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SLEEP APNEA SYNDROMES



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SLEEP APNEA SYNDROMES

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Clinical Overview of the Sleep Apnea Syndromes

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In the last six years over 150 patients presenting a sleep apnea syndrome have been seen at the Stanford Sleep Disorders Clinic. Although the nature of our clinical work-ups and the variables monitored during sleep have changed over the years as our knowledge of the syndrome has increased, the diagnosis in each case was based on at least one nocturnal polysomnogram. This diagnostic measure also permitted subdivision of patients into three major categories based on the predominant type of apnea seen during an eight-hour nocturnal polygraphic monitoring. The standard protocol included electroencephalogram (C_3/A_2 or C_4/A_1 of the International 10-20 System), chin electromyogram (EMG), and eye movement (electrooculogram) for determination of sleep stages. Respiratory effort was monitored by strain gauges (abdominal and thoracic) and respiratory airflow by thermistors (nasal and buccal). Blood oxygen saturation was measured by an ear oximeter. The electrocardiogram was also monitored systematically on all patients. Depending on the protocol (clinical or research) other variables have been monitored, including hemodynamic (pulmonary and femoral arterial pressures, cardiac output), respiratory (expired CO_2), electromyographic (intercostal, diaphragmatic, laryngeal, pharyngeal muscles), oximetric (arterial oxygen electrode, multiple blood gases), and endoesophageal values. Some patients were monitored for as long as ten successive 24-hour periods or for 24 nearly successive nocturnal periods — four nights a week for six weeks. Results of these studies will be presented in following chapters.

We have tried to obtain a clinical profile of sleep apneic patients by reviewing the charts of our many patients.

TERMINOLOGY AND DEFINITIONS

An apnea has been defined as cessation of airflow at the level of the nostrils and mouth lasting at least ten seconds. A sleep apnea syndrome is diagnosed if, during seven hours of nocturnal sleep, at least 30 apneic episodes are observed in both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, some of which must appear repetitively in NREM sleep. Apneic episodes at sleep onset or accompanying bursts of rapid eye movement in REM periods are not considered pathological. In one study, we monitored 20 normal control subjects (between 40 and 60 years of age) over four consecutive eight-hour nocturnal sleep periods. This study disclosed a mean number of apneic episodes per night of 7 (range 1–25) in men and 2.1 (range 0–5) in women. All apneic episodes in this group were seen during REM sleep or at sleep onset. In our controls, apneic episodes were never recorded in stages 2, 3, or 4 NREM sleep.

The smallest number of apneas ever recorded in one individual considered “sleep apneic” was 45 during 245 minutes of nocturnal sleep, or 11 apneas per hour of sleep. (We feel that the use of an “Apnea Index,” ie, the number of apneas per sleep-hour, frequently gives a better indication of the seriousness of the disorder). This lowest number of apneas in a patient can be compared to a maximum of four apneas per sleep-hour in one of our male controls (mean 0.5 apnea/hour).

With strain gauge and thermistor recording techniques, three types of apnea have been defined. Central apnea is characterized by cessation of both airflow and respiratory movements. In obstructive (or upper airway) apnea, airflow past nasal and buccal thermistors is absent despite persistent respiratory effort recorded by thoracic and abdominal strain gauges. Mixed apnea is defined by cessation of airflow and an absence of respiratory effort early in the episode followed by resumption of respiratory effort in the latter part of the episode that eventually reestablishes airflow.

The number of apneic episodes varied from night to night and from patient to patient. A likely factor in such variability was the amount of externally induced sleep disturbances such as equipment- or protocol-directed arousals. In any case, we have never seen marked changes in percentage of “apnea per sleep-hour” during time intervals free of external disturbance. Patients diagnosed with “sleep apnea syndrome” always presented an abnormally elevated apnea index and a similar predominant type of apnea (central, mixed, or obstructive). We have never observed only one type of apnea during a nocturnal polygraphic recording; however, a predominant type usually could be easily identified.

PATIENT POPULATIONS

Sleep apnea may be seen in patients with damaged respiratory centers in the brain, as in bulbar poliomyelitis, brain stem infarct, bilateral cordotomy, Ondine’s

curse syndrome, and Shy-Drager syndrome. It may also occur with drug intoxication (barbiturates and tranquilizers) and with abnormalities of the breathing apparatus, as in muscular dystrophy, kyphoscoliosis, Pierre-Robin syndrome, obstructive lung diseases, etc. Some of these entities are considered in other chapters. The 150 patients reported here did not fit into the above diagnostic categories. Forty patients presented a combination of sleep apnea syndrome and narcolepsy. We will not deal here with the relationship between these two disease entities other than to note that both of them are associated with marked disturbances of sleep. Patients with this combination will be separated from the "pure" sleep apnea syndrome patients.

Two major subcategories are distinguished, based on the predominant type of sleep-induced apnea: obstructive and central sleep apnea.

Predominantly Obstructive Sleep Apnea Patients

Fifty patients in this category have been reviewed. All of them are adults, with ages ranging between 28 and 62 years (mean age 45.5 years). Forty-eight patients are male; the two female patients were 58 and 61 years of age, respectively, at the time of referral.

Causes for referral. Thirty-nine patients, including both women, were referred for a chief complaint of excessive daytime sleepiness. One patient sought consultation because at night during sleep he gasped for breath and felt nauseated. One patient was referred because of an abnormal electrocardiographic Holter monitoring during sleep and loud snoring. One patient was referred for essential hypertension and loud snoring. In another patient, referral was instigated because of morning headaches and confusion, and loud snoring at night. In seven patients, the referral complaint came from the spouse: Patients were referred by their wives after the latter had read articles in the lay press relating abnormal behavior during sleep, observation of apnea, and loud snoring at night.

Race. Four patients were black, four were Mexican-Indian, and 42 were white.

Weight. Ten patients were of normal weight (as computed in Metropolitan Life Statistical Bulletin [1] corrected for age and height); ten patients (20%) were 5 to 15% overweight; 15 patients (30%) were 16 to 30% overweight; and 20 patients (40%) were 31 to 400% overweight. Five patients in this last group had been labeled Pickwickian (Burwell type).

Clinical symptomatology. Loud snoring. During sleep, all patients had noisy, pharyngeal snoring associated with snorting and interrupted by silences (apneic episodes) of 15 seconds or longer. This symptom was reported as a source of embarrassment and annoyance. Snoring was first noted during childhood in 52% of the cases and before 21 years of age in 94%.

Excessive daytime sleepiness. Thirty-nine patients (78%) complained of excessive daytime somnolence and sleep attacks. Nine patients (23%) had complained of this symptom for longer than ten years, ten patients (26%) for five to ten

years, and 20 (51%) for one to five years. Specifically, the patients complained of sudden excessive drowsiness occurring at inappropriate times and producing an irresistible urge to sleep. Twenty-seven patients (54%) had had automobile accidents, and one was nearly struck by a train at a railroad crossing because of his inappropriate sleepiness. Sixteen patients (32%) had difficulties at work or were on the verge of losing their jobs because of daytime sleepiness; seven (14%) were totally unable to work and received disability assistance. Of the 11 patients who denied daytime somnolence, interviews with the families revealed that four of them frequently took naps at work, fell asleep on the couch almost daily while watching television, and often fell asleep while reading the newspaper or when riding in a car.

Excessive daytime sleepiness was accompanied by hypnagogic hallucinations in 22 patients (44%), and automatic behavior was reported by 29 patients (58%).

Intellectual deterioration. This complaint was closely related to automatic behavior. All 39 patients with daytime somnolence reported difficulty in focusing their attention and an inability to concentrate, particularly during the early afternoon hours when somnolence was at its peak. For 12 patients (24%) these problems were more troublesome in the morning hours. Two patients who did not complain of daytime somnolence experienced similar clouding of intellect and deterioration of memory and judgment in the morning. Two patients seemed so confused in the early morning that a brain tumor was suspected.

Personality changes. The families of 24 patients (48%) reported disturbing changes in the patient's personalities; eight patients (16%) had seen psychiatrists for anxiety and/or depression. The personality changes were responsible for three broken marriages in this series. Analysis of Minnesota Multiphasic Personality Inventory (MMPI) profiles in patients revealed abnormal (t scores greater than 70) elevations on at least one clinical scale in 17 patients (34%). Elevations occurred on the depression scale in 12 patients (24%) and on the anxiety scale in 13 (26%). Noticeable confusion, hostility, marked irritability, and aggressiveness were observed in nine patients.

Fourteen spouses (28%) reported dismay at outbursts of completely irrelevant behavior in patients. They reported sudden episodes of jealousy, suspicion, and irrational behavior toward their children. At times the behavior resembled a persecution reaction. These behaviors, in all cases, were totally unlike the patient's normal behavior pattern.

Sexual functioning. Twenty-one patients (42%) reported impotence. These patients noted a diminished libido and difficulty in obtaining erection and ejaculation. Nine of the 21 patients were under 46 years of age.

Nocturnal enuresis. Fifteen patients (30%) complained of intermittent enuretic episodes; four of them had sought urologic evaluations for this complaint.

Morning headaches. Eighteen patients (36%) had recurrent morning headaches that were described as frontal and occasionally diffuse. The headaches, like the nocturnal enuresis, had appeared gradually and intermittently over the years, but had usually become more noticeable during the 18 months before evaluation. Both headaches and enuresis were reported primarily by the overweight patients (88% of the patients were moderately to heavily obese).

Morning nausea. Four patients (8%) reported this symptom. It was the major complaint and cause of referral in one patient.

Abnormal motor activity during sleep. These reports were obtained from spouses and bed partners. All of these patients (100%) moved abnormally during sleep, and some had done so for as long as 34 years. This behavior was observed in every patient during the polygraphic recordings. A patient's sleep is extremely agitated during periods of repetitive apneas; there are frequent abnormal movements, either simple movements of the extremities or gross movements of the whole body. The sleeping patients often unwittingly kicked or slapped their bed partners during large movements of the arms and legs, and this, along with the heavy snoring, led to separate beds for 15 couples. Patients would also sit up abruptly during sleep, as if struggling for breath. Falling out of bed and sleepwalking episodes occurred with varying frequency (weekly to once every six months) in 27 cases (54%). Patients often bruised themselves, and in one case, a humeral fracture was sustained. During these episodes patients might talk or mumble unintelligibly. Patients could not be awakened during these episodes and often spent part of the night sleeping on the floor where they had fallen.

Neck and face. None of our patients could be considered as presenting Pierre-Robin syndrome. However, the two women (4%) fit the "bird-like face" description (see Chapter 17), and 19 men (38%) had a short neck although no obvious cervical abnormalities were detected by standard X ray.

Hypertension. Twenty-six patients (52%) were hypertensive, usually moderately (systolic range 210–150, diastolic range 120–95); ten patients were under treatment for high blood pressure. Seven patients also had pretibial and ankle edema, and five patients had enlarged livers with hepatojugular reflux.

Neurological evaluation. None of the patients had any neurological defect during wakefulness, and EEGs performed during the daytime were within normal limits.

Nocturnal polygraphic recordings. All patients under consideration here presented a predominance of obstructive (upper airway) apnea. Thirty-seven patients had continuous apnea throughout sleep. Their mean Apnea Index (number of apneas per sleep-hour) was 78 (range 48–160). The apnea durations ranged from ten seconds (by definition) to 92 seconds; the mean was 22 seconds duration. An average of 48% of total sleep time was spent without air exchange.

These patients always presented their longest apneic episodes during REM sleep.

Three patients had repetitive apneas during NREM sleep but had normal respiration during REM sleep. Their mean Apnea Index was 65 (range 48–79).

Ten patients had intermittent apnea during both REM and NREM sleep. Their mean apnea index was 42 (range 17–90). The longest apneas in this group were seen during REM sleep in eight cases out of ten. Stages 3–4 NREM sleep, not recorded in the first two groups, were observed in nine of these ten cases and represented a mean of 3% of total sleep time (range 0–6%). Very few apneic episodes were observed during stages 3–4 NREM sleep.

Relationship between weight and polygraphic findings. Patients of normal weight had as many total apneic episodes or as high an Apnea Index as overweight patients. A comparison was made between five normal-weight patients (mean 70.5 kg) and five obese patients (mean 112 kg) who had continuous apnea during sleep. The mean apnea duration was 22 and 21.5 seconds, respectively.

The ten patients who presented intermittent apnea during both NREM and REM sleep were placed on a drastic diet. Weight loss ranged from 20 to 45 kg in five patients. After weight loss, the Apnea Index improved: The mean Apnea Index was 32 before and 14 after the diet regimen. In these patients, obstructive apnea remained the predominant type. The patient's subjective complaint of daytime sleepiness greatly lessened after weight loss and was no longer considered a problem. However, two patients stated that they still felt "overly tired" at the end of the day and still napped regularly on weekends. No objective measurements of daytime sleepiness were obtained (see Chapter 3). Spouses reported that snoring was reduced and intermittent after weight loss. One reported that the symptoms were "less disturbing and more tolerable." Runs of cyclic sinus arrhythmia were still observed in conjunction with obstructive apneas (see Chapter 12). Apneas were observed during polygraphic recording of stage 2 NREM sleep and REM sleep. The longest durations of apnea occurred during REM sleep.

Two of the three patients with apnea occurring only during NREM sleep were placed on a diet for three months (mean weight before dieting was 76 kg). Their mean weight loss was 7 kg; there were no changes in symptomatology or polygraphic variables.

All patients with continuous apnea throughout sleep were placed on a diet. Some of these patients had been dieting for as long as five years. Three patients were hospitalized and maintained on a controlled diet of 800 calories per day for at least 45 days. Each lost over 30 kg without symptomatic improvement. Our most obese patients, despite rigorous diet supervised by the spouse and reportedly followed accurately, were unable to lose more than a mean of 3.5 kg in over four months. It should be emphasized that despite progressive weight increase with age, most of the obstructive sleep apneic patients and their families stated that overeating was the exception. In fact, most of our overweight obstructive sleep

apnea patients reported a continuous and increasingly difficult battle against weight gain since their late teens and had noted that their food consumption was considerably less than that of their peers.

Five grossly overweight obstructive sleep apneic patients (mean weight 115 kg) were compared to a group of five obese patients (three women and two men, mean weight 135.5 kg) who presented alveolar hypoventilation without obstructive apnea during sleep and who also complained of excessive daytime sleepiness. Polygraphic recordings revealed no statistical difference between total sleep time in the two groups. No stages 3–4 NREM sleep occurred; the mean total stage 1 NREM sleep, an index of sleep disruption, was 12% in the first group (obstructive sleep apnea) and 13.25% in the latter. Patients with alveolar hypoventilation had more notable respiratory acidosis during the daytime than sleep apneic patients. The $p\text{CO}_2$ in the five sleep apneic patients was always below 55 mm Hg during sleep (mean 42 mm Hg during wakefulness) in contrast to a mean $p\text{CO}_2$ of 58 mm Hg during sleep in the second group (with a range of 51 to 62 mm Hg during wakefulness). During sleep, oxygen saturation varied much more in sleep apneic patients than in those with alveolar hypoventilation. In the former group, arterial oxygen pressure dropped to 25 mm Hg during REM sleep in association with the longest apneas. There were also fluctuations in the partial pressure of oxygen despite the fact that the mean PaO_2 was usually under 65 mm Hg during the entire sleep period. Hypoxemia varied less in the five obese alveolar hypoventilation patients, usually oscillating between 60 and 40 mm Hg, with low values also seen during REM sleep.

In summary, obese patients with alveolar hypoventilation presented less PaO_2 variation but more severe hypercapnia. Obese sleep apneic patients had marked blood gases variation related to sleep stages and apnea, as well as greater hypoxia and less hypercapnia.

Long-term follow-up of obstructive sleep apnea patients. Twenty-three of the patients reported above have had tracheostomies with positioning of a valve. All subjective symptoms have cleared after surgery. The longest patient follow-up in this group is four years, the shortest one month (see also Chapters 12 and 24). Four other patients are now awaiting surgery. Two patients have had tonsillectomy and adenoidectomy, or submucous resection with marked improvement of symptoms. Two other patients first had similar treatment, did not experience significant subjective or objective improvement, and secondarily had a tracheostomy. Ten tracheostomized patients had previously had, or first requested, nasal repair surgery for deviated septum without improvement.

Three patients who declined surgery died during sleep within six months after diagnosis. Autopsy in two cases revealed no obvious cause of death; a cardiac factor was suspected.

Seven patients who declined surgery have had progressive worsening of their symptoms; one had myocardial infarction during sleep, and two are virtually

bedridden because of cardiac failure. Three patients receive disability payments, unable to lead normal lives because of their illness. The remaining patient of these seven, after three years of hesitation, has asked for a new evaluation and is reconsidering surgery.

The ten patients who had intermittent apnea during sleep have been placed under strict diet, medroxy progesterone, and/or aminophylline, and have been regularly followed. Under such a regimen, improvement has been observed as noted above.

We have lost contact with one patient.

Predominantly Central Sleep Apnea Patients

Ten patients with predominantly central sleep apnea were reviewed. All of these patients were male; one was black and nine were white. Their ages ranged from 27 to 79 years (mean 57). They seemed to be a more heterogeneous group than the predominantly obstructive one. In fact, this group could be divided into two subcategories: group A in which over 80% of recorded apneas were central type, and group B in which 50 to 60% of apneas were central with the rest mixed and/or obstructive. Seven patients (mean age 57) were classified group A; three patients (mean age 60) were included in group B.

Six of the seven patients in group A were referred to the Sleep Disorders Clinic for the complaint of insomnia, and one for sudden awakenings at night with a choking feeling and severe shortness of breath. The three patients in group B were seen for the complaint of excessive daytime somnolence combined with awakenings at night, shortness of breath, and gasping for air. Two of these three patients had a past medical history of head trauma, with loss of consciousness, 20 to 25 years before referral.

Clinical symptomatology. *Sleep complaint.* All patients had short sleep latencies, usually falling asleep in less than three minutes, but the majority of them woke up several times during the course of the night, sometimes gasping for air or with a feeling of choking. This feeling was frequently associated with anxiety which sometimes persisted for several minutes after awakening. None of the group A patients took naps during the daytime, and, although they reported feelings of tiredness and fatigue in the morning, none related this lethargy to their sleep complaint. Group B patients, who reported awakening during sleep — an event not perceived by predominantly obstructive patients — took naps during the daytime and also complained of daytime somnolence.

Snoring. All patients presented some degree of snoring when they started to breathe again, but snoring was frequently light and intermittent.

Depression. All patients showed an elevated depression scale (t score over 70) on the MMPI. Four patients recognized suicidal ideas related to their sleep problems which may have existed as long as 25 years before referral.

Sexual functioning. Four patients reported loss of libido and difficulty having an erection; this symptom may possibly be related to the patients' depressive reaction.

Physical aspects. All group A patients were of normal weight or were underweight for age and height. Faces and necks were normal. In group B, two patients were in the 5 to 15% overweight category. One patient had a relatively short neck.

Neurological evaluation. These examinations were within normal limits in all cases despite the reported head trauma in two patients.

Polygraphic monitoring. Nine of the ten patients had intermittent apneas. The mean Apnea Index was 49 with a mean duration of 30 seconds (range 10 to 180 seconds). The longest apneic episodes were seen in association with bursts of rapid eye movements during sleep. It is unclear why some apneic episodes led to a complete behavioral awakening several times during the night, but this did not seem to be related to hypoxia or hypercapnia; similar levels may occur at other times without leading to complete arousal.

Follow-up. One group B patient who had 52% central apnea and a short neck was recorded after intubation and demonstrated considerable improvement. Central apneas decreased, and he reported a decrease in daytime sleepiness the following morning. A tracheostomy was done after this trial. Central apnea was reduced only slightly at first, but three months later a greater reduction in the number of central apneas was observed, as if some central apneas had been induced by the respiratory problem, ie, some degree of obstruction. This patient's condition was suggestive of a vicious circle characterized by obstruction of the airway inducing slight hypoxia, hypercapnia, and acidosis, further depressing the central nervous system control of breathing and inducing central apnea. This progressive decrease of central apnea with time after tracheostomy was also observed in predominantly obstructive sleep apneic patients. None of the other patients, who presented larger percentages of central apnea, was improved by intubation.

Chemotherapy was instituted which included trials with aminophylline, theophylline, and naloxone intravenously during monitoring, and medroxyprogesterone and clomipramine orally. None of these drugs had a dramatic impact. The only drug which produced some positive results in two cases was clomipramine. It was given at doses between 75 and 125 mg at bedtime for three and five years, respectively, and reduced the mean Apnea Index from 42 to 7. However, the sexual side effects (impotence) of this drug limit its usefulness.

Some Special Cases

Narcolepsy and sleep apnea. The combination of the narcolepsy-cataplexy syndrome with sleep apnea is not uncommon; the most common association is

with central apnea. Narcoleptics frequently present respiratory pauses during REM sleep, more so than the control population. This is particularly obvious in women, where controls have a very low Apnea Index. But about 10% of our total narcoleptic group (20 patients) have an Apnea Index between 6 and 9, which is clearly above the normal range. These apneas are predominantly central (over 90% of recorded apnea), and the impact of these events on the sleep complaint is difficult to evaluate. The possible hemodynamics and cardiac impacts are reviewed in other chapters (see Chapters 11 and 12).

Five patients with narcolepsy had a combination of predominantly mixed and obstructive apnea. Loud snoring and abnormal nocturnal movements were noted during sleep in these patients, and moderate hypertension was present in three cases. Three patients were in the 5 to 15% overweight category (moderate obesity is frequent in narcoleptics without sleep apnea); the two remaining patients were of normal weight. One patient in this group had a tracheostomy which improved the excessive daytime sleepiness and the cardiovascular anomalies seen with repetitive apnea.

Acromegaly and sleep apnea. Two patients (one male and one female) presenting with typical acromegalic syndromes were referred for excessive daytime sleepiness. In one case the daytime somnolence was the symptom which led the patient to seek medical attention; in the other, acromegaly had previously been diagnosed. All symptoms reported above in the obstructive sleep apnea section were observed. The prognathism, macroglossia, and possible growth of hypopharynx soft tissue easily explain the development of obstructive components. As in some other cases of enlarged tonsils and adenoids and obstructive sleep apnea, we cannot yet explain the precipitating role of sleep in producing a complete obstruction ordinarily nonexistent during wakefulness.

Hodgkin disease, lymphoma, and obstructive sleep apnea. One patient with Hodgkin infiltration of the hypopharynx was also referred for excessive daytime sleepiness, loud snoring, and morning confusion. His obstructive Apnea Index was 65. This case should be related to the recent report by Zorick et al [2] of a typical obstructive sleep apneic symptomatology with lymphoma. Radiotherapy in this patient was helpful in relieving most of the symptoms.

CONCLUSION

The sleep apnea syndromes may induce life-threatening pathology (see Chapters 11 and 12) regardless of their diverse causes. Some cases of sleep apnea syndrome are related to micrognathia, acromegaly, and abnormally enlarged tonsils and adenoids, but frequently none of these is observed in our patients. Why are sleep apnea syndromes not seen in all patients with acromegaly or other reported anatomical causes? Is the syndrome in these cases overlooked by clinicians unaware of its existence and is it, in fact, more frequent than reported,

or are some persons particularly susceptible to airway closure during sleep, the anatomical factors then playing only a precipitating role or enhancing a mild defect existent during sleep? When no peripheral causes of obstruction can be found, why does predominantly obstructive sleep apnea still occur? Where is the defect located? What are its causes? These are some of the questions that are considered in the following chapters.

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DISCUSSION

Dr Lugaresi expressed concern about the division of sleep apnea patients into two groups (central and obstructive). He suggested that there may be a continuum during life wherein patients who are heavy snorers develop a mixed syndrome with obstructive and central apneas. Drs Guilleminault and Weitzman, however, strongly defended this division. In New York and at Stanford, a group of patients with the primary complaint of insomnia surprisingly demonstrated a major degree of recurring diaphragmatic apnea. Dr Weitzman also emphasized that in patients with clear-cut, dramatic obstructive apnea, there were no past histories or present complaints of insomnia, but there were histories of increasing sleepiness.

Dr Phillipson commented that the sleep apneic population, judging from Dr Guilleminault's presentation, appeared a heterogeneous group as far as the state of sleep in which apnea occurred, the type of problem, and more importantly, the patients' symptoms. He observed that they really seem quite different, and that the critical question then is whether the fundamental mechanisms are basically different. For example, if the drive to the neurons in the tractus solitarius is reduced, the diaphragm stops. By a movement of a few microns, the

same stimuli also stimulate the upper motor neurons of the upper airway and, if they stop firing, an obstructive apnea occurs. The same withdrawal of stimuli acting less than a millimeter apart can result in diaphragmatic versus obstructive symptomatology. Whether the underlying mechanisms are fundamentally different is yet to be determined.