation of HGH release from the pituitary, it need be only of brief duration or that the 2 might occur simultaneously in the first sleep cycle.

(5) Dehydroisoandrosterone is secreted episodically and synchronously with cortisol by normal man.

The following is a brief summary of results of this study, since the full report was published during the period of this contract (July, 1971 - J. Clin. Endocr. & Metab., 87:33, 1971) and copies are enclosed as part of this report.

In 4 studies in a normal man it was demonstrated that dehydroiso-androsterone (DHA) was secreted episodically and synchronously with cortisol. The studies were done at 20 minute intervals in the early morning (0340-0720 hours) and in the late afternoon (1540-1920 hours). A double isotope derivative method was developed for measurement of the low concentrations of DHA in plasma. DHA never reached zero concentration in plasma, whereas cortisol did. This is explained by the contribution to DHA by hydrolysis of the relatively abundant circulating DHA sulfate. Because of the low plasma concentration a high degree of biological activity can be implied for DHA, the function of which is at present unknown.

(6) Twenty-four hour pattern of luteinizing hormone (LH) secretion in normal men with sleep stage recording.

This study was carried out in our laboratories in collaboration with Drs. R. Boyar, M. Perlow, L. Hellman, and S. Kapen, and has been recently submitted for publication. The following is a brief summary of the results. When the manuscript is accepted for publication, the paper will be sent as part of this report.

Plasma luteinizing hormone (LH) was measured by radioimmunoassay every 20 minutes for 24-26 hours in 5 normal adult men. On the night of the 24-26 hour blood study sleep EEG was monitored while the subjects slept in a sound and light proofed room. All 5 subjects showed major LH secretory episodes characterized by rapid rises and slower declines. The initiation and cessation of these secretory episodes occurred within narrow, well defined LH concentration ranges. We defined these low and high ranges respectively as "low and high set-point ranges" and regard these findings as evidence that LH secretion is in part controlled by negative feedback. LH half-life calculated from the semi-log plot of the 24 hour secretory patterns gave estimates reasonably close to those determined by the measurement of the disappearance of labelled LH. The marked variability in plasma LH concentration throughout the day and night demonstrates the need to interpret with caution isolated LH determinations. In these 5 adult men we could not identify a 24 hour LH rhythm or a relationship between the plasma LH concentration and the sleep-wake cycle.

(7) The following 3 studies are primarily clinical in nature, but the research efforts were supported in part by the NASA contract funds and are therefore acknowledged.

The first was published (August 1970, J. Clin. Endocrin. & Metab., 227:31, 1970) and since copies are enclosed as part of this report, a brief summary is given here.

Effect of o,p'-DDD on Cortisol Secretory Pattern in Cushing's Syndrome.

The pattern of cortisol secretion was studied in a patient with Cushing's syndrome before and during treatment with o,p'-DDD. Plasma samples were obtained every 20 minutes throughout the 24 hour day and analyzed for cortisol by competitive protein binding. It was found that the numbers of cortisol secretory episodes were roughly comparable in the treated and untreated state despite a 60 day interval between the studies. Under the influence of the drug the adrenals were producing cortisol almost constantly during the 24 hour day. This was proved for a 3 hour period in the early afternoon after a tracer amount of cortisol-4-^{14}C was injected. The specific activity of the plasma cortisol diminished progressively at different rates even thouth the plasma cortisol concentration rose and fell during this time. It is concluded that the system: central nervous system-corticosteroid releasing factor - ACTH, was intact, hyperfunctioning and similarly programmed in both the treated and untreated stages of the disease. DDD damages the adrenals' capacity for cortisol production although at this stage of treatment they were still capable of sensible production of cortisol. Treatment with the drug converted the cortisol secretory pattern from a well-defined series of peaks and valleys to an almost level pattern fluctuating about the lowest plasma concentration measured in the untreated state.

The second has not been published as yet, but was presented to the First International Meeting of the Association for the Psychophysiological Study of Sleep, 1971, and will be published as an abstract (Psychophysiology, 1971)

Seventy Two Hour Polygraphic Recording and Twenty Four Hour Plasma Cortisol Measurement in the Differential Diagnosis of Sleep Disorders.

New techniques of 24 hour polygraphic recordings have added to our understanding of narcolepsy. We have applied these techniques and concepts to a group of six patients (ages 20 - 44) who presented with the differential diagnosis of transient sleep episodes during the day.

The patients discontinued all medication for at least one month prior to their admission to the Sleep Unit on the Clinical Research Center at Montefiore Hospital. All patients had 72 - 74 hours of continuous EEG, submental EMG, and electro-oculogram recordings.

Results indicate that three patients had narcolepsy of the "sleep onset REM" type. All three had one or more of the symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis. Thirty-one of the 57 daytime sleep episodes of these patients contained REM periods; 14 of these had sleep onset REM periods as did one nocturnal sleep episode. The remaining 17 daytime REM periods, and 6 of the 11 nocturnal sleep onset followed 1 - 10 minutes of Stage 1 sleep. Of the remaining 3 patients, one had a seizure disorder. His EEG showed a marked increase in seizure activity with sleep. The second had a pattern consistent with recovery of sleep deprivation, and the third showed no evidence of an abnormal sleep pattern.

Previous data indicates that during the second half of normal nocturnal sleep there is maximal elevation of both the amount of REM sleep and the amount of episodic cortisol secretion. Blood samples were obtained every 20 minutes via intravenous catheter for 24 - 26 hours in an attempt to determine if daytime REM periods were associated with cortisol elevations. All six patients showed a normal secretory pattern. There was no clear relationship of the episodic plasma cortisol elevations to REM periods.

Extended polygraphic recordings were found to be useful in the differential diagnosis of narcolepsy and hypersomnia.

The third study of this group has been completed and submitted for publication. When the manuscript has been accepted, the paper will be sent as part of this report.

The Effect of L-DOPA on release of GH in Normal Man.

Oral doses of L-DOPA (0.5 gm.) caused release of human growth hormone (HGH) in 9 of 15 normal male volunteers. HGH release was sustained for up to 60 minutes with the first significantly elevated concentration appearing 40 to 90 minutes after L-DOPA administration. Four subjects who released

HGH prior to L-DOPA administration did not release HGH at this time.
Two subjects did not release HGH during the study period. A group
of 9 control subjects did not release HGH to either oral placebo
(5 subjects) or to the experimental procedure when no capsule was given
(4 subjects). There was no significant alteration in the level of
luteinizing hormone (LH) and the follicle stimulating hormone (FSH) in
response to L-DOPA administration in 4 HGH responders. Confirmation
of the previously reported pulsatile release of LH was obtained. Pul-
satile release of FSH was demonstrated in normal men.

(8) Effects of Vestibular Stimulation during sleep in young adults.

This study has recently begun in our laboratories, in collaboration
with Dr. Edward S. Tauber. As outlined in our progress report (September
15th, 1971), we are continuing to study the Vestibular response of normal
young adults during nocturnal sleep period.

This study was carried out to determine whether vestibular stimula-
tion could elicit nystagmus during different stages of sleep similar to
that found in the alert wakeful state. Although earlier studies indica-
ted that the nystagmic response was not present during drowsiness and
sleep, Reding and Fernandez recently reported the presence of "depressed
nystagmus" in REM sleep in children (ages 6-9).

Each adult was studied for 3 nights, each test night separated by
at least one week. Two electrodes were attached at the outer canthus of
each eye and two additional electrodes were placed above and below the
left eye. Electronystagmographic recording was obtained on four polygraphic
channels measuring horizontal and vertical components. In addition, EEG
and chin EMG were recorded, all on a Grass Model 6 Polygraph. The subject
was seated in a torsion swing such that the horizontal semicircular canals
were at right angles to the axis of rotation. Baseline vestibular nystagmic
response was measured during waking before and after the eight hour noc-
turnal sleep recording. A stimulation trial during sleep consisted of
5 - 10 90° rotational reversals, each cycle lasting 5 seconds. Any evidence
of arousal, such as alpha activity, body movements, or elevation of EMG
caused us to discard the findings for that period of stimulation.

At no time during REM sleep was nystagmus evoked by vestibular stimu-
lation. In addition, no clear nystagmic responses were elicited during
non-REM stages 2, 3 and 4. In all stages of sleep, rotation of the torsion
swing always produced slow compensatory conjugate eye movements. Of special
interest was the finding that REM bursts were immediately suppressed with
onset of rotational stimulation and also that REM bursts emerged immediately
following termination of stimulation.

PAPERS PRESENTED AT SCIENTIFIC MEETINGS
AND RECENTLY PUBLISHED

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2. Hellman, L., Weitzman, E.D., Roffwarg, H., Fukushima, D.K., Yoshida, K., and Gallagher, T.F.: Cortisol is Secreted Episodically in Cushing's Syndrome. J. Clin. Endocrin. & Metab., 30: 686-689, 1970

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5. Hellman, L., Weitzman, E.D., Roffwarg, H., Fukushima, D.K., Yoshida, K., Zumoff, B., and Gallagher, T.F.: Effect of o,p'-DDD on Cortisol Secretory Pattern in Cushing's Syndrome. J. Clin. Endocrin. & Metab., 31: 227-230, 1970.

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7. Perlow, M., McGregor, P., Fukushima, D., Hellman, L., Weitzman, E.D.: 72 hour polygraphic recording and 24 hour plasma cortisol measurement in the differential diagnosis of sleep disorders. TAPSS, 1971.

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9. Sassin, J., Pawel, M., Weitzman, E.D.: Temporal relationships between sleep onset and human growth hormone release. TAPSS, 1971.

10. Kapen, S., Finkelstein, J., Boyar, R., Hellman, L., Weitzman, E.D.: Plasma growth hormone levels during sleep in normal females. TAPSS, 1971.

11. Tauber, E.S., Handelman, G., Handelman, R., Weitzman, E.D.: Effects of vestibular stimulation during sleep in young adults. TAPSS, 1971.

12. Weitzman, E.D., Fukushima, D., Nogeire, C., Hellman, L., Sassin, J., Perlow, M., and Gallagher, T.F.: Departments of Neurology, Oncology and the Institute of Steroid Research, Montefiore Hospital and Medical Center, Bronx, New York, U.S.A. "Studies on Ultradian Rhythmicity in Human Sleep and Associated Neuroendocrine Rhythms." The International Society for the Study of Biological Rhythms, Little Rock, Arkansas, U.S.A. November 8-10, 1971.

13. "Periodicity in Sleep and Waking States: Neural, Neuroendocrine and Environmental Determinants." Elliot D. Weitzman, Chairman - APSS, Bruges, Belgium, June, 1971.

14. "Rhythmic Activity in the Sleep Pattern of Man" presented at the International Round Table Conference on Biological Rhythms in the Nervous Systems held in Kotor, Yugoslavia, July, 1971.