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Insomnia with Sleep Apnea: A New Syndrome

Abstract. *A new clinical syndrome, sleep apnea associated with insomnia, has been characterized. Repeated episodes of apnea occur during sleep. Onset of respiration is associated with general arousal and often complete awakening, with a resultant loss of sleep. An important clinical implication is that patients complaining only of insomnia may be suffering from this syndrome.*

Although patients who complain of insomnia have been studied in this laboratory for several years, we only recently began to include respiratory studies routinely. Using these procedures, we discovered a new syndrome —insomnia with sleep apnea—which is associated with dramatic sleep disturbances.

Sleep apneas have been reported in the cardiopulmonary syndrome of obesity ("Pickwickian") and in other syndromes involving hypersomnia, such as narcolepsy (*1*, *2*). The apneas in hypersomniacs seem to be temporally associated with sleep. Several distinct types of sleep apnea have been defined in these conditions (*2*). They include a "central" type, characterized first by cessation of breathing and then, after the apnea, by a simultaneous resumption of diaphragmatic movements and oral airflow; an "obstructive" or "peripheral" type, characterized by the interruption of airflow secondary to upper airway obstruction, but with continuance of diaphragmatic and thoracic muscle contraction; and a "mixed" type, characterized by an initial central apnea followed by temporary upper airway obstruction at the subsequent resumption of diaphragmatic movements.

We now report observations in two insomnia patients who presented symptoms we have designated as a syndrome of sleep apnea and insomnia. This syndrome can most readily be diagnosed with continuous all-night polygraphic recordings of sleep and respiration.

The patients were males, 57 and 54 years of age. Patient 1 gave a 20-year history of several arousals during the night and difficulty in maintaining his sleep, particularly between 3 and 6 a.m. He noted that he awakened himself and disturbed his wife by his snoring. After we completed our work-up, his wife mentioned that, on several occasions in past years, she had noticed a cessation of her husband's respiratory movements while he was asleep. This patient had taken many types of sleeping pills and reported that barbiturates and chloral hydrate were not only ineffective, but also increased his sleep problem. The sleep problem of patient 2 progressively developed over the past 25 years. He complained of several awakenings during the night and early morning arousals from which he found it very difficult to return to sleep. Finally, his wife complained about his snoring.

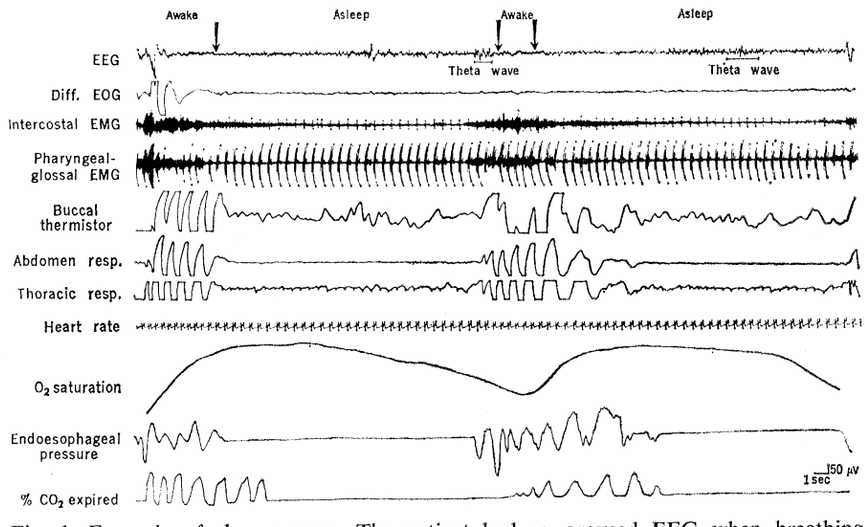

Fig. 1. Example of sleep apneas. The patient had an aroused EEG when breathing and sleep apnea when he fell asleep. There was no real increase in the endoesophageal pressure when he was breathing again. This is a central type apnea. The percentage of expired CO_2, determined from the nostril, shows that the air is expired with a delay directly related to physiological "dead space." Abbreviations: *Diff. EOG*, differential electrooculogram; *EMG*, electromyogram; and *resp.*, respiration.

Our studies during wakefulness included determinations of lung volume, ventilatory mechanics, elastic recoil, airflow resistance, and arterial blood gases. Patient 1 also participated in a more extensive cardiopulmonary study. A multilevel exercise study was conducted, with measurements of the ventilatory response to CO_2. Arterial blood was collected by means of a catheter introduced by percutaneous technique into the brachial artery, with P_{O_2}, P_{CO_2}, and *p*H determined by standard methods. Results of all these tests were well within normal limits during wakefulness. In addition, a posthyperventilation breathing test as described by Plum *et al.* (*3*) was also normal. Cardiac catheterization was performed by floating a Swan-Ganz catheter into the pulmonary artery through an antecubital vein. The catheter was positioned at 3:00 p.m., and continuous recording of pulmonary artery pressure was made over the next 18 hours. As in the other tests, these results were normal during wakefulness.

While the patient was in bed for the night, an ear oxymeter continuously measured arterial oxygen saturation. Arterial blood samples were drawn periodically throughout the night so that the oxymeter could be accurately calibrated. A catheter-tip pressure transducer (Bio-Tec-BT5F) was positioned in the lower esophagus for the recording of intrathoracic pressure changes (*4*), which facilitated accurate determination of the type of apnea involved. Several 0.2-mm wire electrodes were inserted in cricopharyngeal and intercostal muscles for electromyographic recording. A four-channel Sanborn polygraph and a Grass model 7 polygraph were used for the continuous all-night recordings.

Before the respiratory studies, documentation of the insomnia in each patient had been obtained during several all-night or 24-hour sleep studies. However, in the absence of ventilation recordings, the respiratory abnormalities reported here were not appreciated. During the most recent studies with

simple respirograms, the following data for the second night were tabulated for patients 1 and 2, respectively: total time in bed, 400 and 440 minutes; total sleep time, 317 and 226 minutes; and total time awake after sleep onset, 75 and 213 minutes.

It became apparent that these patients had abnormal respiration during their sleep, with frequent and repeated periods of apnea. Recordings of intrathoracic pressure permitted accurate determination of the length of each apnea and the correlation with electroencephalographic (EEG) arousal. The sleep disturbance was directly associated with the apneas (see Fig. 1). Apnea appeared only during a sleep period, and either an arousal or change to lighter sleep preceded or coincided with the end of an apneic period. For example, 200 arousals were scored during 1 night in patient 1, and 42 percent of his sleep time was spent in apnea (average of 3 nights). The apneic periods appeared to be associated less with rapid eye movement (REM) sleep than with non-REM (NREM) sleep; that is, 21 percent of REM sleep and 47 percent of NREM sleep were spent in apnea (Fig. 2).

In spite of these pervasive apneic disturbances, the patients continued to show cyclic REM periods, although there was a marked reduction of NREM stages 3 and 4. The EEG also showed a pattern of slow delta type waves, as reported by Hishikawa *et al.* (*2*) in the cardiopulmonary syndrome of obesity (Pickwickian). These waves always appeared at least 15 seconds after the onset of an apnea and disappeared coincident with the onset of respiratory movements.

Our records indicate that all apneas were largely central in origin, with peripheral airway obstruction playing a negligible role. The mean duration of apneas was 30 seconds. However, the range was from 20 seconds to an extraordinarily high value of 150 seconds. Oxygen levels continuously oscillated during the periodic breathing, rising to 92 mm-Hg after hyperpnea and falling after apnea to as low as 45 mm-Hg. Concurrently measured arterial P_{CO_2} showed an inverse relation to P_{O_2}, ranging from 35 to 40 mm-Hg after hyperpnea to as high as 57 mm-Hg after a long apneic period. Periods of repetitive apnea often lasted for 20 to 30 minutes. The cyclic recurrence of apneas was ended only by complete conscious arousal of the patient for 5 to 15 minutes. However, not all apneas were recurrent. Occasionally during the night, short apneic periods would interrupt normal breathing.

One of the most striking findings in the patient who underwent cardiac catheterization was a rise in pulmonary artery pressure during sleep. Significant periods of increased systolic pulmonary artery pressures (up to 30 mm-Hg) with no increase in diastolic pressure were observed during the night. This suggests an increased cardiac output. When apnea occurred at these times, there were further increases in both systolic and diastolic pressures (to as high as 52 mm-Hg systolic and 20 mm-Hg diastolic) coincident with the development of hypoxemia (Fig. 3).

Could these blood and cardiovascular changes associated with apnea lead to permanent damage of the pulmonary vascular bed? Although this possibility has recently been raised (*5*), it has not been proved that these transient changes would be damaging. Nevertheless, it is possible that they might exacerbate other pathological conditions in a patient.

We recently studied a third patient by the same cardiorespiratory sleep protocol. This patient had complained of insomnia for more than 25 years. His symptoms were similar to those of our previous patients, with many arousals during the night and early morning. He reported that his condition was aggravated each time he was treated with a central nervous system depressant or hypnotic. His recordings showed the same types of respiratory and sleep abnormalities. Total time in bed was 539 minutes, total sleep time was 384 minutes, and total time awake after sleep onset was 155 minutes. During 3 nights of recording, the mean number of arousals per night was 235. Arterial P_{O_2} fell to as low as 42 mm-Hg during apneas that lasted as long as 185 seconds. However, the interpretation of the condition in this patient was complicated by the fact that several electrocardiograms in the past 2 years have shown abnormalities indicating left ventricle failure.

Although the circulatory abnormalities related to this patient's cardiac condition make it difficult to assign the aforementioned causal mechanisms to his apnea, it was nevertheless clear that the insomnia was related to the sleep apnea. The possible interaction of sleep apnea and insomnia with cardiovascular disease should be considered, as

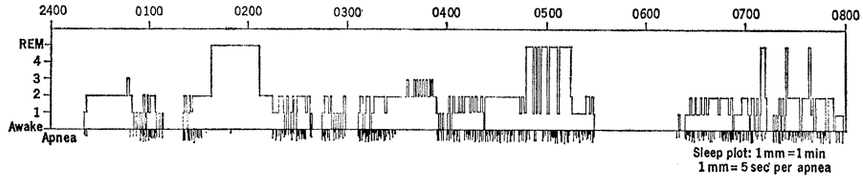

Fig. 2. Graph summary of the temporal pattern of apneic events in patient 1 during the second night of the last recording.

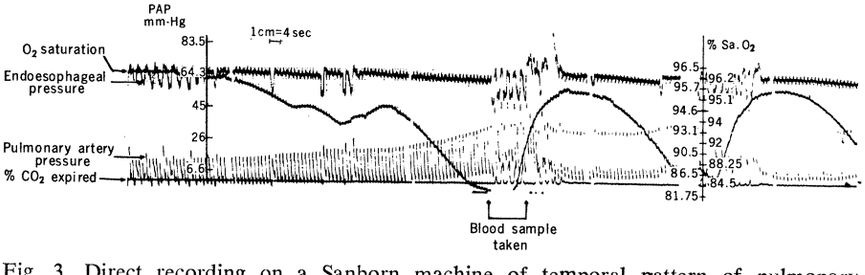

Fig. 3. Direct recording on a Sanborn machine of temporal pattern of pulmonary artery pressure in apneic episodes. The uppermost line indicates a complete cessation of diaphragmatic movement. Diaphragmatic movements appear occasionally during the first apneic episode, and the O_2 saturation ($Sa.O_2$) curve correlates highly with the respiratory movements. The O_2 saturation curve was calibrated by means of several blood samples. Blood gas measurements from this sample had the following values: arterial oxygen, 51.5 mm-Hg; arterial carbon dioxide, 41.0 mm-Hg; O_2 saturation, 91.75 percent; and *p*H 7.30. The pulmonary artery pressure (*PAP*) increased during the apneic episodes. Systolic pulmonary artery pressure before sleep apnea was 14 mm-Hg. At the end of sleep apnea, systolic artery pressure was 30 mm-Hg and diastolic pulmonary artery pressure was 5 mm-Hg. After the first two respiratory movements at the end of sleep apnea, systolic and diastolic pulmonary artery pressures were 47 and 16 mm-Hg, respectively. At the beginning there was an increase of systolic pulmonary artery pressure with no increase in diastolic pressure, which suggests an increased cardiac output. Furthermore, when hypoxia became more severe, diastolic pulmonary artery pressure also increased.

should the possibility that nighttime death in some such patients could be related to sleep apnea.

One obvious and important conclusion can be drawn from our data. An unknown percentage of the larger number of patients complaining of chronic insomnia have profound disorders of respiratory control mechanisms (*6*). There is probably a functional association between the sleep disturbance giving rise to the complaint and the apnea. Our patients have not only nocturnally disrupted sleep, but also long periods of conscious arousals (Fig. 2). Yet, until now, their respiratory problem has been completely occult. We feel that respiratory function during sleep should be evaluated in patients who complain of chronic insomnia characterized by several conscious arousals throughout the night and early morning and who also have a short latency before onset of sleep and a history of heavy snoring.

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6. All sleep studies at the Stanford Sleep Disorders Clinic now include measurement of respiration. The three patients with sleep apnea mentioned in the text were found among an unselected group of the last 30 insomniac patients who underwent all-night sleep recordings.
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Infusion of 2-Deoxy-D-Glucose into the Hepatic-Portal System Causes Eating: Evidence for Peripheral Glucoreceptors

Abstract. *Injections of 2-deoxyglucose into the hepatic-portal system of normal rabbits increased eating to a greater extent and with shorter latency than comparable injections of 2-deoxyglucose into the jugular vein or into the hepatic-portal circulation of the vagotomized rabbit. These differences suggest the existence of vagally mediated peripheral glucoreceptors important in the initiation of food intake.*

The glucostatic theory is a leading hypothesis for the explanation of the short-term control of hunger. One corollary of this theory is that central glucoreceptors signal satiety when glucose utilization is elevated (*1*). Experimental verification of the central loci of glucose-sensitive satiety neurons, however, has not been solidly established (*2*). The existence of peripheral glucose-sensitive areas has also been suggested by Russek and his colleagues (*3*) who have observed that reversible block of the vagii produces a short period of aphagia and that vagal transsection results in a temporary but longer-lasting hypophagia. Niijima (*4*) using an isolated liver preparation has shown that glucose-sensitive fibers are present in the vagus nerve. Hepatic glucoreceptors may, therefore, be important in the control of hunger.

Our experiments represent an attempt to demonstrate peripheral mechanisms that increase food consumption as a result of infusion of 2-deoxy-D-glucose (2DG) in the hepatic-portal system. Glucose utilization at the phosphohexoseisomerase level is blocked by systemic injections of 2DG, and this, in the intact animal, promotes hyperglycemia and deposition of glycogen in the liver (*5*). Cells should, therefore, become deprived of glucose after infusions of 2DG and increased eating should occur according to the glucostatic theory. Indeed, many investigators have shown that increased eating occurs in response to the administration of 2DG; however, all have attributed the effect to central "glucoprivation," although the possibility of peripheral synergism was not ruled out (*6–8*). If there are glucoreceptors in the liver which act on hunger, 2DG, by blocking glucose utilization of the cells in the capillary bed of the hepatic-portal system, should have an early and potent effect on food intake.

The initial experiment was performed with eight female (New Zealand) rabbits with cannulas permanently implanted into one of the larger collecting veins draining the duodenum and threaded as far downstream as possible. This procedure ensured that materials delivered to the cannula perfuse the liver first through the hepatic-portal system. The other end of the cannula was fixed by dental cement to the animal's skull, and the tubing was kept beneath the skin. The subjects were allowed at least 1 week for recovery by which time all animals were eating normally. At this time, infusions of 2DG and equiosmotic saline in counterbalanced order were begun. No infusions of 2DG were made within 4 days of each other because 2DG produced altered food intakes for the next 1 or 2 days. When infusions of 2DG or saline were not made, the cannulas were flushed with saline solutions containing heparin. Infusions were maintained at 1 ml/min with a Harvard Apparatus infusion pump attached to a long section of tubing ending in a needle which was inserted into the intravenous cannula. This allowed injections to be made painlessly in the unrestrained rabbit. The animals were given free access to food and were injected during the morning hours between 9:00 and 11:00 a.m. After the injection, hourly food intakes were recorded for the next 3 hours, and the latency between the beginning of injection and the initiation of feeding was measured. The definition of the initiation of a meal was the interruption for 1 minute of the beam of a photo cell mounted on the entrance to the feeding box. This was associated with at least 0.5 g of food intake. Also, daily food intakes were always recorded.

The infusion of a 7.5 percent (weight to volume) solution of 2DG (250 mg per kilogram of weight) caused eating in all eight animals within a range of 6 to 14 minutes after the beginning of