Primary sleep apnoea syndrome

SUDHANSU CHOKROVERTY, JOHN T SHARP

From the Department of Neurology, CMDNJ-Rutgers Medical School, Piscataway, and Neurology Service, VA Medical Center, Lyons, NJ; the Departments of Medicine and Neurology, VA Medical Center, Hines, and Department of Medicine, University of Illinois College of Medicine, Chicago, Illinois, USA

SUMMARY Polygraphic study in 18 men with the sleep apnoea syndrome showed central, upper airway obstructive, and mixed apnoeas. Fifty per cent of the total apnoea time was central, 33% was obstructive, and 17% was mixed. Apnoeic episodes were accompanied by oxygen desaturation, relative bradycardia and hypotonia of orofacial muscles innervated by ponto-medullary neurons. During regular breathing these muscles revealed tonic and phasic inspiratory EMG activities. The data suggest that the primary sleep apnoea syndrome results from a dysfunction of the central control of breathing.

In 1907 Osler¹ first spoke of an association between obesity and "an uncontrollable tendency to sleep—like the fat boy in Pickwick." Nearly 50 years later Auchincloss *et al.*² and Burwell and associates,³ directed attention to the association of sleep-related respiratory dysrhythmia and obesity. Subsequently many reports of sleep apnoea syndrome with⁴⁻¹¹ and without^{6, 7, 9} obesity appeared. When sleep apnoea is associated with an underlying cause, such as brain stem affection,¹² disorder of the neuromuscular apparatus of respiration,¹³ structural lesion of the upper airway,¹⁴ or chronic obstructive lung disease,¹⁵ it is termed secondary sleep apnoea syndrome. When no cause is found, the term primary sleep apnoea syndrome seems appropriate.

Three types of sleep-related respiratory dysrhythmia have been described:^{5, 7} (1) central apnoea with suppression of diaphragmatic and intercostal muscle activity and absence of air exchange through the nose or mouth, (2) upper airway obstructive apnoea during which there is no air exchange detected by the oronasal thermistors, but the diaphragmatic and intercostal muscle activities persist, and (3) mixed apnoea during which there is an initial period of central apnoea followed by a period of upper airway obstructive apnoea before resumption of regular breathing. Despite numerous publications the pathogenesis of the sleep apnoea syndrome

remains unknown. At first it was thought that obesity was the primary factor causing hypoventilation, initially only during sleep but later even in wakefulness. Since the landmark paper by Gastaut *et al.*⁵ directing attention to the role of the tongue in the genesis of obstructive apnoea in sleep apnoea, the investigative emphasis shifted toward events occurring during sleep and control of breathing.

Clinical observation, polygraphic recordings and pulmonary function studies provide evidence that the primary sleep apnoea syndrome results from a dysfunction of the central control of breathing as we have postulated previously.⁴ The polygraphic findings of predominantly central apnoea are contrary to previous observations⁷ of mainly obstructive apnoea in these patients. The present study further confirms that multiple orofacial muscles receive phasic inspiratory bursts and that during apnoea there is hypotonia not only of geniglossus as shown by other investigators^{9, 16, 17} but also of other muscles in and around the mouth innervated by ponto-medullary neurons. Finally, because of close anatomical contiguity of the respiratory, hypnogenic and baroreceptor neurons in the region of the nucleus tractus solitarius,¹⁸⁻²⁰ we tested autonomic functions in four patients.

Patients

We studied 18 men, ages 29-66 years (mean = 49 yrs). All patients were referred because of excessive daytime somnolence lasting from a few minutes to 2 hours for the

Address for reprint requests: Dr S Chokroverty, PO Box 308, Lyons, NJ 07939, USA.

Accepted 21 July 1981

Primary sleep apnoea syndrome

Table 1 Clinical data in 18 men with primary sleep apnoea syndrome

Case no	Age (yr)	Height (inches)	Weight (pounds)	Blood pressure (mm Hg)	Duration of hypersomnolence
1	31	70	275	130/90	6 mth
2	41	71½	284	130/80	4 yr
3	44	68	238	130/90	3 mth
4	60	72	298	174/100	2½ yr
5	66	66	161	120/84	1½ yr
6	47	70	150	130/80	3 mth
7	57	69	260	170/105	10 yr
8	58	69	278	180/94	3 yr
9	62	67	171	140/80	3 yr
10	43	74	260	150/100	5 yr
11	45	69	210	140/70	32 yr
12	51	72	220	170/110	1 yr
13	54	66	190	160/100	5 yr
14	47	77	275	120/80	28 yr
15	29	76	229	118/72	3 yr
16	52	69	170	130/80	6 mth
17	43	74	290	110/70	5 mth
18	50	70	370	170/100	2 yr

past 3 months to 32 years. None had a history of cataplexy, sleep paralysis or hypnagogic hallucinations. The salient clinical features are summarised in table 1. Eleven patients were obese (cases 1-4, 7, 8, 10, 11, 14, 17, and 18). Four patients (cases 7, 11, 13, 14) felt refreshed or normal after each episode, but the remaining patients complained of fatigue after each episode of daytime somnolence. Twelve patients (cases 1-5, 7, 9-12, 14, 17 had disturbed sleep at night and woke up several times. Four of these (patients 1-3, 5) awakened fighting for breath. Body movements during the night were observed by the bed partners of two patients (cases 1, 2). Fourteen patients (cases 1-5, 7-12, 14, 17 and 18) had excessive nocturnal snoring. Six (cases 2, 4, 9, 11, 14, 18) complained of irritability, depression, impaired libido and sexual potency. Hypertension was noted in seven (cases 4, 7, 8, 10, 12, 13, 18). Four patients (cases 1, 6, 7, 9) had diabetes mellitus. Two of these (cases 6, 9) with long-standing diabetes had absent muscle stretch reflexes; otherwise there were no abnormal neurological findings in any of the patients. None had any history suggestive of brain stem or other central nervous system affection, disorder of the neuromuscular apparatus or chronic obstructive pulmonary disease. Otolaryngological examination was normal except in one patient (case 3) who had enlarged tonsils. Tonsillectomy did not relieve his symptoms nor did it change his polygraphic findings. Four patients (cases 7, 10, 14, 18) followed a strict low calorie diet and they improved symptomatically after losing 40 to 50 pounds in weight. Five patients (cases 7, 9, 10-12) received methylphenidate or amphetamine with slight or no improvement. Patient 11 lost excessive daytime somnolence and regained sexual potency after permanent tracheostomy, but polygraphic study still showed episodes of central apnoea.

Methods

1 Polygraphic study All patients had simultaneous recordings of the electroencephalogram (EEG), electro-

oculogram, electromyogram (EMG) of tongue and other cephalic muscles, electrocardiogram, nasal and oral airflow and abdominal pneumogram on 16-channel EEG equipment. The studies were done in the EEG laboratory, while the patients were in the supine position, mostly in the morning and occasionally in the afternoon. Most patients had more than two daytime recordings, and three (cases 7-9) also had all night recording. Details of the recording technique have been described in a previous publication.²¹ Surface electrodes were used to record electromyograms of the mentalis, orbicularis oris, submental, genioglossal (EGG), palatopharyngeal (EPG), sternocleidomastoid and intercostal muscles. A Hewlett Packard ear oximeter recorded oxygen saturation (S_aO₂) continuously during the polygraphic study.

2 The Respiratory magnetometer recording In eleven patients (cases 1-10, and 16) additional studies were done in the pulmonary function laboratory in the morning. During this study thoracoabdominal motion was recorded by anteroposterior and lateral respiratory magnetometers according to the technique described previously.¹⁰

3 Pulmonary function study Spirometric measurements were performed according to a standard method used in this pulmonary function laboratory. All values were corrected to body temperature and pressure saturated with water vapour (BTPS). Oxygen tension (P_aO₂) and carbon dioxide tension (P_aCO₂) of arterial blood were determined. Hypercapnic and hypoxic ventilatory responses were measured in seven patients (cases 3, 5-7, 9, 10 and 16) using a standard technique. Patients breathed 5%-8.5% CO₂ in room air until ventilation had reached a constant value (15 to 20 minutes), and then P_aCO₂ and minute ventilation at standard BTPS were measured. Similar measurements of minute ventilation and P_aO₂ were made before and during breathing of 10 to 11% oxygen in nitrogen for 10 to 11 minutes.

4 Autonomic function study In four patients (cases 3, 7, 8 and 10) circulatory responses (blood pressure and heart rate) after tilting the table upward (30° to 60° tilt) and immersion of one hand in ice-cold water were determined. The Valsalva ratio (ratio of the longest R-R to the shortest R-R interval) was measured by the method of Levine.²² The electrocardiogram was monitored continuously by a chest lead. In two patients plasma renin activity in supine and erect (60° for 30 minutes) positions was also determined by a radioimmunoassay method.

Results

A POLYGRAPHIC DATA

1 Breathing pattern Polygraphic study recorded repeated episodes of apnoea during sleep beginning generally in expiration. In one patient (case 10) three periods of central apnoea lasting for 15-20 seconds were also noted during relaxed wakefulness. Tables 2 and 3 summarise the polygraphic data. There were 17 to 504 episodes of apnoea during 50 to 579 minutes of recording. After pooling the polygraphic data from all patients we found that the mean number of apnoeic episodes per hour of sleep was 61 with

Table 2 Polygraphic data in 18 patients with primary sleep apnoea syndrome

Case no	Duration recording (min)	Apnoeic episodes						Total no
		Central		Upper airway obstructive		Mixed		
		% of total apnoea time	Duration (s) M ± SE	% of total apnoea time	Duration (s) M ± SE	% of total apnoea time	Duration (s) M ± SE	
1	51	71	19.0 ± 0.6	14.5	15.3 ± 0.9	14.5	21.3 ± 1.1	90
2	153	61.6	25.4 ± 0.6	0	0	38.4	37.9 ± 0.7	231
3	202	19.1	14.6 ± 0.4	17.6	20.8 ± 0.9	63.3	25.9 ± 0.5	252
4	197	13.1	16.8 ± 1.4	83.9	23.0 ± 1.3	3.0	24.0 ± 3.2	111
5	86	4.0	14.0 ± 1.0	96.0	20.8 ± 1.7	0	0	17
6	129	87.6	24.8 ± 1.4	0	0	12.4	37.0 ± 4.8	46
7	417	88.9	12.7 ± 0.2	2.5	11.6 ± 1.1	8.6	23.9 ± 1.6	317
8	477	63.3	13.4 ± 0.2	18.2	28.0 ± 1.8	18.5	26.9 ± 0.8	310
9	440	69.5	25.7 ± 0.6	4.9	30.4 ± 3.3	25.6	35.8 ± 1.1	317
10	579	27.2	15.4 ± 0.4	47.2	24.4 ± 0.7	25.6	34.2 ± 1.4	504
11	150	64	22.1 ± 1.1	36	32.3 ± 1.2	0	0	117
12	70	100	13.7 ± 0.3	0	0	0	0	87
13	75	83.3	16.7 ± 0.6	0	0	16.7	19.3 ± 1.4	78
14	50	0	0	100	17.7 ± 0.9	0	0	40
15	88	32.5	11.3 ± 0.6	12	14.0 ± 1.3	55.5	13.4 ± 0.9	44
16	60	69.0	18.9 ± 1.4	31.0	36.1 ± 1.6	0	0	37
17	70	18.2	11.6 ± 0.4	75.2	13.1 ± 0.5	6.6	19.0 ± 1.9	44
18	130	39.7	17.7 ± 0.8	48.4	23.0 ± 1.4	11.9	27.4 ± 1.4	77

M ± SE: Mean ± Standard error of mean 0: Nil—; Not determined

Table 3 Polygraphic data in 18 patients with primary sleep apnoea syndrome

Case no	Apnoeic episodes		Oxygen saturation (SaO ₂ %)		Heart rate M ± SE		Stages of sleep (% of total sleep)				
	Number per hour of sleep	Total duration (min)	Highest	Lowest	During apnoea	After apnoea					
							Non-REM I	II	III	IV	REM
1	129	28	96	66	85.4 ± 1.6	95.3 ± 1.8	8.4	91.6	0	0	0
2	91	112	96	68	61.0 ± 1.0	69.3 ± 1.8	5.2	94.6	0	0	0
3	80	87	100	60	73.0 ± 2.4	84.2 ± 2.2	12.9	50.2	3.1	6.1	27.7
4	39	41	90	71	83.5 ± 0.5	91.5 ± 0.8	15	85	0	0	0
5	13	59	95	79	63.2 ± 3.0	72.0 ± 6.0	10	90	0	0	0
6	32	20	96	—	71.6 ± 3.1	79.0 ± 2.6	18.6	81.4	0	0	0
7	75	70	94	—	62.7 ± 0.9	70.8 ± 0.8	78.8	21.2	0	0	0
8	57	92	98	78	66.1 ± 1.1	73.7 ± 1.0	17.6	55.9	15.1	0	11.4
9	56	120	97	82	70.6 ± 1.4	90.3 ± 1.1	17.1	37.9	28.0	5.7	11.3
10	71	193	96	50	59.7 ± 1.4	66.1 ± 1.7	40	60	0	0	0
11	61	49	96	—	72.4 ± 0.8	80.6 ± 1.3	20	50	30.0	0	0
12	87	20	—	—	78.0 ± 0.3	86.1 ± 0.5	10	90	0	0	0
13	78	17	—	—	50.5 ± 0.9	66.2 ± 1.4	10	90	0	0	0
14	60	10	—	—	57.4 ± 1.2	60.9 ± 0.2	5	95	0	0	0
15	35	10	95	—	76.2 ± 1.6	87.6 ± 2.6	35	65	0	0	0
16	40	14	98	88	—	—	5	95	0	0	0
17	44	15	—	—	63.1 ± 2.1	72.0 ± 2.5	90	10	0	0	0
18	44	43.9	—	—	—	—	6.4	74.4	0	0	19.2

M ± SE: Mean ± Standard error of mean 0: Nil—; Not determined

a range of 13 to 129; the mean duration of central apnoea was 17.9 seconds; the mean duration of obstructive apnoea was 22.9 seconds; and the mean duration of mixed apnoea was 27.2 seconds. Apnoeic episodes of less than 10 seconds were not considered significant.

We observed central, upper airway obstructive and mixed apnoeas (table 2; figs 1-6). On many occasions periodic central apnoea resembled the waxing and waning pattern of Cheyne-Stokes

respiration. Ten patients had predominantly central apnoea (cases 1, 2, 6-9, 11-13, and 16), six had obstructive apnoea (cases 4, 5, 10, 14, 17 and 18) and two had mixed (cases 3 and 15) apnoea. In patient 12 apnoea was purely central whereas in patient 14 apnoea was purely obstructive in type. The pooled data showed that 50% of the total apnoea time in all patients was central; 33% was obstructive and 17% was mixed. It is notable that compared with the day-time study the all night recording in cases 7-9 showed

Fig 1 Polygraphic recording of two channels of EEG (C_3-A_1 , C_4-A_2), electromyograms (EMG) of orbicularis oris (ORIS), submental (SUBMENT), mentalis (MENT) and intercostal (INT) muscles, vertical electro-oculogram (EOG_v), electroglossogram (EGG), nasal and oral airflow and abdominal pneumogram (ABD PNEUMO) in case 2. Note central apnoea of 26 s and portion of a second period of central apnoea during stage 11 non-REM sleep. In addition to the phasic inspiratory (downward deflection in airflow and pneumogram) bursts in the EMG and EGG there are occasional bursts of muscle activities in expiration. Electrocardiogram is shown in all EMG and EGG.

Fig 2 Polygraphic recording in a patient with sleep apnoea (case 3) showing 4 channels of EEG (C_3-A_1 , C_4-A_2 , O_1-A_1 , O_2-A_2), vertical electrooculogram (EOG_v), electromyograms (EMG) of mental (MENT), submental (SUBMENT), orbicularis ORIS and intercostal (INT) muscles, electroglossogram (EGG), electropharyngogram (EPG), nasal and oral airflow, abdominal pneumogram (ABD PNEUMO) and oxygen saturation by ear oximeter (EAR OX $SaO_2\%$). During the left half of the recording the patient has obstructive apnoea and the EEG shows stage 1 non-REM sleep. Arousal is signalled by resumption of nasal airflow, increased phasic inspiratory (upward deflection in airflow and pneumogram) bursts in EMG, EGG and EPG and tongue movements in EGG and EPG. Note decrease of saturation from 90% to 70% during apnoea.

Fig 3 Recording of EEG (C_3-A_1 , C_4-A_2), electromyogram (EMG) of orbicularis oris (ORIS), submental (SUBMENT), mental (MENT) and intercostal (INT) muscles, vertical electrooculogram (EOG_v), electroglossogram (EGG), nasal and oral airflow and abdominal pneumogram (ABD PNEUMO) in case 2, during stage II non-REM sleep. Note 27 s of mixed apnoea in the left hand side of the tracing and 15 s of central apnoea in the right hand side of the recording. Note also the phasic inspiratory (downward deflection in nasal airflow and pneumogram) bursts in the EMG and EGG.

Fig 4 Same case as in fig 3. Note a portion of an episode of mixed apnoea (only 14 s of a total duration of 36 s are shown) during stage I non-REM sleep followed by resumption of normal breathing, EEG arousal and increased muscle activities. Arrow points to phasic muscle activities during inspiration. Ear oximeter (OX) shows oxygen desaturation during apnoea.

Fig 5 Polygraphic recording during REM sleep (case 3). The tracing shows 4 channels of EEG (C_3-A_1 , C_4-A_2 , O_1-A_1 , O_2-A_2), vertical and horizontal electrooculograms (EOG_v , EOG_h), electromyograms (EMG) of mentalis (MENT), submental (SUBMENT), orbicularis oris (ORIS), sternocleidomastoid (SCM) and intercostal (INT) muscles, electroglossogram (EGG), nasal and oral airflow and abdominal pneumogram (ABD PNEUMO). Note mixed apnoea (initial period of 8 s of central followed by 32 s of obstructive apnoea) during REM sleep associated with rapid eye movements in electrooculogram and decreased tonic activities in EMG. Oxygen saturation (S_aO_2) decreased from 100% to 63% during apnoea. EMG and EGG show phasic inspiratory bursts.

marked increase in the number of obstructive apnoeas and decrease of central apnoeas.

Apnoeic episodes occurred in all stages of sleep. Most, however, were recorded during non-rapid eye movement (non-REM) sleep stages I and II. Rapid eye movement (REM) sleep was recorded in patients 3, 8, 9 and 18 (table 3). REM sleep was accompanied by several episodes of central, mixed or obstructive apnoea (fig 5). In some recordings REM sleep was associated with regular breathing.

2 Electroencephalograms There were no focal or generalised slow waves and no epileptiform activities in the EEG of any patients. All attained non-REM stages I and II sleep and only patients 3, 8, 9 and 11 had brief periods of stages III and IV (table 2). Four patients (cases 3, 8, 9, 18) had REM sleep 40-50 minutes after onset of sleep. In most instances, EEG changes preceded the onset of apnoeic periods

but occasionally these events were seen simultaneously. The termination of apnoea was signalled by K-complexes, alpha rhythm or a change from stage II to stage I EEG sleep pattern. Sometimes EEG changes preceded by 1 to 3 seconds the resumption of normal breathing after an episode of apnoea.

3 Oxygen saturation S_aO_2 recorded from the ear oximeter showed a decrease of 10% to 46% during and immediately after apnoeic periods (table 3). The sudden rise of S_aO_2 lagged behind the resumption of effective gas exchange as shown by a deflection in the thermistor tracings and pneumographs by about 6 to 12 seconds (figs 2 and 4) representing the circulation time from the lung to the ear where S_aO_2 was being registered.

4 Heart rate In all patients each apnoeic episode was accompanied by relative bradycardia followed

Fig 6 Polygraphic recording in case 10. Note regular breathing accompanied by phasic inspiratory (upward deflection in airflow and pneumogram) bursts in all EMG and EGG during wake EEG preceded and followed by obstructive apnoea (only a small portion is shown in the tracing) during stage I non-REM sleep.

by relative tachycardia as normal breathing resumed (table 3; figs 2-4). Apnoea and sinus bradycardia were associated with ventricular extrasystole in two patients (cases 3 and 9) during non-REM and REM sleep.

5 Genioglossal EMG Two types of activities were observed in the genioglossal EMG during normal breathing in relaxed wakefulness and in sleep stages I and II: tonic and phasic. The tonic activities diminished slightly but did not disappear during non-REM sleep stages I and II. The phasic activities coincided with the inspiratory bursts in the intercostal and sternomastoid EMG, and were noted during the inspiratory phase of respiration (figs 1-6). One patient (case 2) also displayed occasional phasic muscle activities during expiration (fig 1). During episodes of central, mixed or obstructive apnoeas the tonic activities decreased considerably or disappeared (figs 1-4 and 6). The phasic activities ceased during central apnoea (figs 1, 3 and 4) but reappeared during obstructive apnoea with progressive recruitment during successive inspiratory efforts (figs 2-4). Tonic activities in the genioglossal EMG also ceased during REM sleep with or without apnoea (fig 5). During REM sleep without apnoea phasic inspiratory bursts were seen but these were less intense than those seen during non-REM sleep and frequently even the phasic activities ceased.

6 EMG of other orofacial muscles The EMG of the mentalis, submental, orbicularis oris and pharyngeal muscles displayed changes similar to those seen in the genioglossal muscles (figs 1-6). Rhythmic tongue movements²¹ were observed in the EGG and EPG during REM but not during non-REM sleep.

B THE RESPIRATORY MAGNETOMETER RECORDINGS

In nine patients (cases 1, 3-5, 7-10 and 16) the presence of upper airway obstruction was established from the respiratory magnetometer recording of thoracic and abdominal motion. Fig 7 shows magnetometer tracings of thoracic and abdominal movement taken from patient 10 with mixed apnoea.

Fig 7 An example of mixed apnoea occurring during stage II non-REM sleep in case 10. Shown is a 20 s period of central apnoea (no respiratory efforts) followed by a 22 s period of obstructive apnoea. SEO_2 refers to blood oxygen saturation via ear oximeter. The second line from top with vertical bracket labelled 40 cm H_2O represents oesophageal pressure, the equivalent of pleural pressure. Therm is a thermistor tracing indicating oronasal air flow. The bottom four tracings are magnetometer records of lateral and anteroposterior motion of the rib cage (RC) and abdomen (abd). The calibration is equal in all magnetometer channels and the vertical bracket labelled 2 cm indicates the deflection in all four channels corresponding to 2.0 cm of linear displacement of diameter change. Note that during the latter part of the apnoeic period the inspiratory effort produced outward motion (upward deflection) of the abdomen (AP) but simultaneous inward (downward) deflection of the rib cage (AP) representing obstructive apnoea. At the termination of apnoea the rib cage and abdominal motion became concordant moving in the same rather than in opposite directions.

C PULMONARY FUNCTION TESTS

The spirometric values for forced expiratory reserve volume, forced vital capacity, maximum voluntary ventilation, residual volume and functional residual

capacity were normal except in three patients (cases 3, 5, 18) showing evidence of mild obstructive lung disease. P_{aO_2} and P_{aCO_2} were also normal except for mild hypoxaemia in case 18 during wakefulness. Hypercapnic and hypoxic ventilatory responses showed normal increase of minute ventilation in all cases including the two patients (cases 3 and 5) showing evidence of mild obstructive lung disease.

D AUTONOMIC FUNCTION DATA

The tilt table study showed no orthostatic hypotension after tilting the table upward for 10-15 minutes; heart rate increased normally in the erect posture. The cold pressor test produced a normal rise of blood pressure and heart rate during the period of cold stress. The Valsalva ratio was normal. In summary, the results failed to show any functional abnormality of the baroreceptor reflex arc. Plasma renin activity was normal in the supine position and rose normally in the erect posture.

Discussion

CLINICAL ASPECTS

All patients exhibited characteristic clinical features of the sleep apnoea syndrome.^{4-7 9-11} These features and the polygraphic findings of absence of sleep onset REM clearly differentiate these patients from those with the narcolepsy syndrome. The incidence of obesity (61%; table 1) in our series is higher than that reported in the Stanford series.⁶ Weight reduction in four individuals (cases 7, 10, 14, 18) was associated with considerable symptomatic relief and reduction in the number of apnoeas during repeat polygraphic study, but periodic central apnoea persisted. However, improvement following tracheostomy (case 11) suggests that upper airway obstruction plays a major rôle in the production of symptoms.^{6 23} The incidence of hypertension (table 1) in our series is less than that reported by others.⁶

What is the cause of excessive daytime somnolence in sleep apnoea patients? It has been suggested⁷ that disturbed nocturnal sleep resulting from repeated arousals associated with recurring apnoeic episodes and oxygen desaturation is responsible for daytime hypersomnolence. Amelioration of symptoms after tracheostomy,^{6 23} which prevents periodic upper airway obstruction during sleep, supports this suggestion. However, Orr *et al*²⁴ found no significant difference in the number of airway obstructions in symptomatic and asymptomatic sleep apnoea patients. The disappearance of daytime somnolence after tracheostomy,^{6 23} and reports of sleep apnoea patients without daytime somnolence,^{7 9 24} cast doubt on the suggestion that^{6 7 24}

daytime hypersomnolence results from a defect in the CNS structure controlling sleep. The suggestion^{7 25} of disturbed monoamine metabolism due to recurrent hypoxia remains speculative.

ELECTROENCEPHALOGRAMS IN SLEEP

APNOEA PATIENTS

Findings of abnormal sleep EEG patterns in sleep apnoea patients are in agreement with observations reported by other.^{5 7 26} Sleep was spent mostly in Stage II and partly in Stage I (table 3). Four patients (cases 3, 8, 9 and 18) went into REM stage 40 to 50 minutes after the onset of sleep during daytime polygraphic recording. One possibility is that these four patients belong to an intermediate category, that is in a borderland between narcolepsy and the sleep apnoea syndrome or a combination of the two. Another possibility²⁷ is that the early onset REM periods resulted from sleep deprivation secondary to repetitive arousals at night.

EEG signs of sleep usually preceded cessation of breathing, and so apnoea was related to sleep. The simultaneous occurrence of EEG arousals and resumption of breathing suggests a common mechanism, such as a critical level of oxygen desaturation as indicated by the ear oximeter recordings. Sometimes EEG changes preceded resumption of normal breathing implying that the structures responsible for EEG arousals were more sensitive to hypoxia than the respiratory neurons. However, on several occasions the period of apnoea was brief and accompanied by mild oxygen desaturation (a difference of less than 10%) and so the resumption of breathing and EEG arousal could not always be related to hypoxia. It was suggested by Krieger and Kurtz²⁶ that during obstructive apnoea proprioceptive stimuli from respiratory muscles resulting from ineffectual respiratory movements may be responsible for EEG arousals.

Apnoeas have been noted in normal individuals²⁸ during both non-REM and particularly REM sleep, but the brevity and infrequent occurrence of the episodes, and the lack of excessive daytime somnolence differentiate these apparently normal individuals from sleep apnoea patients.

PATTERN OF BREATHING

Our polygraphic findings confirm the existence of central, obstructive and mixed apnoeas (figs 1-6) in these patients.^{5 7 9 10} The mean duration of obstructive or mixed apnoea was longer than that of central apnoea. Our findings of a purely central apnoea in one (case 12), purely obstructive in one (case 14) and predominantly central apnoea in 10 patients (table 2) differ from those reported by others.⁷ In most of the previous reports⁷ upper airway obstructive apnoea

was the predominant abnormality in sleep apnoea patients. In the present study approximately 50% of the total apnoea time was central.

It is noteworthy that in a previous communication¹⁰ based on the respiratory magnetometer study of sleep apnoea patients, we reported that 81% of all apnoeic episodes was purely obstructive. This apparent discrepancy between the two series may have been related to the fact that in the previous study¹⁰ a greater percentage of patients had all night recordings. The predominance of central apnoea in the present study may be due to the fact that we performed diurnal rather than nocturnal polygraphic recordings. As indicated above a comparison of the daytime and all night polygraphic data in cases 7-9 would tend to support this suggestion. Lugaresi *et al*¹¹ and Kurtz and Krieger²⁹ also stated that central apnoeas were more abundant during daytime than during nighttime recordings.

GENIOGLOSSAL AND OTHER OROFACIAL EMG IN SLEEP APNOEA PATIENTS

There is increased genioglossal activity^{16 17} during inspiration and protrusion of the tongue forward (figs 1-6). On the other hand, negative intrathoracic pressure during inspiration would tend to pull the tongue backward toward the oropharynx. A disturbance of this balance between forward and backward forces (for example during genioglossal hypotonia) may promote upper airway obstructive apnoea.⁸ We found a general inhibition of tone not only in the genioglossus and pharyngeal muscles but also in many other muscles innervated by pontomedullary neurons during central, obstructive and mixed apnoeas (figs 1-6). We observed phasic inspiratory bursts in addition to the tonic activities in the EMG not only of the intercostal, sternocleidomastoid and genioglossus but also of the palatopharyngeal, orbicularis oris, mentalis and submental muscles. Apparently, the motor neurons of all the above muscles seem to receive an automatic respiratory drive during inspiration. It has been suggested recently^{9 30} that the muscles of the upper airway are respiratory in nature. Trains of impulses with inspiratory periodicity and essentially synchronous with phrenic excitation have been recorded from the motor nerves to the tongue, pharynx and larynx.³⁰ In a very real sense these upper airway muscles should be included among the inspiratory muscles. Simultaneous activation of the genioglossus and other orofacial muscles along with the inspiratory muscles suggests that the same neural mechanisms may be responsible for both actions.

WHAT IS THE SITE OF OBSTRUCTION IN UPPER AIRWAY OBSTRUCTIVE APNOEA?

There is no consensus of opinion in this respect.

Gastaut *et al*⁵ favoured prolapse of the tongue backward as the mechanism of obstruction. The findings of Remmers *et al*⁸ and Harper and Sauerland¹⁶ support Gastaut's⁵ original suggestion. The observations of Weitzman,²⁵ Guilleminault³¹ and co-workers favoured obstruction at the pharyngeal level. Lugaresi *et al*¹¹ concluded that upper airway obstruction may result from collapse of the oropharyngeal walls due to hypotonia of the genioglossal and oropharyngeal muscles. Weitzman and associates²⁵ suggested that there was a sphincter-like closure of the lateral and posterior pharyngeal walls, apparently by active muscle contraction. However, Severinghaus³² mentioned that the apparent sphincter-like closure could result from negative inspiratory pressure inside the airway. The EMG findings of Kurtz *et al*³³ indicate obstruction at the laryngeal level with disappearance of laryngeal muscle tone.

Thus various investigators suggested hypotonia of genioglossal, pharyngeal or laryngeal muscles as the mechanism of airway obstruction. Present polygraphic findings suggest that loss of tone occurs not only in the genioglossus (figs 1-6), but also in the pharyngeal muscles (figs 2 and 4) contributing to the upper airway obstruction. The release of obstruction after pharyngeal intubation^{8 9} speaks in favour of oropharyngeal and not laryngeal obstruction. The previous observations by one of us (JT)⁹ that the pharyngeal occlusion occurred not only in the supine but also in the lateral body position indicates that genioglossal hypotonia alone is not responsible for pharyngeal obstruction in sleep apnoea syndrome.

SITE OF LESION IN SLEEP APNOEA SYNDROME

The diminished ventilatory response to CO₂ during normal sleep in man³⁴ and a reduction of central respiratory drive during sleep in cats³⁵ would suggest that there is a normal potential for respiratory failure in sleep. In patients with sleep apnoea syndrome there may be an exaggeration of this normal potential³⁶ explaining central sleep apnoea. The recent report of episodes of apnoea and oxygen desaturation in apparently normal individuals²⁸ would support this hypothesis. The resumption of normal breathing after both central and obstructive apnoeas is secondary to activation of brainstem respiratory and arousal mechanisms due to progressively rising hypoxic chemical stimuli during apnoea. Additionally, hypoxia will increase the phasic inspiratory activity of the tongue thereby favouring its forward motion to overcome airway obstruction. The following points would favour a central ventilatory dysfunction: the predominance

Primary sleep apnoea syndrome

of central apnoea in our series; the presence of central apnoea often preceding obstructive apnoea (mixed apnoea); the persistence of central apnoea after tracheostomy in one of our patients; the unmasking of central apnoea by tracheal intubation which bypasses the pharyngeal obstruction;³⁷ hypotonia not only of the genioglossus but also of multiple other muscles innervated by ponto-medullary neurons during both central and obstructive apnoeas; and the occurrence of similar sleep-related respiratory arrhythmias in certain neurodegenerative diseases of CNS origin, such as the spinocerebellar degenerations,³⁸ motor neuron disease,³⁸ and the Shy-Drager syndrome,^{38 39} and in other CNS disorders, such as narcolepsy^{6 21 40} and poliomyelitis.⁴¹

Phillipson⁴² commented that whether the underlying mechanisms for central or obstructive apnoeas were fundamentally different remains to be determined. We would agree with Kurtz and Krieger²⁹ that central and obstructive apnoeas may have the same significance. Following evidence suggests that these two types of apnoeas should not be strictly compartmentalised: in most patients central and obstructive apnoeas coexist; the predominance of central or obstructive apnoea may depend upon the timing of the study as stated above; orofacial muscle hypotonia was noted not only during central but also during obstructive apnoea; the decrease of activities observed during apnoeas in the genioglossal and pharyngeal muscles as part of a general cranial motor inhibition would promote upper airway obstruction. Therefore both central and obstructive apnoeas result from central dysfunction and the type of apnoea may depend upon the balance between severity of inhibition of the brainstem respiratory and motor neurons; finally, the orofacial muscles appear to receive phasic inspiratory bursts behaving like respiratory muscles and this would support the idea that central and obstructive apnoeas differ in degree but not in kind.

If the primary sleep apnoea syndrome results from a defective central control of breathing, then what is the nature of this central ventilatory dysfunction? In non-REM sleep respiration is regulated primarily by the automatic or metabolic control system.^{34 43} Hence apnoea at this stage may result from derangement of this system. Phillipson and Sullivan⁴³ suggested that apnoea in non-REM sleep may result from the following (1) dysfunctional brainstem respiratory neurons, (2) inadequate afferent input from central or peripheral chemoreceptors, and (3) active inhibition of inspiration due to increased inhibiting vagal stimuli. In patients with Pickwickian or obesity-hypoventilation syndrome, decreased chemosensitivity^{3 44} may support

the first two suggestions of Phillipson and Sullivan.⁴³ But in our patients hypoxic and hypercapnic ventilatory responses at least in the waking state were normal. This of course did not exclude decreased chemosensitivity of the respiratory neurons in sleep. We might point out that frequent and prolonged periods of apnoea after oxygen inhalation in sleep apnoea patients as described by us previously,⁴ and confirmed later by Motta and Guilleminault,⁴⁵ would indirectly suggest that the hypoxic drive of the respiratory neurons was intact in these patients. Regarding the rôle of excessive vagal stimuli⁴³ the slowing of the heart rate during apnoea in sleep apnoea patients may have resulted from increased vagal stimuli during apnoeic episodes. Guilleminault and co-workers⁴⁶ found that atropine sulphate blunted sinus bradycardia and accentuated sinus tachycardia in five patients with sleep apnoea suggesting a direct vagal inhibition in these patients.

The voluntary respiratory control system is thought to be involved in the control of breathing during REM sleep,^{34 43} although there is no direct evidence to support this notion. Respiration is virtually unaffected by vagal stimuli in REM sleep.^{34 43} Hence active inhibition of inspiration by vagal stimuli cannot be responsible for apnoea in REM sleep, but increased vagal action may still be causing relative bradycardia in apnoea.^{34 43} The termination of apnoea may still be due to hypoxic stimuli because hypoxic chemosensitivity is intact during REM sleep.^{34 43} The presence of apnoea in both non-REM and REM sleep in our patients implies that both the respiratory control systems (voluntary and automatic) are somehow implicated. These two systems are closely interrelated in the lower brainstem and functionally integrated in the upper cervical spinal cord^{18 47-49} and a dysfunction in these regions might cause sleep apnoea syndrome. Structural lesions in these areas are known to cause sleep apnoea.^{7 12 49}

Finally, Phillipson⁵⁰ suggested that a defect in the cortical arousal system may play a rôle in the sleep apnoea syndrome. Bowes and Phillipson⁵¹ provided experimental data in sleeping dogs to indicate that following brief periods of sleep fragmentation the arousal, ventilatory and airway responses to laryngeal stimulation were impaired. The presence of prolonged periods of apnoea accompanied by profound arterial desaturation in our patients with obstructive and mixed apnoeas may indicate an associated defect in the arousal system as suggested by Phillipson.⁵⁰ On the other hand, the presence of many brief episodes of apnoea and mild arterial desaturation would suggest intact cortical arousal system.

WHAT IS THE ROLE OF OBESITY IN PRIMARY SLEEP APNOEA SYNDROME?

There is no doubt that severe obesity is a respiratory handicap⁹ causing reduction of functional residual capacity, vital capacity, maximal voluntary ventilation and varying degrees of hypoxaemia but normal arterial PaCO₂ values.⁹ These factors alone are not, however, responsible for the sleep apnoea syndrome.⁵² It is noteworthy that severe obesity is quite common while obesity associated with hypoventilation and sleep apnoea is uncommon.^{6,9} It has also been shown that alveolar hypoventilation is not directly related to the degree of obesity.⁹ On the other hand one can speculate that in obese patients excessive accumulation of adipose tissue in the oropharyngeal region may influence the airway size and promote upper airway obstructive apnoea. Also a single case has been reported of fatty infiltration of the intercostal muscles and diaphragm in a patient who died of the obesity hypoventilation syndrome.⁵³ Finally, functional improvement noted by us^{4,9} and others⁶ after weight loss would favour a rôle for obesity in the sleep apnoea syndrome. Thus it appears that obesity, although it may not play a primary rôle, acts as a secondary aggravating factor to the central dysfunction of ventilatory control.

In conclusion, the available data support the suggestion that the sleep-related central, obstructive and mixed apnoeas in the primary sleep apnoea syndrome most likely result from a central disturbance of ventilatory function. The study of Guilleminault *et al*⁴⁶ while alluding to a previous suggestion⁴ and the physiological studies of the respiratory mechanics and timing by Martin *et al*⁵⁴ also favoured a central nervous system dysfunction in upper airway obstructive sleep apnoea. The close contiguity of hypnogenic¹⁹ and respiratory neurons¹⁸ in the region of the nucleus tractus solitarius makes it the most probable site of a lesion causing sleep-related respiratory dysrhythmia. The nature of the lesion remains to be determined. In some it may be genetically determined⁵⁵ or may be related to neurochemical alterations, possibly due to recurrent hypoxia.^{7,25} Further suggestions include impairment of growth hormone and prolactin secretory responses,⁵⁶ and reduction of blood flow⁵⁷ in the brain stem gray matter region. A lack of disturbance of circulatory homeostasis observed in four of our patients (cases 3, 7, 8 and 10) implies that the baroreceptor neurons,²⁰ although closely related to respiratory¹⁸ and hypnogenic neurons¹⁹ in the nucleus tractus solitarius, may not necessarily be implicated in the primary sleep apnoea syndrome.

We thank Roger Duvoisin, MD, for reviewing the

manuscript, the physicians on the Neurology Service, VA Medical Center, Hines, Illinois, for directing our attention to some of the patients, and Robert C Taylor for technical help.

This work was supported in part by USPHS grant No HL08789.

References

- Osler W. *The principles and practice of medicine*. Sixth edition. New York: Appleton, 1907, 431.
- Auchincloss JH, J Norcass R, Cook E, Renzetti AD. Clinical and physiological aspects of a case of obesity, polycythemia and alveolar hypoventilation. *J Clin Invest* 1955;**34**:1537-45.
- Burwell CS, Robin ED, Whaley RD, Bikelman A. Extreme obesity associated with alveolar hypoventilation: a Pickwickian syndrome. *Am J Med* 1956;**21**:811-8.
- Chokroverty S, Barrocas M, Barron KD, Sharp JT. Hypoventilation syndrome and obesity: a polygraphic study. *Trans Amer Neur Assoc* 1969;**94**:240-2.
- Gastaut H, Tassinari CA, Duron B. Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwickian syndrome. *Brain Res* 1966;**2**:167-86.
- Guilleminault C, Hoed JVD, Mitler MM. Clinical overview of the sleep apnoea syndromes. In: Guilleminault C and Dement WC, eds. *Sleep apnoea syndromes*. New York: Alan R Liss, Inc, 1978:1-12.
- Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *Ann Rev Med* 1976;**27**:465-84.
- Remmers JE, deGroot WJ, Sauerland EK. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978;**44**:931-8.
- Sharp JT, Barrocas M, Chokroverty S. The cardio-respiratory effects of obesity. In: Williams MH, ed. *Clinics in chest medicine*. Philadelphia: Saunders, 1980, Vol 1, 103-118.
- Sharp JT, Druz WS, Foster JR, Wicks MS, Chokroverty S. Use of the respiratory magnetometer in diagnosis and classification of sleep apnoea. *Chest* 1980;**77**:350-3.
- Lugaresi E, Coccagna G, Mantovani M. EEG and polygraphic aspects of HPA. In: *Hypersomnia with periodic apnoeas*. New York: Spectrum, 1978, 68.
- Devereaux MW, Keane JR, Davis RL. Automatic respiratory failure associated with infarction of the medulla. *Arch Neurol* 1973;**29**:46-52.
- Bergofsky EH, Turino JM, Fishman AP. Cardio-respiratory failure in kyphoscoliosis. *Medicine* 1959;**38**:267-317.
- Menashe BD, Farrehi C, Miller M. Hypoventilation and corpulmonale due to chronic upper airway obstruction. *J Pediatr* 1965;**67**:198-203.
- Wynne JW, Block AJ, Hemenway J, Boysen PG. Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive pulmonary disease. *Chest* 1978;**73** (suppl):301-3.
- Harper RM, Sauerland EK. The rôle of the tongue in sleep apnea. In: Guilleminault C and Dement WC,

- eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978, 219-34.
- ¹⁷ Sauerland EK, Harper RM. The human tongue during sleep: electromyographic activity of the genioglossus muscle. *Exp Neurol* 1976;**51**:160-70.
- ¹⁸ Berger AJ, Mitchell RA, Severinghaus JW. Regulation of respiration. *New Eng J Med* 1977;**297**:92-97, 138-143, 194-201.
- ¹⁹ Bremer F. Cerebral hypnogenic centers. *Ann Neurol* 1977;**2**:1-6.
- ²⁰ Miura M, Reis DJ. The rôle of the solitary and paramedian reticular nuclei in mediating cardiovascular reflex responses from carotid baro- and chemo-receptors. *J Physiol (Lond)* 1972;**223**:525-48.
- ²¹ Chokroverty S. Phasic tongue movements in human rapid eye movement sleep. *Neurology (Minneapolis)* 1980;**30**:665-8.
- ²² Levin AE. A simple test of cardiac function based upon the heart rate changes induced by the Valsalva maneuver. *Am J Cardiol* 1966;**18**:90-9.
- ²³ Hill MW, Simmons FB, Guilleminault C. Tracheostomy and sleep apnea. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978, 347-52.
- ²⁴ Orr WC, Martin RJ, Imes NK, Rogers RM, Stahl ML. Hypersomnolent and non-hypersomnolent patients with upper airway obstruction during sleep. *Chest* 1979;**75**:418-22.
- ²⁵ Weitzman ED, Pollak CP, Borowiecki B, Burack B, Shprintzen R, Rakoff S. The hypersomnia-sleep apnea syndrome: Site and mechanism of upper airway obstruction. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978:235-48.
- ²⁶ Krieger J, Kurtz D. EEG changes before and after apnea. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978:161-76.
- ²⁷ Carskadon MA. The rôle of sleep-onset REM periods in narcolepsy. In: Guilleminault C, Dement WC and Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976, 491-519.
- ²⁸ Block AJ, Boysen PG, Wynne JW, Hunt LA. Sleep apnea, hypopnea and oxygen desaturation in normal subjects. *New Eng J Med* 1979;**300**:513-7.
- ²⁹ Kurtz D, Krieger J. Analysis of apnea in sleep apnea. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978:145-59.
- ³⁰ Weiner D, Mitra J, Salamone J, Nochomovitz M, Cherniak NS. Effect of chemical and reflex stimulation on phrenic (P), hypoglossal (H), and recurrent laryngeal (RL) nerve activity. *Fed Proc* 1980;**39**:372.
- ³¹ Guilleminault C, Hill MH, Simmons FB, Dement WC. Obstructive sleep apnea: Electromyographic and fiberoptic studies. *Exp Neurol* 1978;**62**:48-67.
- ³² Severinghaus JW. Quoted in discussion of reference no 25, 246-247.
- ³³ Kurtz D, Krieger J, Stierle JC. EMG activity of cricothyroid and chin muscles during wakefulness and sleeping in the sleep apnea syndrome. *Electroencephalogr Clin Neurophysiol* 1978;**45**:777-84.
- ³⁴ Phillipson EA. Control of breathing during sleep. *Am Rev Respir Dis* 1978;**118**:909-39.
- ³⁵ Orem J, Montplaisir J, Dement WC. Changes in the activity of respiratory neurons during sleep. *Brain Res* 1974;**82**:309-15.
- ³⁶ Jung R, Kuhlo W. Neurophysiological studies of abnormal night sleep and the Pickwickian syndrome. In: Akert K, Bally C, and Schade JP, eds. *Progress in Brain Research: Sleep Mechanisms*. Amsterdam: Elsevier Publishing Company, 1965, Vol 18, 140-59.
- ³⁷ Barrocas M, Chokroverty S, Baum GL, Schwartz A, Sharp JT. Hypoventilation-obesity syndrome: central origin of the ventilatory dysrhythmia. *Chest* 1975;**68** (suppl):401.
- ³⁸ Chokroverty S. Sleep apnea in neurodegenerative diseases. *Electroencephalogr Clin Neurophysiol* (In Press).
- ³⁹ Briskin JG, Lehrman KL, Guilleminault C. Shy-Drager syndrome and sleep apnea. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978, 317-22.
- ⁴⁰ Laffont AF, Autret A, Minz M, Beillevalaire T, Cathala HP, Castaigne P. Sleep respiratory arrhythmias in control subjects, narcoleptics and non-cataplectic hypersomniacs. *Electroencephalogr Clin Neurophysiol* 1978;**44**:697-705.
- ⁴¹ Guilleminault C, Motta J. Sleep apnea syndrome as a long term sequela of poliomyelitis. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978, 309-15.
- ⁴² Phillipson EA. Quoted in discussion in reference no 6, p. 11.
- ⁴³ Phillipson EA, Sullivan CE. Respiratory control mechanisms during NREM and REM sleep. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978, 47-64.
- ⁴⁴ Zwillich CW, Sutton FD, Pierson DJ, Creagh EM, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am J Med* 1975;**59**:343-8.
- ⁴⁵ Motta J, Guilleminault C. Effects of oxygen administration in sleep-induced apneas. In: Guilleminault C and Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R Liss, Inc, 1978, 137-59.
- ⁴⁶ Guilleminault C, Tilkian A, Lehrman K, Forno L, Dement WC. Sleep apnea syndrome: States of sleep and autonomic dysfunction. *J Neurol Neurosurg Psychiatry* 1977;**40**:718-25.
- ⁴⁷ Mitchell RA, Berger AJ. Neurol regulation of respiration. *Am Rev Respir Dis* 1975;**111**:206-24.
- ⁴⁸ Plum F. Neurological integration of behavioural and metabolic control of breathing. In: Porter R, ed. *Breathing: Hering-Breuer Centenary Symposium*. London: Churchill, 1970, 159-75.
- ⁴⁹ Krieger AJ, Rosomoff HL. Sleep-induced apnea. Part I: A respiratory and autonomic dysfunction syndrome following bilateral percutaneous cervical cordotomy. *J Neurosurg* 1974;**39**:168-80.
- ⁵⁰ Phillipson EA. Arousal: the forgotten response to respiratory stimuli. *Am Rev Respir Dis* 1978;**118**:807-9.
- ⁵¹ Bowes G, Phillipson EA. Arousal, ventilatory and

- airway responses to laryngeal stimulation following sleep fragmentation. *Am Rev Resp Dis* 1980;**121**: 316.
- ⁵² Lourenco RV. Diaphragm activity in obesity. *J Clin Invest* 1969;**48**:1609-14.
- ⁵³ Fadell EJ, Richman AD, Ward WW. Fatty infiltration of respiratory muscles in the Pickwickian syndrome. *New Eng J Med* 1962;**229**:861-3.
- ⁵⁴ Martin RJ, Pennock BE, Orr WC, Sanders MH, Rogers RM. Respiratory mechanics and timing during sleep in occlusive sleep apnea. *J Appl Physiol* 1980;**48**:432-37.
- ⁵⁵ Strohl KB, Saunders NA, Feldman NT, Hallett M. Obstructive sleep apnea in family members. *New Eng J Med* 1978;**229**:969-73.
- ⁵⁶ Clark RW, Schmidt HS, Malarkey WB. Disordered growth hormone and prolactin secretion in primary disorders of sleep. *Neurology (Minneap)* 1979;**29**: 855-61.
- ⁵⁷ Meyer JS, Sakai F, Karacan I, Derman S, Yamamoto M. Sleep apnea, narcolepsy, and dreaming: regional cerebral hemodynamics. *Ann Neurol* 1980;**7**:479-85.