SLEEP AS A TEACHING TOOL FOR INTEGRATING RESPIRATORY PHYSIOLOGY AND MOTOR CONTROL

Stephen R. Thompson,[1,3] Uwe Ackermann,[1] and Richard L. Horner[1,2]

Departments of [1]Physiology and [2]Medicine, University of Toronto, Toronto, Ontario, M5S 1A8; and [3]Department of Theory and Policy Studies in Education (Higher Education Group), Ontario Institute for Studies in Education of the University of Toronto, 252 Bloor Street West, Toronto, Ontario, Canada, M5S 1V6

Sleep exerts major effects on most fundamental homeostatic mechanisms. Current data suggest, however, that students of physiology and medicine typically receive little or no formal teaching in sleep. Because sleep takes up a significant component of our life span, it is proposed that current teaching in systems and integrative physiology is not representative if it is confined to functions describing wakefulness only. We propose that sleep can be readily integrated into various components of physiology and medical curricula simply by emphasizing how commonly taught physiological processes are importantly affected by sleep mechanisms. In our experience, this approach can be used to reinforce basic physiological principles while simultaneously introducing sleep physiology into the students' training. We find that students have a general and inherent interest in sleep and related clinical disorders, and this proves useful as an effective means to teach the material. In this paper, examples of how sleep influences motor control and the respiratory system will illustrate these points. These considerations also highlight some important gaps in traditional teaching of respiratory physiology.

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Rationale for Integrating Sleep into Basic Teaching in Physiology

As knowledge of the broad physiological changes associated with sleep has expanded over the last several decades, it has become increasingly apparent that most, if not all, fundamental homeostatic mechanisms are significantly affected by sleep processes. Current data suggest, however, that students of physiology and medicine typically receive little or no formal teaching in sleep, despite the fact that one-third of the human life span is spent in this state. This deficiency has been recognized as especially problematic in the medical curriculum (12, 13), chiefly because common disorders of sleep are a major public health burden affecting at least 10% of the population including respiratory, cardiovascular, and neurological problems (6, 9). A recent survey of medical schools in the United States showed that typically <2.5 h of the undergraduate curriculum included sleep physiology and pathology (12). The median time a medical student in the United Kingdom was exposed to educa-

Address for reprint requests and other correspondence: R. L. Horner, Rm. 6368, Medical Sciences Bldg., Univ. of Toronto, 1 Kings College Circle, Toronto, ON, Canada M5S 1A8 (E-mail: richard.horner@utoronto.ca).

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tion in sleep was typically <15 min in preclinical teaching and 0 min in clinical education (14). An informal survey of common textbooks of physiology and medicine further emphasizes that students receive little or no teaching in sleep and that there is little resource to access this material. In view of its whole body physiological effects, time occupied in our lives, and associated pathophysiological syndromes, we suggest that current teaching in systems and integrative physiology is not representative if it is confined to functions describing wakefulness only. Because of this potential problem, there is a growing demand for education in sleep, although lack of qualified faculty and curriculum time have been cited as major obstacles (12).

We propose here that sleep physiology can be readily integrated into various components of undergraduate physiology and medical curricula simply by emphasizing how commonly taught physiological processes are importantly affected by sleep mechanisms. We have selected only two physiological systems, realizing full well that similar integrations are possible between sleep and other systems, for example, cardiovascular, endocrine, or metabolic functions.

The impetus for this article arose from an enthusiastically received undergraduate and graduate course in sleep physiology. Accordingly, we have experienced at first hand that students have a general and inherent interest in sleep physiology and related clinical disorders. This inherent interest may stem from the fact that the students can relate to the normal changes in physiological processes that they themselves undergo in sleep and because sleep-related disorders, particularly respiratory, are so common that they probably know individuals with such disorders. With the use of this inherent student interest as a base, we built an integrative course whose framework is the alliance of sleep mechanisms with a variety of physiological processes. The main purpose of this paper is to provide knowledge of sleep as related to integrating respiratory physiology and motor control to educators who are in a position to incorporate this material into their curriculum. We offer examples in this article and suggest ways of demonstrating the relevance of these basic physiological mechanisms to normal health and common clinical disorders. In the last section of this paper, we include selected examples of clinical disorders with commonly recognized daytime symptoms whose pathophysiology is linked to nighttime sleep. These are presented as classroom-ready case discussions in which the clinical disorder is discussed from the standpoint of basic respiratory physiology and motor control. They could also be adapted to the purpose of student assessment.

General Overview Of Sleep

We find that students typically need to be initially introduced to the basic concepts and terminology of sleep as a foundation for subsequent teaching. Accordingly, a brief introduction to the basics of sleep is included here to facilitate fuller understanding of later sections that involve the effects of sleep on motor and respiratory control.

Measurement of sleep. Sleep occurs in all mammals and can be distinguished across species using three basic electrophysiological signals recorded from surface electrodes. The electroencephalogram (EEG) is used to measure brain activity and is recorded from electrodes placed on the head overlying the cortex. Separate electrodes placed beside each eye are used to record the electrooculogram, a marker of eye movements. The electromyogram is used to monitor postural muscle tone by surface electrodes placed under the chin. Figure 1 shows typical electrode placements and the recorded signals across the different sleep and waking states. On the basis of recordings from such electrodes, two major sleep states have been identified as rapid eye-movement (REM) and non-REM sleep, and these are described in more detail below. An important consequence of the landmark discovery of REM sleep (1) was the dispelling of the common notion that sleep is a passive process associated with the simple withdrawal of wakefulness. Rather, the current notion is that sleep is composed of distinct states each actively generated by different brain regions, with each of these sleep states having distinct effects on a variety of physiological processes.

REM sleep. REM sleep occupies ~20% of the total sleep time. REM sleep is also associated with generalized heightened brain activity and periodic intense eye movements that give this sleep state its name. REM sleep is also associated with dreaming and periods of widely fluctuating respiratory and cardiovascu-

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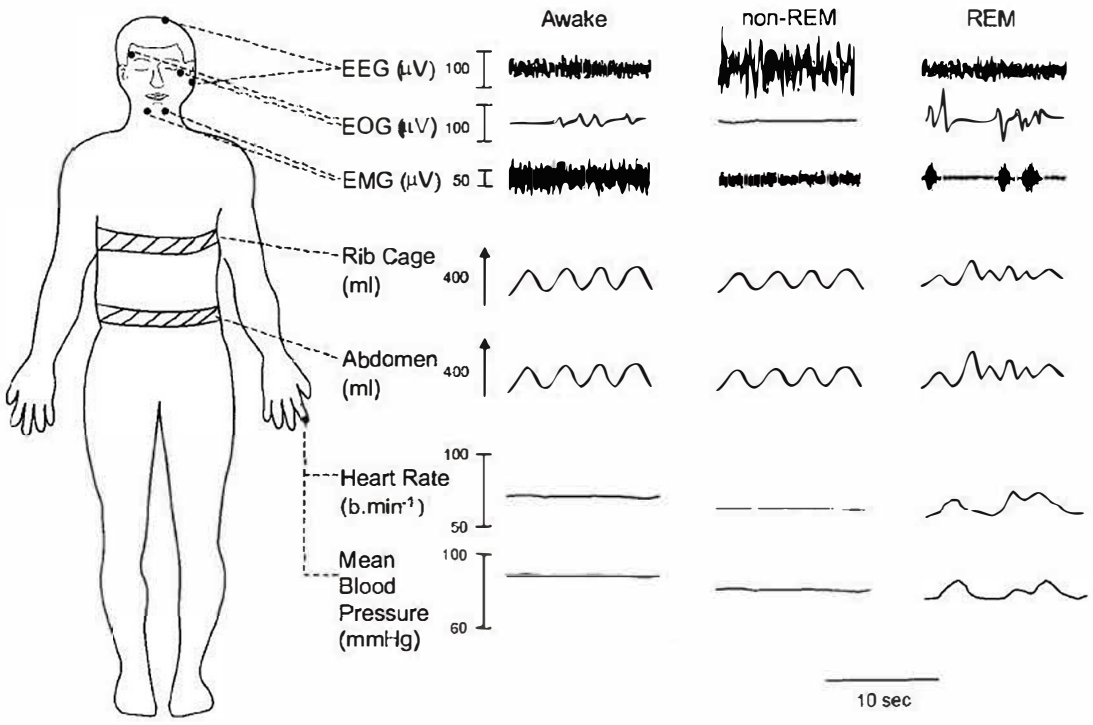

FIG. 1.
Typical electrode placements to distinguish sleep-wake states from the electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) signals. Respiratory inductance plethysmography can be used to measure breathing noninvasively from bands placed around the rib cage and abdomen. Blood pressure and heart rate can also be continuously monitored, noninvasively, via a finger cuff and photoplethysmography. Note the typical low-voltage/high-frequency EEG signal in wakefulness and rapid eye-movement (REM) sleep and the high-voltage/low-frequency signal in non-REM sleep. Note also the progressive decline in postural EMG activity from wakefulness to non-REM sleep, with minimal EMG activity in REM, except for brief muscle twitches, associated with the rapid eye movements recorded by the EOG. REM sleep is also associated with rapid and irregular breathing and variable heart rate and blood pressure.

lar activities (Fig. 1). It is not known whether these latter phenomena are simply correlated with the heightened brain arousal of REM sleep or with the context of the dream. Many of the neurophysiological features of REM sleep are mirrored in the brain during alert wakefulness, and for this reason, this state is also termed "active" or "paradoxical" sleep. Despite the internal state of heightened brain arousal in REM sleep, responsiveness to external arousing stimuli such as noise, and even internal signals related to physiological stress such as hypoxia, are markedly reduced in REM sleep compared with non-REM sleep.

Postural muscle tone is almost completely suppressed in REM sleep apart from occasional muscle twitches. As will be seen in a subsequent section, this absence of skeletal muscle tone in REM sleep is due mainly to processes of motor inhibition resulting in what is commonly likened to sleep "paralysis." A small region of the brain stem in the pons is responsible for this generalized muscle inhibition, and lesions at this site lead to brain electrophysiological signs of REM sleep but without motor inhibition. Indeed, animals lesioned in this way and being in REM sleep can show motor behaviors that are typical of wakefulness (5). Such lesions may, therefore, predispose individuals to act out behaviors in REM sleep.

Non-REM sleep. Non-REM sleep is also not a homogenous state and is composed of four subdivisions

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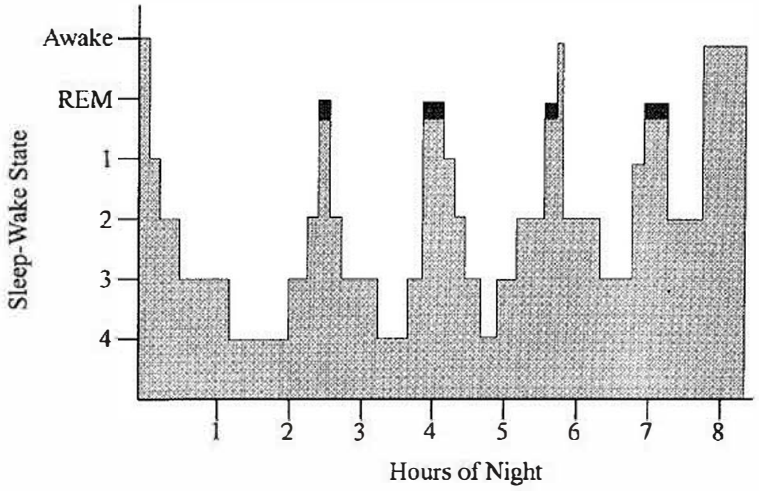

FIG. 2.
Histogram showing the typical distribution of overnight sleep patterns in a young adult. The dark shading highlights periods of REM sleep, whereas other areas indicate wakefulness and the 4 stages of non-REM sleep.

labeled I to IV in humans. Stage IV non-REM sleep is commonly referred to as "deep" or "slow wave" sleep. The latter term is used with reference to the frequency of waves in the EEG signal that are of slowest frequency at this time (0.5–4 Hz compared with ~10–25 Hz in wakefulness) and of the highest amplitude (>75 μV compared with ~20–40 μV in wakefulness). The body appears to be at its most obviously quiescent during this stage of sleep and shows little postural muscle tone. Breathing, heart rate, and blood pressure are at their most stable in stage IV non-REM sleep compared with REM sleep and wakefulness. Responses to external stimuli such as noise, or internal arousing stimuli such as hypoxia, are progressively reduced from stages I to IV of non-REM sleep.

The sleep cycle. Sleep is not a simple linear process whereby an individual enters into stage I non-REM sleep at the beginning of the night, progresses through to stage IV sleep, enters REM sleep, and then wakes up in the morning. Rather, repeated episodes of non-REM and REM sleep alternate cyclically through the night (3). In humans, sleep begins with ~80 min of non-REM sleep followed by a REM period of ~2–10 min. This 90-min non-REM-to-REM sleep cycle is then repeated about three to six times during the night (Fig. 2). In successive cycles, the amount of stages III and IV sleep decreases and the proportion of the cycle occupied by REM sleep increases (3). Stages III and IV sleep, the "deeper" non-REM stages, are most prominent at the beginning of the night. This prominence is thought to indicate that the need for restorative sleep builds up as a function of prior wakefulness and hence deep sleep shows a peak at the beginning of the night (2).

Sleep and physiological processes. Sleep deprivation quickly leads to impaired physiological function, deteriorating health, and death, thereby illustrating the ultimate importance of sleep to an organism (10). Not all the physiological changes associated with sleep, however, are necessarily beneficial. For example, the changes in brain neural activity that produce generalized muscle relaxation in sleep also affect the muscles of breathing and these effects can lead to common sleep-related breathing problems. Likewise, such breathing abnormalities produce repeated episodes of nighttime asphyxia leading to decreases in arterial O_2 and rises in CO_2. The ventilatory and respiratory muscle responses to such alterations in blood O_2 and CO_2 levels are universally taught in basic physiology courses, but these brisk and robust respiratory responses in wakefulness are prone to

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failure in sleep. Moreover, in some cases, the only way that a sleep-related breathing problem and the subsequent asphyxia can be corrected is by a return to wakefulness. However, the severity of stimuli needed to produce awakening from sleep can be markedly different between non-REM and REM sleep, and this can predispose to potentially life-threatening events in the latter state. In addition, it is also incorrect to think of sleep as a state of cardiovascular rest. There is profound modulation of autonomic nervous system activity in REM sleep and this has marked effects on heart rate and blood pressure (Fig. 1) (*4*). The cardiovascular changes between sleep and wakefulness have particular relevance to cardiovascular abnormalities associated with sleep and breathing disorders (see case reports). Specific examples of how sleep mechanisms exert major influences on motor control, respiratory muscle activity, and ventilatory responses to altered blood gases are given below. These examples also illustrate how knowledge of these effects can be used as a teaching tool in traditional respiratory physiology courses.

Motor Control

The stretch reflex is often used to introduce students to basic principles in motor control. Considering the effects of sleep on motor outflow to skeletal muscle can readily expand on these basic principles. Furthermore, sleep physiology can simply illustrate three important principles of motor control: *1*) integration of excitatory and inhibitory inputs to a motoneuron at the postsynaptic membrane to determine net motor output; *2*) modulation of motoneuron excitability by subthreshold drives; and *3*) suppression of motor output by processes of inhibition and disfacilitation (i.e., withdrawal of excitation). Inhibition and disfacilitation are recruited to differing degrees during non-REM and REM sleep and are primarily responsible for the changes in muscle activity across sleep and waking states.

As shown in Figs. 1 and 3, postural muscle tone is highest in wakefulness, decreased in non-REM sleep, and minimal or absent in REM sleep with the exception of occasional muscle twitches that are associated with vigorous eye movements in "phasic" REM sleep. Ultimately, these changes in postural muscle tone are due to changes in action potential discharge of the motoneurons that innervate the muscle. The membrane potential of a motoneuron changes across states of wakefulness and sleep because of varying degrees of converging excitatory or inhibitory inputs originating from sleep-wake related cells in the brain stem.

During wakefulness, a prevailing level of tonic excitatory drive to postural motoneurons raises their membrane potential above threshold for the generation of action potentials resulting in tonic motoneuron firing and an associated level of resting muscle tone (Fig. 3*A*). This tonic excitatory drive to postural motoneurons arises chiefly from brain stem cells that have higher activity in wakefulness compared with with sleep. Some of these neurons release excitatory neurotransmitters, for example, 5-hydroxytryptamine (5-HT; serotonin) (11). In non-REM sleep, reduced firing of such wakefulness-active excitatory cells leads to withdrawal of excitatory drive. This disfacilitation lowers the membrane potential of motoneurons and reduces their action potential discharge such that postural muscle tone decreases in non-REM sleep compared with wakefulness (Fig. 3*B*). In REM sleep, the excitatory input to the motoneurons may decrease even further as certain wakefulness-active but REM sleep-inactive cells (termed "REM-off") achieve minimal or zero discharge. This effect leads to further disfacilitation of motoneurons and contributes to additional suppression of motor output and muscle tone in REM sleep (Fig. 3*C*).

Increased activity of brain stem "REM-on" cells gives rise to the onset of the REM-sleep state itself (Fig. 4). REM sleep is associated with both heightened brain stem arousal and recruitment of powerful inhibitory mechanisms that hyperpolarize motoneurons by way of the neurotransmitters glycine and GABA (11). In addition to disfacilitation, therefore, this inhibition is largely responsible for taking the membrane potential of the motoneuron well below the threshold for action potential discharge such that motor output ceases and muscle tone is minimal in REM sleep (Fig. 3*C*). However, during REM sleep, there are occasional excitatory motor drives that can overcome the inhibitory inputs and transiently bring the membrane potential above threshold and elicit a flurry of action potentials and muscle twitches in phasic REM sleep

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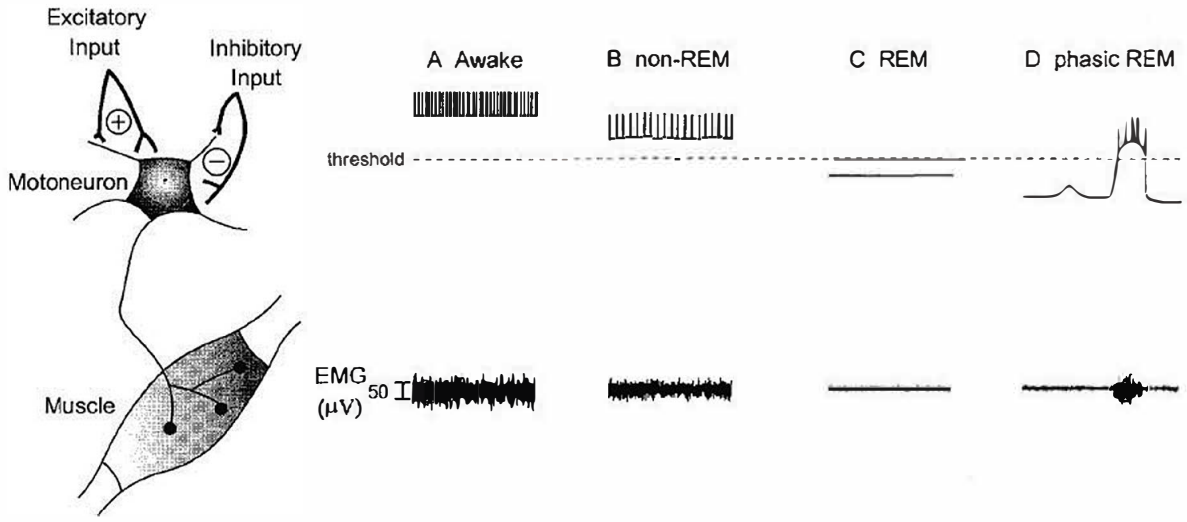

FIG. 3.
Schema to show how converging excitatory and inhibitory inputs to a motoneuron can produce alterations in membrane potential and action potential discharge, resulting in changes in muscle activity across sleep-wake states. Reduced excitatory inputs from wakefulness (*A*) to non-REM sleep (*B*), coupled with further reductions in excitation and recruitment of inhibition in REM sleep (*C*), lead to progressive membrane hyperpolarization, reductions in action potential discharge, and decreased muscle tone. Transient membrane depolarizations can also produce brief muscle twitches in phasic REM sleep (*D*) if these depolarizations are of sufficient magnitude to transiently raise membrane potential above the threshold for action potential discharge (dotted line). See text for further details.

(Fig. 3*D*). It is important to emphasize to students that the apparent absence of activity recorded in the muscle in REM sleep cannot be taken as evidence that the controlling circuitry is inactive, because there are clearly presynaptic excitatory and inhibitory events taking place that are subthreshold (Fig. 3*D*). Before emphasizing these subthreshold events in the context of muscle twitches, we mention REM-behavior disorder as an example that will help students immediately appreciate the balance between brain stem excitatory and inhibitory processes. Individuals who have relatively weak or absent inhibitory processes acting at postural motoneurons in REM sleep are more likely to have motor behaviors in REM, because in them, excitatory potentials are free to bring the membrane potential above threshold. Indeed, individuals who act out components of their dreams may become a danger to themselves or their bed partner. Such individuals may be the human equivalent of animal studies showing that disruption of a small region of the pons releases the inhibition that is normally placed on REM-sleep motor behaviors (5).

In our experience, the association of muscle tone in sleep (Figs. 1 and 3) with the control of motor output (Fig. 4) has several far-reaching uses. First, it demonstrates and expands on the original teaching of Sherrington that motor output is ultimately determined by the net summation of temporally related excitatory and inhibitory drives impinging on a motoneuron and that the motoneuron is the final common pathway to initiate or suppress muscle contraction and muscle tone. Second, it emphasizes the important concept that transient motoneuron depolarization in REM sleep (due to the brief excitatory inputs) may or may not bring the motor unit membrane potential above threshold for action potential discharge. We find this a particularly useful exercise to enforce the realization that motoneuron excitability and responsiveness to excitatory inputs are importantly affected by drives that set the level of membrane potential below threshold. In our experience, this association with sleep, especially with the brief muscle twitches in REM sleep, is readily understood by the students. Moreover, this association allows direct and immediate

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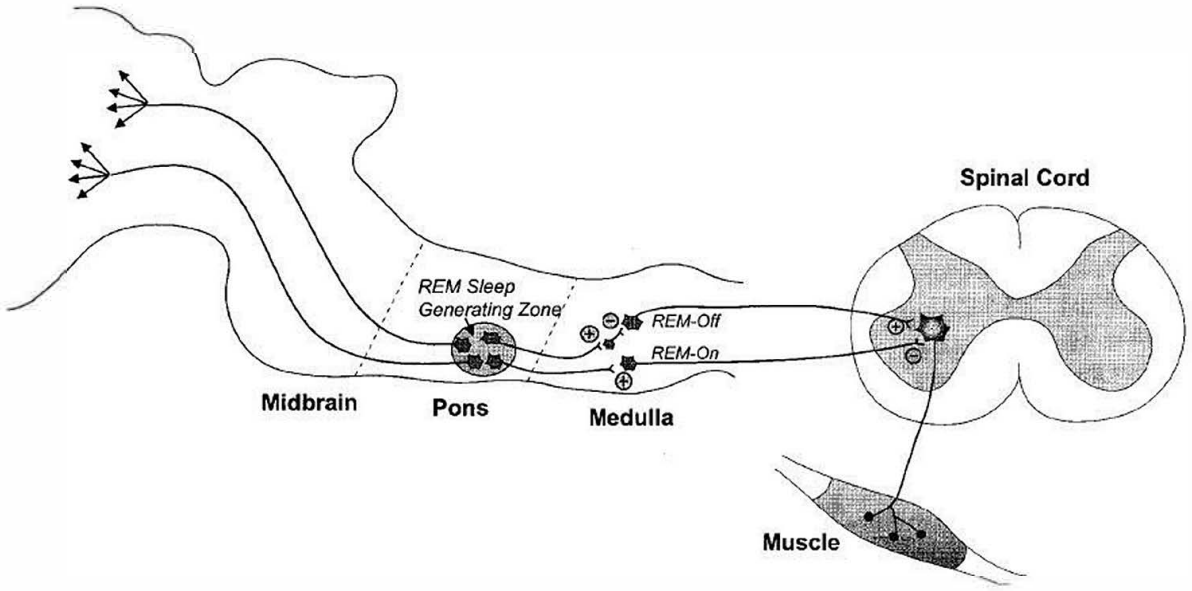

FIG. 4.
Schematic diagram to show how activation of a set of discrete neurons in the pons can produce motor suppression in REM sleep. Suppression of motor tone in REM sleep is achieved by recruitment of inhibitory neural pathways (i.e., REM-on cells in the medullary reticular formation) and suppression of excitatory pathways (i.e., REM-off cells). REM sleep is also characterized by brain arousal produced via diffuse ascending projections to the thalamus and cortex from the REM sleep-generating zone (rostral projections shown by arrows at *left*).

comparisons with the control of respiratory muscles. The students quickly realize that the transient excitatory drive to a postural motoneuron associated with a muscle twitch is directly analogous to the excitatory drive received by a respiratory motoneuron that innervates a respiratory muscle and is associated with the act of breathing. Indeed, at this point, the students also understand that the only essential difference between a postural motoneuron and a respiratory motoneuron is the additional breathing-related signal to the respiratory motoneuron. The following section shows how this important concept can be used to understand the control of motor output to respiratory muscles and how sleep therefore exerts significant influences on the fundamental physiological process of breathing.

Sleep and Breathing

Of all the effects of sleep on basic physiological processes, its effects on breathing are among the most profound and clinically relevant. They provide a rich resource of teaching material. For example, sleep affects respiratory muscle activity, and this can be best understood with reference to the concepts of motor control discussed above. Such understanding extended to the potential clinical consequences leads to new insights into respiratory physiology. For example, traditional teaching of lung ventilation commonly only emphasizes the role of respiratory pump muscles such as the diaphragm. However, without appropriate activation of pharyngeal muscles in the upper airway, diaphragmatic activation would be ineffective. The pharyngeal muscles maintain the upper airway as an effective conduit for airflow, and this role is compromised in sleep. Sleep also has fundamental effects on the classic ventilatory responses to alterations in arterial O_2 and CO_2 levels, and they that can be used to reinforce the importance of these respiratory responses in ventilatory control. Given that sleep physiology incorporates an array of traditional and new concepts in muscle and respiratory physiology, we propose that sleep is at least as good a tool for introducing integrative principles as is the more commonly taught example of exercise. Indeed, as shown below, insights from sleep physiology can introduce

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students to several fundamental concepts that cannot be incorporated into exercise.

Effects of sleep on respiratory motoneurons and muscle activity. Sleep, compared with wakefulness, is associated with reduced lung ventilation mainly due to decreases in tidal volume. Although a decline in metabolic rate from wakefulness to sleep will contribute to the decline in ventilation, the fact that arterial CO_2 levels rise in sleep shows that a significant component of the hypoventilation is unexplained by changes in metabolic rate (8). The mechanisms that produce a decline in ventilation out of proportion to the decrease in metabolic rate are related to principles of motor control. If sleep were used as a teaching example, then Fig. 1 might be used as a starting point to show that overall tidal volume and respiratory rate are stable in non-REM sleep but are characteristically irregular in REM sleep. Then motor control could be reviewed by reminding students of the major determinants of postural motor output across sleep and waking states, emphasizing resting membrane potential and its response to excitatory inputs (Fig. 3). They can also be reminded that in REM sleep, motoneurons are most hyperpolarized, and their membrane potential is highly variable as a result of time-varying inhibitory and excitatory inputs. Most importantly, the students can be encouraged to think of a respiratory motoneuron as resembling a postural motoneuron except that it receives an additional rhythmic drive related to respiration. Because the effects of sleep on tonic drives to postural motoneurons were previously described (Fig. 3), the effects of sleep on a respiratory motoneuron can be readily understood by direct analogy. In this case, however, total respiratory motor outflow is the sum of the respiratory and nonrespiratory inputs as shown in Fig. 5. This figure also makes it readily apparent that tonically driven fluctuations in membrane potential of respiratory motoneurons may contribute significantly to the observed variations in tidal volume and respiratory rate in REM sleep. Although the effects of sleep on tonic (nonrespiratory) drives to respiratory motoneurons are emphasized in Fig. 5, changes in the magnitude and frequency of respiratory inputs also contribute to the observed breathing patterns, especially the variable breathing of REM sleep (7).

Direct comparisons between postural and respiratory motoneurons during sleep emphasize the importance of tonic nonrespiratory drives in setting the total level of membrane potential. This aspect is especially important for understanding the control of respiratory motoneurons, because it is the tonic inputs that are most affected by sleep mechanisms. Differences in tonic drives explain why the diaphragm, which has an almost sole respiratory function, is less affected by sleep than are other respiratory muscles, which often have both respiratory and nonrespiratory functions.

Effects of sleep on lung ventilation. Traditional teaching in respiratory physiology typically places sole emphasis on the respiratory pump muscles such as the diaphragm and the intercostals. It is rightly stated that they are the primary muscles of breathing because their contraction expands the thoracic cavity and brings air into the lungs. However, before effective lung ventilation can occur, air has to pass through the potentially collapsible segment of the upper airspace in the pharynx (Fig. 6). This region is the only segment of the major air passages that is supported by skeletal muscle and not surrounded by rigid cartilaginous support. Given that these pharyngeal muscles, such as the genioglossus muscle of the tongue, have both respiratory and nonrespiratory (e.g., phonation) functions, and given that nonrespiratory inputs are most affected by sleep mechanisms, it is readily understood that sleep leads to reductions in pharyngeal muscle activity, especially in REM sleep. In contrast, the diaphragm is less affected by sleep mechanisms, because motoneurons to this muscle are almost exclusively driven by respiratory inputs (7). The reduction in pharyngeal muscle tone in sleep leads to upper airway narrowing or even complete collapse in sleep (Fig. 6*B*) producing snoring and episodes of obstructive sleep apnea, which is an absence of effective breathing due to an airway obstruction (see subsequent clinical case studies).

A discussion of sleep in this setting, therefore, serves to highlight two major factors that are useful in the teaching of integrated respiratory physiology: *1*) that a complex behavior such as respiratory muscle activation can be understood in terms of modulations of excitatory and inhibitory tonic drives and their interactions with concomitant descending respiratory drives; *2*) and perhaps of more importance, that cur-

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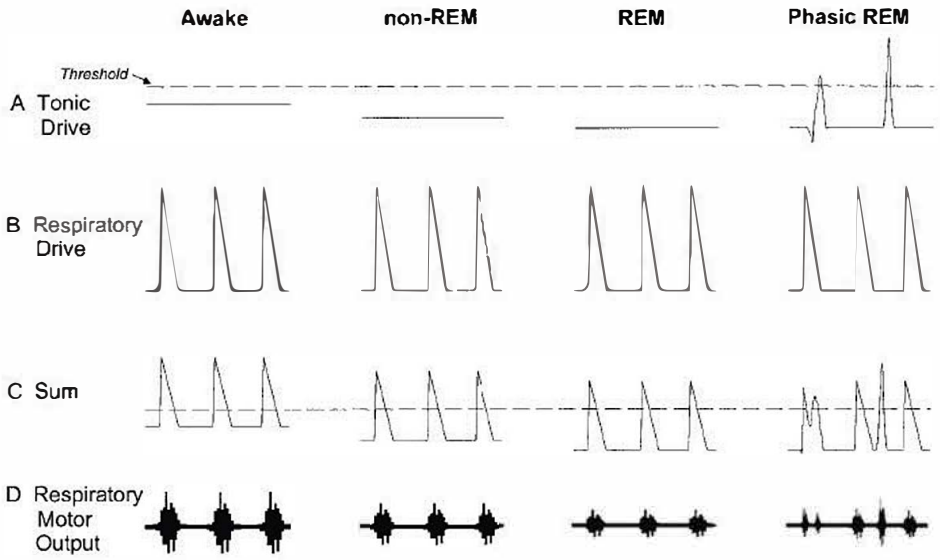

FIG. 5.

Schema to show how changes in nonrespiratory ("tonic") drives to a respiratory motoneuron can lead to changes in resting membrane potential and affect the subsequent response of the neuron to a depolarizing potential that is associated with respiratory ("phasic") drive. In this scheme, the net activity of the respiratory motoneuron is the sum (*C*) of the tonic and phasic drives (*A* and *B*, respectively). In each case, respiratory drive is indicated as 3 depolarizing potentials associated with respiration. The motor output recorded in the respiratory muscle is shown in *D*. [For clarity, in the summed signal (*C*), the action potentials produced by the motoneuron when the membrane potential exceeds threshold are not shown.] The figure shows that progressive hyperpolarization of the respiratory motoneuron from wakefulness to REM sleep is associated with reduced depolarization above threshold in response to the respiratory drive and that this effect can lead to reduced motor output recorded in the respiratory muscle. Moreover, a source of the variable respiratory motor output in phasic REM sleep may be the transient fluctuations in membrane potential related to tonic drives. As such, a component of respiratory muscle activation in phasic REM sleep may be unrelated to respiratory inputs per se. Variations in the magnitude and frequency of respiratory inputs to the motoneuron can also importantly contribute to respiratory variability in REM sleep (7).

rent teaching should expand on the view that the diaphragm and thoracic respiratory pump muscles are the sole important muscles of breathing. In this respect, continuing contraction of the diaphragm in the face of an upper-airway obstruction in sleep is futile for effective generation of airflow. The pharyngeal muscles therefore serve a crucial role in lung ventilation in addition to their other roles in more recognized functions such as phonation and alimentation. Indeed, the students should be encouraged to think of the pharyngeal muscles as secondary muscles of breathing to highlight that this muscle group importantly modulates the passage of air into the lungs. The indirect, but important, respiratory role of pharyngeal muscles becomes especially apparent when their diminished activity in sleep produces intermittent airway obstructions and asphyxia. This problem leads to the clinical syndrome of obstructive sleep apnea in adults (see case reports) and is thought to be involved in the pathogenesis of the sudden infant death syndrome.

Effects of sleep on the respiratory chemoreflexes. The response of the respiratory system to alterations in arterial O_2 and CO_2 levels is essential to homeostasis and is a fundamental principle taught in respiratory physiology. Sleep has major effects on the classic respiratory chemoreflexes, such that for any

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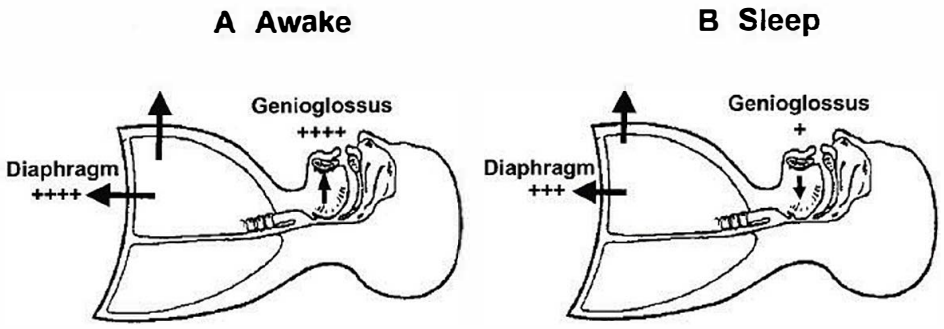

FIG. 6.

Diagram illustrating the importance of pharyngeal muscle activation to effective breathing. Contraction of the diaphragm expands the thoracic cavity and generates airflow into the lungs. Activation of the genioglossus muscle promotes effective breathing by opening up the pharyngeal airspace, thereby allowing the passage of air (*A*). Suppression of genioglossus muscle activity in sleep (*B*) can lead to airway narrowing and even occlusion of the pharyngeal airspace due to relapse of the tongue.

given level of arterial hypoxia or hypercapnia, ventilation is reduced in sleep, especially REM sleep, compared with wakefulness (Fig. 7, *A* and *B*). These effects of sleep on the respiratory responses to disturbances in O_2 and CO_2 levels also have significant clinical relevance, and as a useful teaching axiom, we emphasize to the students that any individual with compromised respiratory function in wakefulness (for any one of a host of potential clinical reasons) is *always* predisposed to major respiratory problems during sleep. The reasons for this are readily apparent with reference to the oxy-hemoglobin dissociation curve (Fig. 7*C*). For example, sleep is associated with reduced ventilation even in normal subjects, but this leads to only minimal reductions in arterial O_2 saturation because of the position on the flat part of the oxy-hemoglobin dissociation curve (Fig. 7*C*). However, an individual with diseased lungs has impaired gas exchange and low O_2 levels in wakefulness. In such an individual, even a normal decline in ventilation from wakefulness to sleep will lead to a major decrease in arterial O_2 saturation because this person is already positioned on the steep part of the oxy-hemoglobin dissociation curve (Fig. 7*C*).

The effects of sleep on respiratory muscle activity and the compensatory ventilatory responses in health and disease are most cogently illustrated with case reports. We use such cases to encourage students to think integratively.

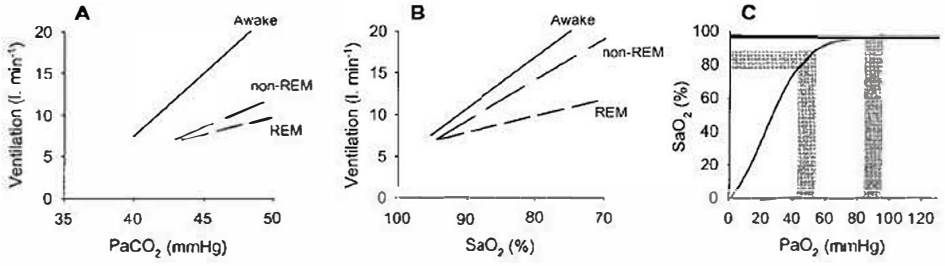

FIG. 7.

Graphs showing the relationships between lung ventilation and arterial P_{CO_2} (*A*) and arterial O_2 saturation (Sa_{O_2}; *B*) across sleep-wake states. Responses to both hypercapnia and hypoxia are reduced in sleep, especially REM sleep, compared with wakefulness. *C*: the magnitude of the decrease in Sa_{O_2} from wakefulness to sleep is dependent on the starting arterial P_{O_2}. For example, a normal decrease in Pa_{O_2} leads to only a small decrease in Sa_{O_2} in sleep if the starting Pa_{O_2} is on the flat portion of the oxy-hemoglobin dissociation curve. However, the same decrease in Pa_{O_2} can lead to a large decrease in Sa_{O_2} in sleep if an individual is initially hypoxic and positioned on the steep portion of the dissociation curve. This situation may occur, for example, in lung disease or at altitude.

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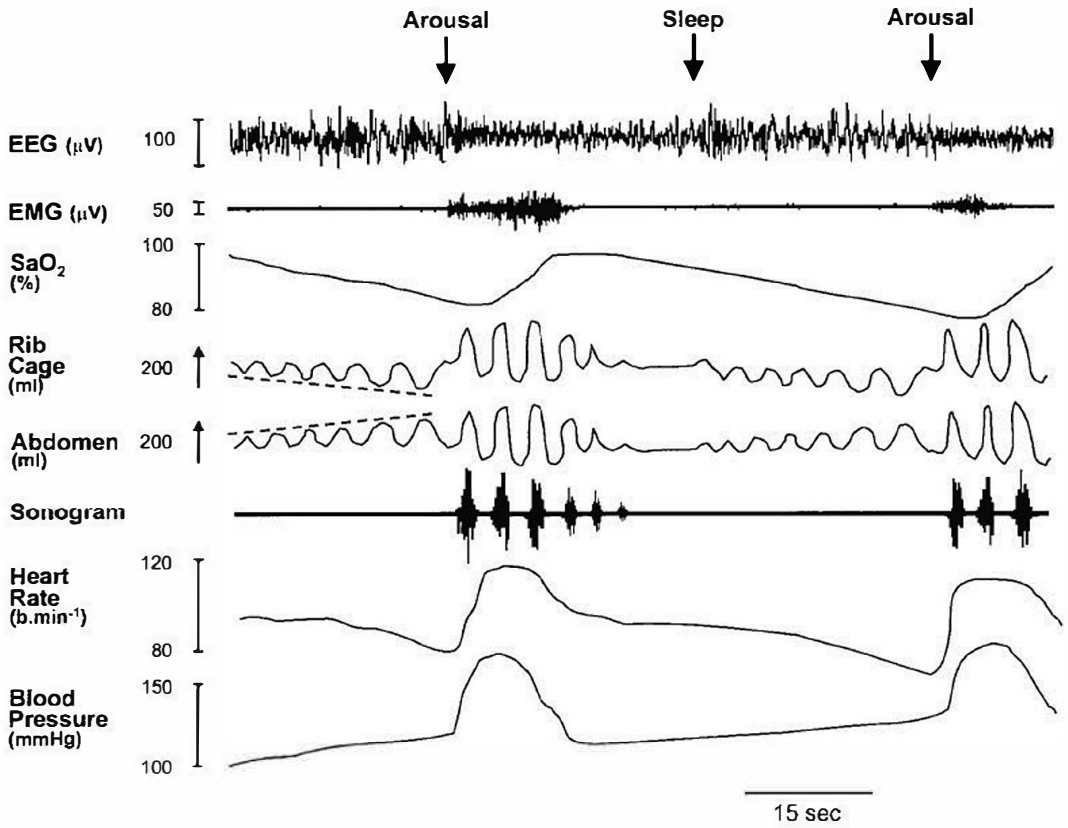

FIG. 8.
Sample record of the overnight traces in a patient with obstructive sleep apnea. See text of *Clinical example 1* for specific points of interest. The arrows indicate arousals from sleep and sleep onset as determined from the EEG and EMG traces. The sonogram indicates breathing sounds due to snoring.

Application of Basic Physiological Principles to Clinical Cases

We find that the following clinical examples are a natural extension of the previous teaching on basic physiology involving sleep. In the class setting, these scenarios can be discussed openly, and the students are actively encouraged to act as the diagnosing clinician by creating their own diagnoses based on the presented chart records. We inject frequent reminders of the previously taught basic physiological principles.

Clinical example 1: obstructive sleep apnea. PRESENTATION. John is an obese 37-yr old who has daytime hypertension and was referred to the sleep clinic based on his wife's complaints of "annoying snoring" and her worries that he is "choking at night." John is also excessively sleepy to the point that his work performance has decreased and he has had three minor car accidents in the last 2 yr because of falling asleep at the wheel. In the last month, after a period of weight gain, he has also woken up at night and then experienced chest pain and a racing heart. A physician who recognized potential signs of sleep apnea referred John to a sleep clinic.

CLINICAL PHYSIOLOGY. Figure 8 shows a sample record of the overnight traces from John's visit to the sleep laboratory. The physician recognizes several major points that confirm her initial diagnosis.

1) Note the repetitive drops in arterial O_2 levels in sleep, the first sign of a potentially serious breathing problem in sleep.

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2) The persistence of breathing movements during the hypoxia also suggests that even though the patient is attempting to breathe, the efforts are ineffective. The persistence of breathing movements indicates that an airway obstruction in sleep is the most likely cause for the breathing problem.

3) Note also that the abdominal and rib cage compartments of breathing (recorded from the bands placed around the chest; see Fig. 1) are out of phase, i.e., moving in opposite directions. This is further confirmation of an airway obstruction. Students readily appreciate this effect if they attempt to breathe with their nose and mouth closed. When they breathe against a closed airway in this way, they immediately notice that as the diaphragm distends the abdominal cavity, the rib cage gets sucked into the chest instead of normally expanding.

4) It is also apparent that during the period of airway obstruction, the respiratory efforts increase in response to the progressively worsening hypoxia. The recruitment of respiratory muscle activity can be seen from the progressively increasing abdominal signal and increasing opposite motion of the rib cage (sloped dashed lines in Fig. 8). However, although the classic respiratory response (Fig. 7, *A* and B) is to increase respiratory efforts in the face of worsening hypoxia, these efforts are ineffective because the upper airway remains collapsed.

5) It is not until the patient awakes that the pharyngeal obstruction is relieved, because wakefulness increases pharyngeal muscle tone and opens the airway. This observation highlights the importance of arousal mechanisms in respiratory physiology. As Phillipson and Bowes said some time ago, *"arousal from sleep in the presence of oro-nasal occlusion by a pillow allows the pillow to be removed whereas the ventilatory response alone (increasing respiratory efforts against the occluded airway) may be futile!"* (8).

6) At each awakening after an obstruction, the snoring is very loud and can reach up to 100 dB. This sound intensity is similar to that of crowd noise in a loud sports arena or a jet flying overhead and can be recorded with a common sound meter (Fig. 8). No doubt, this is the reason that the bed partner complained of "annoying snoring." The repeated arousals from sleep after each obstruction, however, produce excessive daytime sleepiness in the patient, and this inattentiveness increases the risk of accidents.

7) Note that after the arousal from sleep, there is a surge in heart rate and blood pressure. These cardiovascular effects of arousal highlight that sleep is not a state of cardiovascular rest in such patients. Moreover, after arousal triggered by respiratory distress and sleep-related asphyxia, blood pressure and heart rate surge at a time when blood O_2 levels are still low (Fig. 8). However, at this time, the O_2 requirements of the heart muscle are high because the heart is beating at a fast rate and against a high resistance due to the surge in blood pressure. These effects pose increased risk for myocardial infarction in individuals with underlying heart problems.

This example of obstructive sleep apnea serves to highlight the integration of the previously discussed physiological processes. This example is also useful because airway obstructions can occur hundreds of times per night and, thereby, produce repeated episodes of nighttime asphyxia, sleep disturbance, and hypertension, leading to increased risk of stroke, angina, and tiredness-related accidents (9). Such disorders can affect at least 4% of adults (16) and are therefore as highly prevalent as more recognized disorders such as diabetes. It is also useful to remind students that because of the suppressed ventilatory and arousal responses to stimuli, such as hypoxia in REM sleep (Fig. 7), the respiratory problems associated with airway obstructions are typically worse in this state compared with non-REM sleep. As an additional anecdote, we also mention that alcohol can act to suppress pharyngeal muscle activity so that after alcohol consumption, individuals who would normally have no breathing difficulties at night may start to snore because of partial airway obstruction or may even have full airway obstructions.

TREATMENT. Airway obstruction in this clinical example is in the pharynx and is caused by relaxed pharyngeal muscles. The most common and effective treatment is for the patient to sleep with a small mask over the nose, with the inlet connected to a source of positive-airway pressure. Such pressure, applied to the pha-

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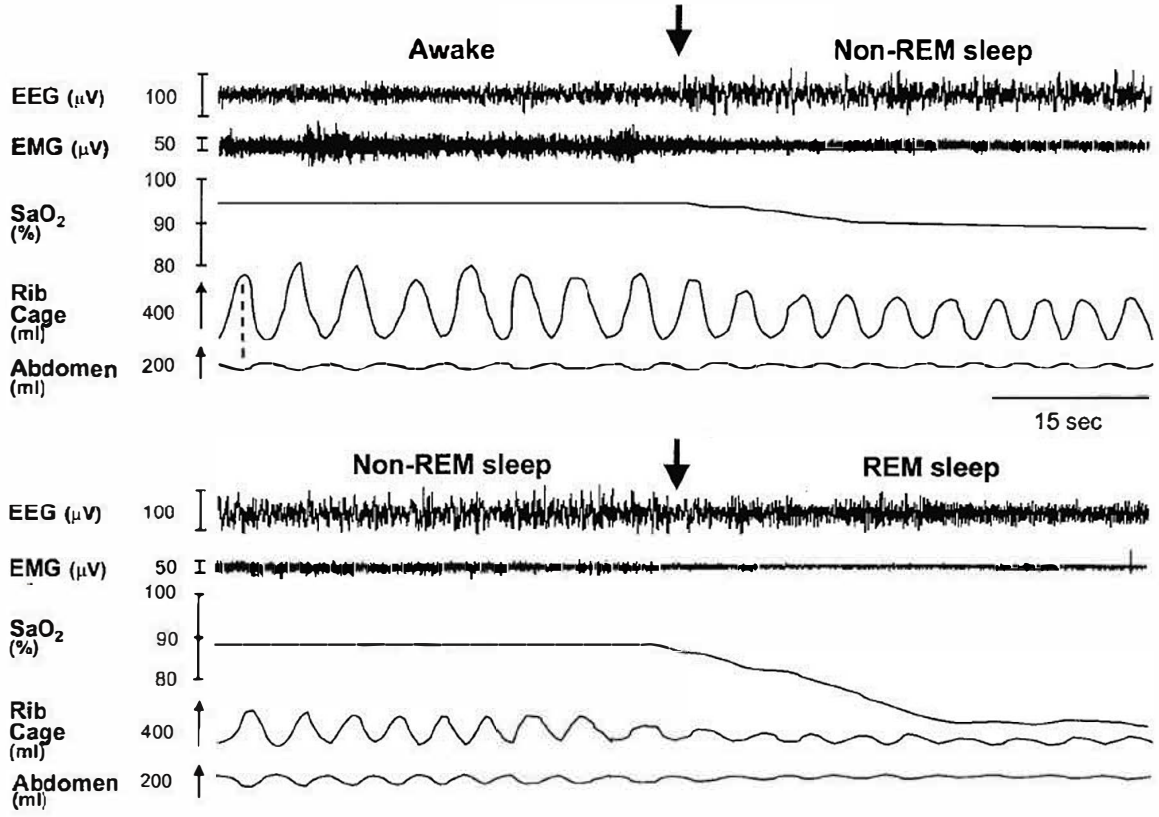

FIG. 9.
Sample record of the overnight traces in a patient with partial diaphragm paralysis. See text of *Clinical example 2* for specific points of interest. The arrows indicate transitions from wakefulness to non-REM sleep and from non-REM to REM sleep, respectively (as determined from the EEG and EMG traces).

ryngeal airway, keeps this essential passage open (15).

Clinical example 2: partial diaphragmatic paralysis. PRESENTATION. Jane is a 22-yr old who suffers from partial diaphragmatic paralysis after a car accident in which the phrenic nerve was damaged in a traumatic neck injury. Since the accident, Jane has had trouble sleeping and frequently awakes gasping for breath. This problem occurs in cycles, approximately every 1–2 h when asleep. Initially, her doctor thought that her problem was associated with posttraumatic stress. However, after a life-threatening event when she was in near respiratory failure and hospitalized, a nurse noted that her face and fingertips became blue at night at times when she had difficulty breathing. She was subsequently referred to a sleep laboratory for tests of breathing during sleep.

CLINICAL PHYSIOLOGY. Figure 9 shows a sample record of the overnight traces from Jane's sleep and breathing test. The physician recognized several major points that suggest a problem arising from the interaction between sleep mechanisms and motor control.

1) Note the normal levels of arterial O_2 saturation in wakefulness suggesting that ventilatory compensation is normal during wakefulness despite the partial diaphragm paralysis.

2) Notice, however, that in this patient, the rib cage compartment is predominantly responsible for pro-

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ducing breathing movements in wakefulness. This can be explained once it is appreciated that the intercostal muscles are used for respiration in the face of diaphragm paralysis. Also, as in the previous clinical example, note the out-of-phase motion of the rib cage and abdominal signals (denoted by the dashed line). It should be noted, however, that in this case, it is the abdominal compartment that is sucked during breathing due to the flaccid diaphragm.

3) Blood O_2 saturation falls slightly but not dramatically from wakefulness to non-REM sleep. Nevertheless, this is somewhat abnormal because she had a normal starting position on the oxy-hemoglobin dissociation curve. This clinical observation implies that in this patient, ventilation is decreasing more than normal from wakefulness to non-REM sleep. The probable cause of this excessive decline in ventilation is that the patient is relying on the intercostal muscles for breathing. These muscles have dual respiratory and postural functions and are therefore more prominently affected by sleep. In this patient, the intercostal muscles have reduced activity during sleep, and the resulting slight hypoxia and probable hypercapnia do not elicit an appreciable ventilatory response because such responses to altered blood gases are also reduced in sleep (Fig. 7, *A* and *B*).

4) However, this patient has major difficulties in REM sleep. One reason is that intercostal muscle activity, on which she is relying for effective breathing, decreases in REM sleep because the intercostals, like other muscles with tonic, postural inputs, become actively inhibited. In the sleep laboratory, this inhibition of intercostal activity is observed as small excursions of the rib cage bands during breathing in REM sleep compared with non-REM. Compensatory chemoreflex responses to override the hypoventilation are severely compromised in this patient because the paralyzed diaphragm cannot be activated and the intercostal muscles are inhibited during REM sleep. In this patient, the hypoxia becomes so severe that only arousal can restore effective breathing, because the intercostal muscles can then be recruited in wakefulness as they are released from the inhibitory mechanisms operative in REM sleep. At this time, the patient has the sensation of gasping for breath and suffocation. An additional complication is that in time, tiredness and sleep disruption can lead to greater tolerance of more severe hypoxia and desensitization of the mechanisms that trigger awakening. This problem can eventually progress to respiratory failure.

TREATMENT. Because the primary cause of this clinical problem is the neural effects of REM sleep on respiratory muscle activity in the absence of the diaphragm, there are two obvious potential treatments. First, we could prevent REM sleep, although this is not the treatment of choice because the long-term effects of REM sleep deficit are not well understood. Second, we could provide artificial ventilation to the patient by using a ventilator. This second choice is better as new developments in ventilator technology now allow the detection of insufficient breathing and provide compensatory artificial respiration only as needed.

Clinical example 3: chronic bronchitis. PRESENTATION. George is a 60-yr old who is a chronic smoker with lung disease. He has resting hypoxemia and hypercapnia and has been admitted several times to hospital in respiratory failure. His physician suspects nighttime breathing abnormalities may contribute to his respiratory problems and therefore organizes a sleep study.

CLINICAL PHYSIOLOGY. Figure 10 shows a sample record of the overnight traces from George's test. The results confirm the physician's fears but also suggest that giving this patient inhaled O_2 to correct the hypoxemia will be less than simple.

1) Note that levels of arterial O_2 are low in wakefulness but that this hypoxemia is worse in sleep, especially REM sleep. This can be explained on the basis of the starting position on the oxy-hemoglobin dissociation curve (Fig. 7*C*). This curve shows that a normal decline in lung ventilation from wakefulness to sleep produces a major decrease in arterial O_2 saturation if starting O_2 levels are low (a simple reminder to the student is that a similar situation occurs at altitude).

2) The hypoxia and hypercapnia are even worse in REM sleep as the ventilatory responses to these altered blood gases are minimal in this state and arousal responses are reduced.

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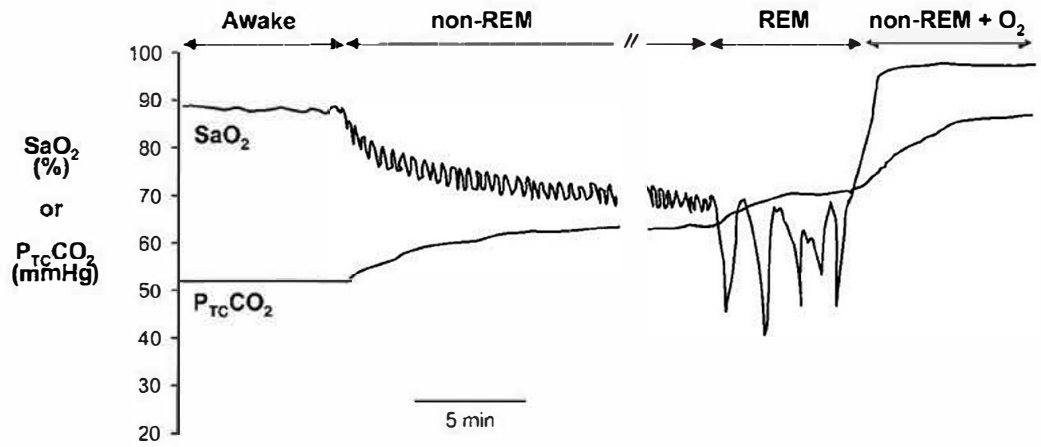

FIG. 10.
Sample record of Sa_{O_2} and transcutaneous PCO_2 ($P_{TC}CO_2$) across sleep-wake states in a patient with existing lung disease due to chronic bronchitis. See text of *Clinical example 3* for specific points of interest.

TREATMENT. The students are initially reminded that the peripheral chemoreceptors are responsible for the respiratory responses to hypoxia. In this patient, correction of hypoxia by inhaled O_2 restores arterial O_2 levels to normal (Fig. 10). However, because his ventilation is being driven largely by hypoxia, the CO_2 levels have a tendency to rise as this hypoxic drive is removed. The physician, therefore, has to keep a careful watch on the degree of hypercapnia that develops during such treatment with O_2, because CO_2 at too high a level can act as a narcotic.

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