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Editorial

Hypoxaemia during sleep

The pattern of breathing, in terms of tidal volume and duration of each breath, must vary widely during speech and the other activities of the waking day. However, it is traditional that breathing becomes more regular when one is at rest and relaxed, as in sleep. Thus, in *Endymion,* Keats asserts

"A thing of beauty is a joy for ever,
Its loveliness increases; it will never
Pass into nothingness; but still will keep
A bower quiet for us, and a sleep
Full of sweet dreams, and health,
And quiet breathing."

The occurrence of a rhythmic periodic variation in both rate and depth of breathing in disease was apparently known to Hippocrates, over two millennia before either Nicolas described it in French in 1786, or the classic English description by John Cheyne in 1818, which led William Stokes to include his own cases in his book of 1854. The relative regularity of the cyclical changes in tidal volume and rate which characterise Cheyne-Stokes breathing are not infrequent in the sleep of older normal subjects,[1 2] and are particularly common at altitude,[3] presumably as a result of hypoxia. Debate continues as to the mechanism of Cheyne-Stokes respiration in disease, particularly between the role to be played by either "the weakened state of the heart" which Stokes thought to be always present in such cases, or the pathological lesions in the brainstem, as proposed by Plum and Brown[4]; nevertheless, Cheyne-Stokes respiration is clearly different from the irregular non-cyclical variation in breathing pattern which characterises the sleep apnoea syndromes described in recent years.[5–7]

The continuous polygraphic recording of the EEG, electro-oculogram (EOG), thoracic pneumogram, airflow at nose and mouth, and the ear oxygen saturation (Hewlett Packard ear oximeter) now allows study of the relationships between the phase of sleep, the respiratory movements, and the level of arterial oxygenation. By continuous record of the EEG pattern the night sleep of healthy human adults can be divided into four stages of increasing depth, with an additional phase of rapid eye movement (REM) sleep, this latter occupying 20–25% of the sleep time and accumulated in periods of variable length, usually occurring four to five times per night at intervals of 90-100 minutes. Most dreams occur during REM sleep, when there are also changes in autonomic activity, including respiration and circulation. Rapid eye movement sleep is divided into two forms, one associated with depression of muscle tone, and another with bursts of rapid eye movements and respiratory irregularities.[8]

The methods described above have now shown that the pattern of breathing is often far from regular in healthy subjects during sleep, and that transient arterial hypoxaemia may also be relatively frequent. Thus in 49 asymptomatic subjects (30 men, 19 women) who had a normal FEV_1 and arterial oxygen saturation when awake, Block *et al*[9] found that oxygen saturation fell by more than 4% from their baseline values in 17 of the men from time to time during the night's sleep, but in none of the women, and that hypopnoeic or apnoeic episodes were almost confined to the men. Although these differences between the sexes in the prevalence of breathing abnormalities in sleep were statistically significant, the women that they studied were on average nine years younger than the men. Again, their subjects slept for a shorter time than usual, presumably from unfamiliarity with the recording equipment during the one and only night of study.[10] Despite these criticisms this important study has shown that both breathing abnormalities and transient arterial desaturation during sleep are relatively common in normal healthy people, although further work is needed to confirm that this predominates so much in men. The lowest level of ear oxygen saturation found was 68%, indicating a probable arterial P_{O_2} of 4·7–5·3 kPa (35–40 mmHg), although in most subjects desaturation was much less marked. It is to be emphasised that these levels occurred in subjects with normal lungs.

Guilleminault *et al*[11] have described their experience of over 150 patients with sleep apnoea syndromes who were referred to the Stanford Sleep Disorders Clinic since 1971. They

define apnoea as cessation of airflow at the nostrils and mouth lasting for at least 10 seconds, and diagnose a sleep apnoea syndrome if 40 such apnoeic episodes occur during seven hours of nocturnal sleep, when in addition these episodes also occur in both REM and non-REM sleep. In studies of 20 normal control subjects aged 40–60 years, over four consecutive nights, between one and 25 such apnoeic episodes occurred in the men, but only five in women, and these episodes only occurred in REM sleep. They follow the earlier French descriptions[5] of three types of apnoea: *central*, occurring when airflow and respiratory movements both cease; *obstructive*, recognised by continuation of respiratory movements despite cessation of airflow at nose and mouth; and *mixed*, where an initial central apnoea is later followed in the same episode by recurrence of respiratory movements despite continued absence of airflow.

Sleep apnoea syndromes have been recognised in many neurological disorders—after bilateral cervical cordotomy, in brainstem lesions, narcolepsy, the Shy-Drager syndrome, and muscular dystrophy—and also after overdosage with respiratory depressants and in two cases of acromegaly. Elsewhere in this issue Perks *et al*[12] also describe obstructive apnoea in two boys with Scheie's syndrome (a mucopolysaccharidosis) with shortness, abnormal facies, and the tongue impeding the upper airway. In one of the two siblings with this condition sleep apnoea was relieved by tracheostomy. Of their 150 patients, Guilleminault *et al*[11] found 50 presented with predominantly obstructive apnoea, all being adults aged 28–62 years, and only two were women. They usually complained of excessive daytime sleepiness and loud snoring at night, and many had intellectual deterioration and personality changes, with morning headache and impotence. All had abnormal movements during sleep, leading many of their sleeping partners to seek refuge in a separate bed. Almost half had modest systemic hypertension, but none had a neurological or EEG abnormality when awake. Only 10 out of the 150 patients were normal in weight, some being up to four times their ideal weight.

Moderate arterial desaturation, with widening of the alveolar to arterial P_{O_2} gradient, is relatively common in the obese, particularly when they lie down.[13–15] This arises largely as a result of their breathing at low lung volumes, which causes airways in the dependent zones of the lungs to close,[16] but as these zones are still perfused, the resultant shunt-like effect gives rise to arterial hypoxaemia.

In the extremely obese patients with the Pickwickian syndrome central cyanosis is particularly marked when they are asleep or recumbent, arterial blood analysis showing that a high P_{CO_2} with compensated respiratory acidosis accompanies the hypoxia. This hypercapnia is combined with relative normality of FEV_1, gas mixing and transfer factor. Hypoxaemia thus results from alveolar hypoventilation of relatively normal lungs. Secondary polycythaemia and right ventricular hypertrophy, leading eventually to right ventricular failure, are also secondary to the hypoxaemia, which can be corrected for a time by voluntary hyperventilation.[17] These patients also have a poor ventilatory response to carbon dioxide, which is also a feature of primary alveolar hypoventilation in the non-obese.

The Pickwickian syndrome is also characterised by periodic apnoea during sleep, which may be of central, obstructive, or mixed type.[6] Treatment with oral medroxyprogesterone acetate has been shown to correct both the waking hypoxaemia and hypercapnia in outpatients with the Pickwickian syndrome, despite their failure to lose weight.[18] However, this treatment failed to prevent the recurrent obstructive sleep apnoea in seven morbidly obese men with severe daytime hypersomnalence and recurrent obstructive sleep apnoea,[19] although it was apparently successful in three out of four other patients with obstructive sleep apnoea.[20] In six men with sleep-induced obstructive apnoea, the more drastic step of permanent tracheostomy almost doubled the mean arterial P_{O_2} during apnoeic episodes from 5·0 kPa (38 mmHg) to 9·3 kPa (71 mmHg) after tracheostomy, in addition to lowering the elevated pulmonary arterial pressure during sleep.[21]

In amazing studies using a fibreoptic endoscope to visualise the pharynx, along with simultaneous recording of EMG activity in pharyngeal muscles from implanted electrodes, and standard polygraph sleep recording, Guilleminault *et al*[22] have recently shown that obstructive apnoea results from invagination of the posterolateral pharyngeal walls, as EMG activity in the muscles dilating the pharynx disappeared in inspiration. The heroic patients apparently slept throughout this procedure, and the authors conclude that the obstruction arises from absence of this normal inspiratory activity of the pharyngeal dilator muscles as well as the genioglossus muscle.[23] Obstructive apnoea may have a familial basis, as apnoea in some adults of one family

was associated with absence of EMG activity in the pharyngeal dilators in another asymptomatic member during sleep, and also with sudden death in infancy in a 4-month-old child of a further member of the family who had asymptomatic obstructive sleep apnoea.[24] Another family has been described with obesity, excessive snoring, and obstructive apnoea in three siblings.[25]

Respiratory physicians will be particularly interested in the recent recognition of similar patterns of disturbance of breathing in sleep, associated with profound but transient hypoxaemia, which seems to be quite common in "blue and bloated" patients with chronic bronchitis and emphysema in whom hypoxaemia, carbon dioxide retention, secondary polycythaemia, and cor pulmonale complicate the irreversible airways obstruction.[26-29]

Sudden profound dips in ear oxygen saturation in these non-obese patients have been confirmed as reflecting arterial P_{O_2} by direct sampling, P_{O_2} values as low as 3·5 kPa (26 mmHg) being found. The dips in saturation are particularly prominent during REM sleep and have been associated with a further rise in the already elevated mean pulmonary arterial pressure,[27 30] very similar to that seen in apnoeic episodes in Pickwickian patients.[31] In dogs the ventilatory response to carbon dioxide was depressed during REM sleep,[32] whereas the drive to breathing from hypoxia was maintained in REM sleep.[8] However, in the hypoxic chronic bronchitic with cor pulmonale, nocturnal oxygen therapy, although raising arterial P_{O_2}, did not abolish transient hypoxaemia in REM sleep, although the dips in saturation were then to less profound levels of hypoxaemia.[27] These authors have also found that such episodes of transient hypoxaemia, which they found to be more associated with hypopnoea than sleep apnoea, were of greater depth and more frequent during sleep in the "blue and bloated" bronchitics, than in patients with similar degrees of airways obstruction, but without carbon dioxide retention or severe hypoxaemia when awake, who thus could be described as "pink and puffing."

This observation, coupled with the increase in pulmonary hypertension during transient hypoxaemia in sleep, has led to the suggestion[33] that patients with chronic bronchitis and emphysema who develop the "blue and bloated" syndrome may have been prone to episodes of sleep hypopnoea, with transient hypoxaemia, before they developed severe chronic bronchitis and emphysema, whereas patients with the "pink and puffing" type of chronic bronchitis and emphysema would not have this pre-morbid tendency to recurrent nocturnal hypoxaemia. The hypoxic drive to breathing is blunted in at least some "blue and bloated" bronchitics,[34] and this hypoxic drive appears to vary in intensity by up to sixfold in normal healthy men.[35] This leads to the additional proposal that a feeble hypoxic drive may prevent an adequate correction of transient sleep hypoxaemia, so increasing the severity of this hypoxaemia. Recurrent nocturnal transient hypoxaemia, presumably occurring more or less every night, over many years, may then lead to the sustained pulmonary hypertension and right ventricular hypertrophy which characterises cor pulmonale in the "blue and bloated" bronchitic. Needless to say this hypothesis will require a prospective study over many years to sustain or refute. However, as Charles de Gaulle is reputed to have said on being told that a problem would take 20 years to solve, "Toutes les raisons sont bonnes pour remettre au lendemain ce qu'on peut faire le jour même"; possibly translated as "all the more reason for starting tomorrow! "

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