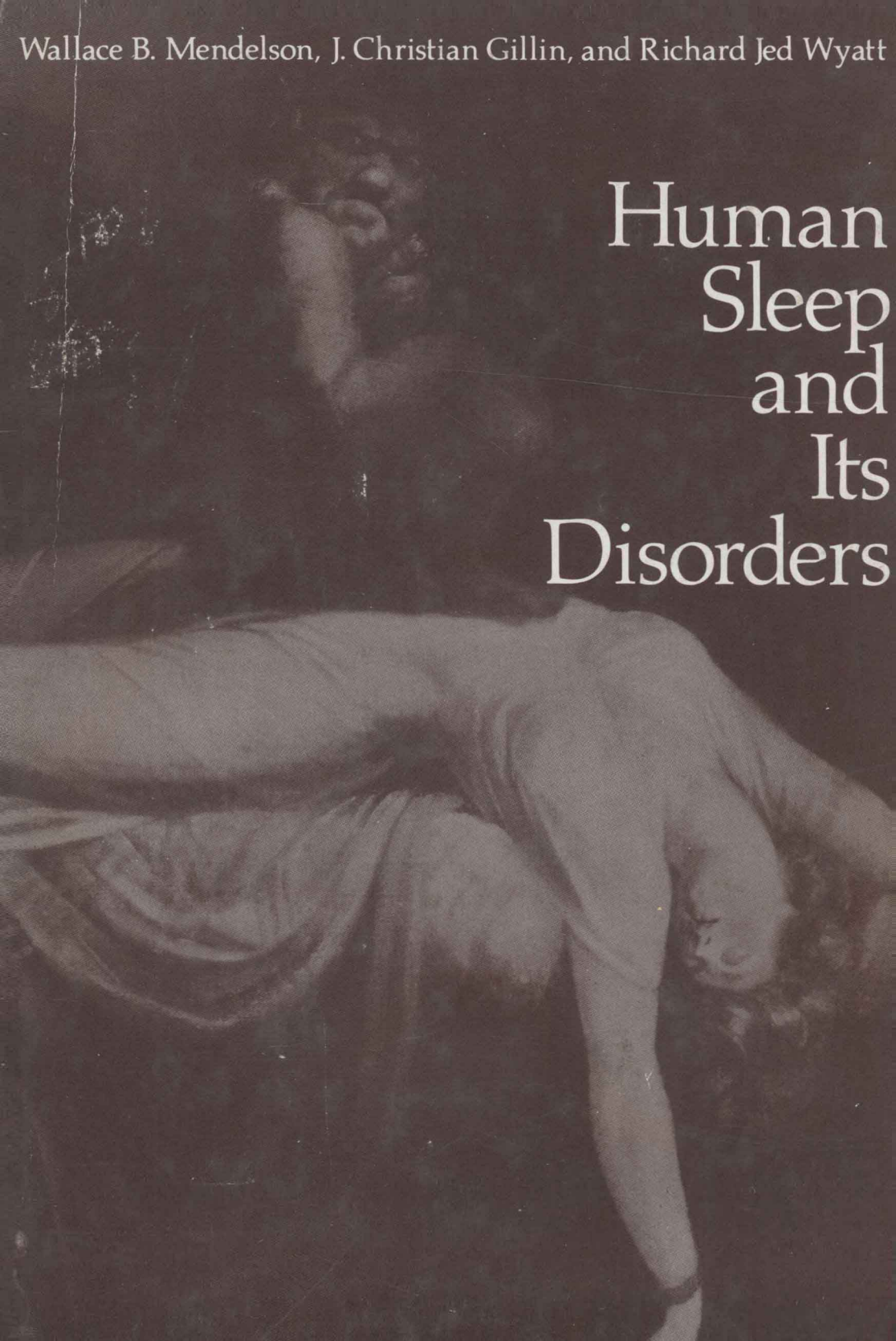
Wallace B. Mendelson, J. Christian Gillin, and Richard Jed Wyatt

Human Sleep and Its Disorders



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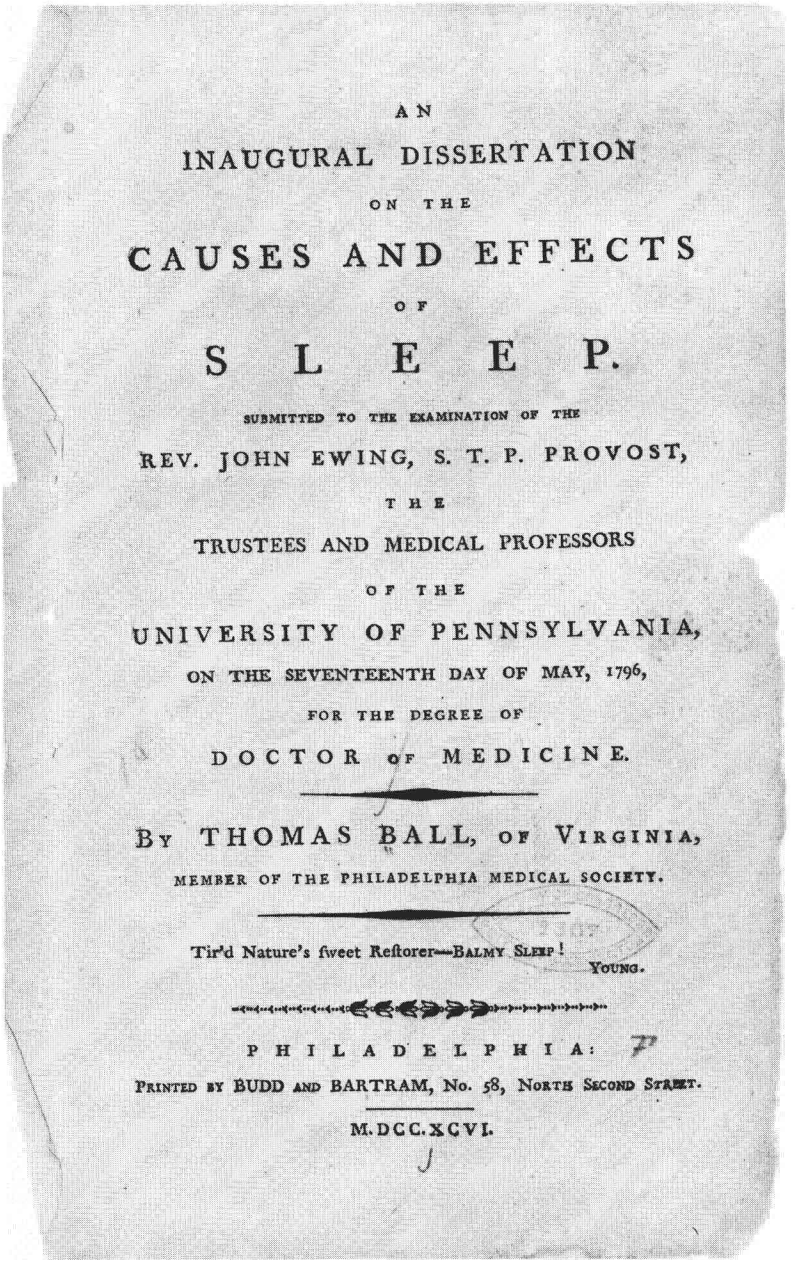

AN

INAUGURAL DISSERTATION

ON THE

CAUSES AND EFFECTS

OF

SLEEP.

SUBMITTED TO THE EXAMINATION OF THE

REV. JOHN EWING, S. T. P. PROVOST,

THE

TRUSTEES AND MEDICAL PROFESSORS

OF THE

UNIVERSITY OF PENNSYLVANIA,

ON THE SEVENTEENTH DAY OF MAY, 1796,

FOR THE DEGREE OF

DOCTOR OF MEDICINE.

BY THOMAS BALL, OF VIRGINIA,

MEMBER OF THE PHILADELPHIA MEDICAL SOCIETY.

Tir'd Nature's sweet Restorer—BALMY SLEEP!

YOUNG.

PHILADELPHIA:

PRINTED BY BUDD AND BARTRAM, No. 58, NORTH SECOND STREET.

M.DCC.XCVI.

Title page of a dissertation on sleep written by Thomas Ball, an 18th century American physician. This fascinating work contains comments on such subjects as the effectiveness of hypnotics and causes of excessive sleepiness. (Courtesy of the Library of Congress)

In Memoriam

Robert A. Woodruff

Preface

In this book we trace the development of several major themes in sleep research, from the first formal description of REM sleep in the early 1950s through the present. Chapter 1 provides those less familiar with this area with a perspective on the many possible ways to examine sleep. Chapter 2 describes in detail a major viewpoint of this book: that observations of pharmacological interventions affecting the neurotransmitters may aid in the understanding of sleep regulation. The remainder of the book is devoted to endocrine systems related to sleep (chap. 3) and to the contribution of sleep research to the understanding of various pathological states (chaps. 4–7). The areas of investigation open to those who wish to understand sleep are much broader than the traditional problems of insomnia and narcolepsy. Such disorders as depression, schizophrenia, and alcoholism have long been associated with disordered sleep. Our search for an understanding of the latter phenomena may clarify the nature of these conditions.

We have emphasized the study of *human* sleep. There are, of course, some scientific disadvantages to this approach. Because of ethical considerations, we obviously cannot, and do not wish to, employ the invasive procedures of the animal laboratory. Hence our inferences must often be indirect, and we may sometimes be observing epiphenomena, rather than the physiologic events themselves. On the other hand, there are several unique advantages to studying human sleep. First of all, sleep has a dual nature: It can be seen as both a physiological function and a subjective experience. In order to study the interworkings of these two phenomena, we must necessarily deal with humans. Second, it is our intention that our studies will ultimately be useful in solving human problems. In the absence of adequate

animal models, we must study such conditions as the affective disorders and schizophrenia in persons suffering from them. Third, there is a technical advantage. The human REM-nonREM cycle lasts approximately 90 minutes, much longer than that of most laboratory animals. We are becoming more and more convinced that it is useful to study the effects of drugs that are infused briefly at different points in the sleep cycle. We also wish to examine substances in the blood that may appear in a specific stage of sleep. This can only be done when the cycle is long enough to be broken down into its constituent parts, as is the case in the human REM-nonREM cycle.

Finally, a few comments about our method of presentation are in order. We have tried to write in a manner that is understandable to the student as well as the professional researcher. For this reason, we have provided a section at the beginning of each chapter that outlines the basic concepts in the field. (In chapter 7, for example, we begin by briefly describing the symptoms and natural history of depressive disorders.) We have also tried to avoid giving the text a sedative quality of its own, which is often the result of narrating the results of one experiment after another. Since it is important that this information be available, however, we have made a series of tables describing the data from all the studies in a given area. In the text, we have emphasized the interplay of ideas derived from these studies. One approach that we found particularly useful was to determine the criteria needed to confirm or refute a hypothesis (e.g., that the secretion of a hormone is related to the occurrence of a sleep stage), and to determine how well these criteria have been met. Finally, we have tried to convey to the reader the sense of excitement we have experienced in studying the nature of sleep, a phenomenon both universal and exceedingly mysterious.

We wish to recognize the people who inspired and supported our work over the years: Drs. Frederick Snyder, William Bunney, Robert Cohen, Robert A. Woodruff, Donald W. Goodwin, Eli Robins, Irwin W. Feinberg, William Dement, and Alan Hobson.

In particular, we would like to thank Drs. Donald W. Goodwin, Lawrence S. Jacobs, and James F. Leckman for their valuable suggestions regarding various portions of this book. The responsibility for all statements in the text, however, lies with the authors.

Bethesda, Maryland
and
Washington, D.C.

WALLACE B. MENDELSON
J. CHRISTIAN GILLIN
RICHARD JED WYATT

Contents

CHAPTER 1

An Introduction to Sleep Studies

Although spontaneous electrical discharges in the brains of animals were reported as early as 1875, the first recordings from humans were attributed to Hans Berger in 1929. Over the next decade he wrote a remarkable series of papers confirming previous animal studies and showing that the electrical activity was derived from neuronal tissue, that it responded to sensory stimulation, and that abnormal discharges occurred during epileptic seizures (Berger, 1929; Berger, 1938). He used the term *electroencephalogram* (EEG) to refer to his recordings of this electrical activity.

In 1937, Loomis, Harvey, and Hobart described the results of 30 all-night EEG recordings from humans. They discovered that, in terms of EEG observations, sleep is composed of a series of discontinuous stages. They pointed out that changes between these stages occurred spontaneously, apparently as a result of "internal stimuli." Although the classification of these stages has changed, the concept that sleep is made up of discrete, recurring stages, regulated by neural mechanisms, is basic to much of modern sleep research. These concepts led the way to the discovery some years later of rapid eye movement (REM) sleep.

The formal description of REM sleep was anticipated by clinical observations of several of its characteristics prior to the advent of the electroencephalogram. Griesinger in 1868 (and others later) suggested that dreaming is associated with periods of eye movements. Freud (1895) mentioned that the major muscles of the body become very relaxed during dreaming. MacWilliam (1923) distinguished between

"undisturbed" and "disturbed" sleep. The latter was associated with increased blood pressure and pulse, and changes in respiratory rate.

In 1953, Aserinsky and Kleitman presented a polygraphic study demonstrating the occurrence of periods of sleep characterized by conjugate rapid eye movements. During these periods, the EEG showed an activated pattern consisting of low amplitude waves generally of 15–20 and 5–8 cycles per second frequencies. Associated with this sleep stage were increased rates of heartbeat and respiration. Aserinsky and Kleitman awakened patients during this REM sleep and found that about three-fourths of them reported that they were experiencing dreams involving visual imagery. Another small percentage reported "the feeling of having dreamed" but could not recall details. When subjects were awakened during sleep that did not contain REMs (referred to as nonREM sleep), only about 9% described dreams and another 9% reported the feeling of having been dreaming.

In the next few years after the description of REM sleep, two findings in particular led to a more complete understanding of its physiology. Jouvet and Michel (1959) reported that in animals there was a marked decrease in muscle tone during REM sleep; this was confirmed in humans by Ralph Berger in 1961. The second finding was a report by Dement and Kleitman in 1957 that REM sleep appeared to recur in a cyclic fashion throughout the night, interspersed by periods of nonREM sleep. Each REM-nonREM cycle was thought to last 90–100 minutes. Dement and Kleitman then proposed a classification system, in which REM was differentiated from nonREM sleep, which in turn was divided into four stages. This was the basis of an approach to classification that, with some revisions (Rechtschaffen and Kales, 1968) is still in use. Authors such as Oswald (1962) and Jouvet (1962) began to emphasize the concept that sleep is not a unitary process, but rather is composed of REM and nonREM sleep, which differ fundamentally in most physiological parameters when measured over time. Thus, REM sleep, nonREM sleep, and waking have come to be thought of as the three *states of consciousness.*

An improved understanding of the sleep stages has resulted from studies of a number of physiological systems that vary with them, differences between species, changes with age, and effects of depriving people of them. The results of some of these approaches will be described briefly in this chapter. For further information on the development of sleep research, the reader may wish to see historical reviews written by some of the men who helped create that history (Dement and Mitler, 1974; Bremer, 1974; Jouvet, 1969).

TECHNIQUES OF HUMAN SLEEP STUDIES

Sleep studies on humans are usually performed by using a polygraph to record three types of data: the electroencephalogram (EEG), electromyogram (EMG), and electrooculogram (EOG). Each of these procedures, which are described by Rechtschaffen and Kales (1968), may be summarized as follows:

EEG: Electrodes (generally concave metallic disks) are put next to the scalp and held in place by small cotton gauze patches that have been covered with collodion, a sticky proteinaceous substance. The surface of the electrode that touches the skin has been coated with an electrolytic jelly that facilitates transmission of the electric potentials. The electrode is usually attached to the scalp above the ear, two inches below the top of the skull (technically referred to as C_3 or C_4). Recordings may be made from either the left or right sides, as the signals from the two homologous areas are generally the same. The polygraph amplifies and traces on paper an electrical signal that represents the difference between voltage from this electrode and a relatively electrically neutral area (the *reference* lead). The latter is usually placed on the earlobe or on the mastoid bone behind the ear (A_1 or A_2). This arrangement is referred to as *unipolar recording*.

EOG: Electrodes are attached with plastic tape to the skin beside the outer corners (canthi) of the eyes. The signal that represents the difference between each eye lead and the reference electrode is amplified and displayed on paper. When the eyes move conjugately (as if following a moving object), the tracings of the two eye channels appear as mirror images of each other.

EMG: Two electrodes are attached beneath the chin. The difference between the potentials of these two electrically active electrodes is amplified and displayed on paper (bipolar recording). The amplitude (vertical height) of the signal is considered to be directly proportionate to the degree of muscle tone.

THE SLEEP STAGES

A determination of the sleep stage is based on the combined information from the EEG, EOG, and EMG. The records are read in *epochs*, usually of 20 or 30 seconds; i.e., a determination is made of what the dominant sleep stage is for each sequential 20- or 30-second period. The most widely accepted criteria for defining the stages are