most postpubertal patients with this disease to metabolize galactose (*3*).

In spite of the evidence that the Gal-transferase and UDPGal-pyrophosphorylase activity of liver tissue increases with age, the data presented here demonstrate a decrease with age in the ability of liver tissue to utilize galactose. One possible explanation for the discrepancy between the enzyme levels and the activity of whole tissues, is that these particular enzymes are not rate-determining for the series of reactions converting galatose to glucose. The rate-limiting step may be the initial phosphorylation of galactose by the enzyme, galactokinase, according to the reaction,

$$\text{Galactose} + \text{adenosine-triphosphate (ATP)} \longrightarrow \text{adenosinediphosphate} + \text{Gal-1-P},$$

and, indeed, Kirkman and Kalckar (*6*) have presented some evidence that this is the case for red blood cells.

If the diminished rate of galactose utilization demonstrated here in the adult liver were, in fact, due to a decrease in the phosphorylation of galactose (whether because of lowered galactokinase activity or lowered ATP availability, or for other reasons) this would imply a decreased rate of galactose-1-phosphate production in the adult, and would be consistent with the speculation that the accumulated galactose-1-phosphate is the toxic agent.

STANTON SEGAL
HENRY ROTH
DOLORES BERTOLI

National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Maryland

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26 August 1963

Blood Pressure Changes during Human Sleep

Abstract. *Systolic blood pressure measurements were made on normal human subjects throughout entire nights of natural sleep and were correlated with cyclical changes in electroencephalographic patterns. During the recurrent rapid-eye-movement phase of sleep mean blood pressure levels were found to be generally higher, and the minute-to-minute variability of level was much greater than during the remainder of sleep.*

The distinctive and regularly recurring electroencephalographic (EEG) phase of sleep [rapid-eye-movement (REM) sleep] associated with human dreaming (*1*), is accompanied by changes in many physiological systems (*2*). As part of a broader investigation of vegetative changes during human sleep (*3*) the present study tests the hypothesis that periodic changes in blood pressure are concomitant with the alternating EEG phases of sleep, though existing evidence did not predict the nature of the changes. The very similar phase of sleep in the cat is reported to be accompanied by lowered blood pressure levels (*4*), while it was much earlier suggested that marked and sudden increases of blood pressure in response to dreaming might account for cardiovascular catastrophes during sleep (*5*). Previous investigations of blood pressure during human sleep (*6*) consistently report a fall at sleep onset and a gradual rise toward morning, but do not relate the detailed time course of blood pressure to the EEG cycle. To attempt such a correlation requires frequency and reliability of measurements which are difficult to reconcile with the conditions of natural sleep.

To our knowledge there is no existing method of blood pressure measurement, including the one employed here, which is ideally suited to these requirements and conditions. However, certain modifications of the conventional indirect blood pressure measurement provided a technique which did demonstrate significant changes in relation to the EEG patterns of sleep. This technique involved the recording of pulse sounds through a microphone taped over the posterior tibial artery at the ankle, while an ordinary blood pressure cuff upon the lower leg was automatically inflated and deflated over a 1-minute cycle. As compared with measurements from the arm, this location is much less disturbing to the sleeper, and the range or frequency of positional changes with reference to heart are smaller, though still not negligible. Pressure levels within the cuff were recorded on the polygraph by means of an electrical manometer (Beckman Infratron FBR-2A) which produces a series of coded pulses as in Fig. 1. As shown in the same figure, this allows an estimate of systolic pressure as that coinciding with the first sound impulse, and of diastolic level as the point of abrupt diminution in intensity of this impulse. In practice the diastolic measure was not sufficiently reliable to be used.

Subjects were normotensive "normal control volunteers" (*7*), five male and seven female, ranging in age from 18 to 26. The first one or two nights for each subject were somewhat broken by periods of wakefulness and were not used, but after adaptation the EEG records were typical of those obtained under laboratory conditions, and the subjects generally denied awareness of the inflating cuff from sleep onset until final awakening.

For one night of uninterrupted sleep from each subject the time course of

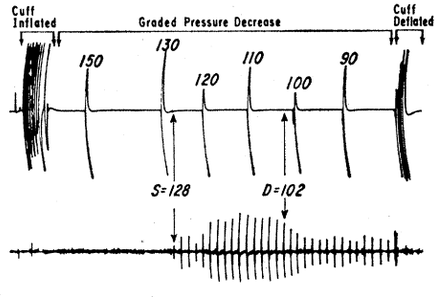

Fig. 1. Ilustration of one cycle of blood pressure recording by the method described; portion of the cycle shown was of 55 seconds duration. Upper trace: signal from manometer, showing phases of inflation cycle and graded pressure decrements. Lower trace: signal from microphone over posterior tibial artery, showing estimates of systolic (*S*) and diastolic (*D*) blood pressure.

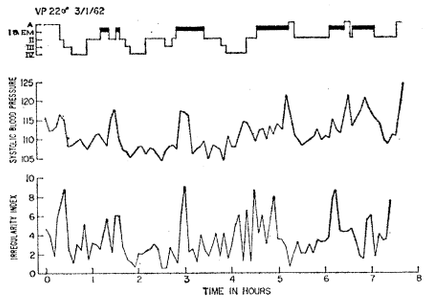

Fig. 2. Typical curves of systolic blood pressure level and irregularity over the course of uninterrupted sleep. Top line is a schematic representation of the EEG cycle, with REM periods indicated by heavy bars.

EEG changes was scored by one of us (F.S.) from a separately recorded EEG record, making use of the categories of Dement and Kleitman (*8*), while the second investigator (A.H.) scored the minute-to-minute blood pressure levels without reference to the EEG changes (Fig. 2). Readings occurring within 1 minute of an electrographically detectable body movement were eliminated. The records were then divided into 5-minute intervals, and a measure of irregularity "*d*" was obtained for each interval (*9*). Statistical evaluation of results from a larger series of records will be reported later, but the analysis which follows refers to this sample of 12 records scored in their entirety.

The all-night trends in systolic blood pressure level were found to be essentially as previously described. There is a rapid decrease in systolic level beginning prior to sleep onset and reaching its nadir within the first 1 or 2 hours, after which there is a gradual and irregular upward trend throughout the rest of the sleep period. Aside from numerous and transient elevations which accompany gross body movements or brief arousals, the variability of systolic level within non-REM sleep takes the form of minor oscillations around a relatively stable base line. Occasionally the base line appeared to shift abruptly after a body movement and to remain at the new level until the next gross movement, which indicates a residual of unreliability in the method. Despite these unpredictable shifts the periodic changes which accompanied REM sleep were usually consistent, and sometimes dramatic. In 69 percent of the REM periods there was at least a small increase in mean systolic level as compared with the prior 20 minutes of sleep (two-tailed *t*-test, $p < .025$), and in 79 percent of the periods the mean level was higher than the subsequent 20-minute periods of non-REM sleep (two-tailed *t*-test, $p < .025$). As shown in Fig. 3, analysis of the successive REM periods of the night revealed that the mean systolic changes were much more conspicuous for the third and fourth REM periods than for the first and second. These changes could reflect overnight trends, and it is therefore more important that there were equally significant falls following the first, second, and third REM periods as illustrated in the same figure. Marked and erratic variability of systolic levels during the REM periods was more consistent and of considerably greater magnitude than the mean level changes. Although our subjects were normotensive, these transient and unpredictable excursions were occasionally as high as 30 mm-Hg above the neighboring levels.

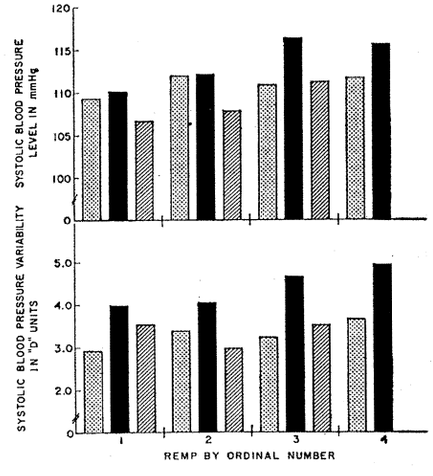

Fig. 3. Mean levels (top) and mean variability indices (bottom) of systolic blood pressure from pooled data of 12 subjects during the successive REM periods (REMP) of the night (solid), 20-minute periods immediately prior (dotted), and 20-minute periods following (diagonals).

Just as heart rate increases during REM sleep in humans (*10*) and tends to fall during the comparable phase of sleep in the cat (*11*), so the trend toward elevation in mean systolic level during REM sleep found here contrasts with reports of lowered blood pressure in the cat. The more striking changes in variability correspond to the characteristic changes in respiration and heart rate noted in both species (*11*).

The mechanism of the described changes is not directly clarified by this study. While regulation of the blood pressure level is probably a complex function of the integrated central nervous system, recent evidence (*12*) suggests that brain stem centers mediate the specific pattern of REM sleep changes and, perhaps, the erratic variability of blood pressure as an integral part of this constellation. Since blood pressure changes do not appear to be as constant as many other characteristics of REM sleep it is also possible that they are a more nonspecific accompaniment, perhaps reflecting emotional or other variations occurring during the psychological experience of dreaming. Regardless of the interpretation, these observations point to the possible medical significance of the abrupt alterations in circulatory dynamics occurring during dreaming sleep.

FREDERICK SNYDER
J. ALLAN HOBSON
FREDERICK GOLDFRANK
National Institute of Mental Health, Bethesda 14, Maryland

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$$d = \frac{1}{N-1} \sum_{i=1}^{N-1} \left| X_{i+1} - X_i \right|$$

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