Alveolar hypoventilation and hypersomnbia in myotonic dystrophy

GIORGIO COCCAGNA, MAGDA MANTOVANI, CLAUDIO PARCHI, FILIPPO MIRONI, AND ELIO LUGARESI

From the Clinica delle Malattie Nervose e Mentali dell’Università di Bologna, Italy

SYNOPSIS A case of myotonic dystrophy accompanied by alveolar hypoventilation and hypersomnia is presented. Radiological studies and EMG examination of the intercostal muscles demonstrated that the respiratory muscles were affected by the disease, while polygraphic recordings showed that the alveolar hypoventilation and pulmonary hypertension worsened during sleep. The hypersomnia preceded the appearance of clinical signs of the muscular disease by many years and persisted even after treatment when the blood gas analysis values were greatly improved. During both diurnal and nocturnal sleep, the patient frequently fell asleep directly into a REM stage. The possibility is discussed that, concomitant with the respiratory musculature involvement, there is an alteration in the central nervous system in myotonic dystrophy which is at least partially responsible for both the alveolar hypoventilation and the hypersomnia.

The presence of acrocyanosis in a case of myotonic dystrophy was reported by Adie and Greenfield in 1923. Twelve years later at the necropsy of another case, Londres (1935) observed microscopic alterations in the diaphragm similar to those found in the skeletal muscles. However, the first detailed description of the clinical picture of alveolar hypoventilation in a patient with hypofunction and myotonia of the respiratory muscles was provided by Benaim and Worster-Drought in 1954. Some other similar cases have subsequently been described (Bashour et al., 1955; Kilburn et al., 1959a; Cannon, 1962; Gillam et al., 1964; Kohn et al., 1964; Lee and Hughes, 1964).

Very recently, attention has been focused on the fact that respiratory distress constitutes the principal problem in the neonatal forms of myotonic dystrophy (Aicardi et al., 1974; Bossen et al., 1974). Moreover, it has often been reported that patients with myotonic dystrophy are particularly susceptible to respiratory infections and have a high incidence of respiratory distress after general anaesthesia (Dundee, 1952; Lodge, 1958; Kaufman, 1960; Kohn et al., 1964; Telerman-Toppet, 1970). It has not yet been determined whether this anaesthesiological complication should be attributed to central or peripheral causes.

Anatomical, electromyographic, and radiological evidence that both the diaphragm and the intercostal muscles may be affected in myotonic dystrophy may account for the possible appearance of alveolar hypoventilation (Benaim and Worster-Drought, 1954; Bashour et al., 1955; Caughey and Pachomov, 1959; Aicardi et al., 1974; Bossen et al., 1974).

Nevertheless, the hypothesis that there is a primary hypoxicatability of the respiratory centre should not be disregarded (Kilburn et al., 1959b).

Hypersomnia has been mentioned in some case reports of myotonic dystrophy, but only rarely has it been given particular attention; this condition has usually been considered secondary to the hypercapnia (Caughey and Myrianthopoulos, 1963; Kohn et al., 1964), although there

1 Address for reprint requests: Giorgio Cocagna, Clinica delle Malattie Nervose e Mentali, Via Ugo Foscolo 7, Bologna, Italy.
2 Present address: Servizio di Cardiologia, Ospedale Maggiore C.A. Pizzardi, Bologna, Italy.
3 Present address: Istituti Ospedalieri C. Poma—Divisione Neurologica, Mantova, Italy.

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are some observations in which this correlation must certainly be excluded (Kilburn et al., 1959a; Phemister and Small, 1961; Gillam et al., 1964).

The neurophysiological and respiratory function studies that we carried out on a patient with myotonic dystrophy who presented a clinical picture of alveolar hypoventilation with secondary polycythaemia, pulmonary hypertension, and hypersomnia may contribute to an improved pathogenetic understanding of these syndromes.

CASE REPORT

B.G., a 50 year old, male, unskilled factory worker, entered our clinic on March 30, 1974 complaining of hypersomnia and cyanosis resulting from myotonic dystrophy.

The family history of the patient is quite significant: four brothers died very young from unspecified causes; one unmarried brother has myotonic dystrophy; one sister, who died of unspecified causes, suffered from the same disease as do three of her six children. The patient's oldest daughter (aged 20 years) is in a psychiatric hospital for a severe form of oligophrenia associated with distal muscular atrophy of the upper limbs. Another daughter (aged 19 years), whom we were able to follow personally, has a typical form of myotonic dystrophy. Five other children, aged from 5 to 16 years old, are apparently free of neuromuscular disease. At the age of 20 years the patient had diphtheria and at 45 he underwent surgery for cataract of the left eye.

For several years he has noted a certain difficulty in relaxing his grasp and wasting of the muscles of the forearm, to which he has never paid great attention. The diagnosis of myotonic dystrophy had been made one year before he was admitted when he was called for a clinical examination by the neurologist of the hospital where a niece was being treated for the same disease.

The patient stated that since adolescence he has required an unusual amount of sleep and his wife confirmed that he spent all his free time sleeping. Approximately two months ago his need for sleep increased; often when he returns home from work at 5:00 p.m., he goes to bed and does not wake until the following morning; he frequently falls asleep during meals or at his job on an assembly line. He has never presented cataplectic attacks or sleep paralysis. His wife stated that recently he had become cyanotic during sleep. During the last three years he has had a diminution of libido and been unable to achieve erection.

CLINICAL EXAMINATION On examination the patient showed a characteristic myotonic facies with almost complete baldness, bilateral ptosis, and atrophy of the temporal and sternomastoid muscles. There was cyanosis of the lips and nail beds. His speech was monotonous and expressionless. Cataract was present in the right eye, while there was postoperative absence of the left lens.

We also found mechanical myotonia of the tongue, which was furrowed by deep longitudinal fissures, muscular atrophy of the four limbs, greater distally, with active myotonia of the hands and mechanical myotonia of the thenar eminence and the extensor muscles of the forearm. The deep reflexes were weak in the upper limbs, absent in the lower limbs. The abdomen was prominent and the abdominal muscles thin. The testicles and penis appeared normally developed. Arterial pressure was 130/90 mmHg.

From a psychological point of view, the patient was clearly oligophrenic and rather uncooperative despite his apparent willingness.

LABORATORY DATA Urinalysis and levels of blood urea nitrogen, azotaemia, fasting blood sugar, blood Wassermann reaction, and the erythrocyte sedimentation rate were within normal limits. The red blood cell count was 7.58 × 10⁸ mm⁻³ haemoglobin 19.5 g/dl; mean corpuscular volume 81 μm²; haematocrit 65%; white blood cells 9.5 × 10³ mm⁻³ with a standard formula; platelets 340 × 10³ mm⁻³.

RADIOGRAPHY Skull radiography showed no abnormalities. Radiography of the thorax showed that both halves of the diaphragm were elevated and there was a diffuse reduction in the lung field transparency, especially at the bases, due to the upward displacement of the diaphragm. The cardiovascular shadow, while normal in placement and configuration, appeared to be inserted in the depression between the two raised halves of the diaphragm. On screening, the diaphragm showed a very limited respiratory excursion.

The electrocardiogram was normal.

EEG The occipital activity consisted of an unstable rhythm at 7 Hz which reacted to eye opening; on all the derivations polymorphous theta activity at 4–6 Hz predominated. During hyperpnoea the occipital activity became more stable.

EMYTOPHYLOGRAPHY Several muscles of the limbs were studied (right deltoid, left extensor communis digitorum, abductor pollicis brevis, right tibialis anterior). In all the muscles examined, numerous myotonic discharges (dive-bomber type) appeared
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when the needle was inserted. On voluntary contraction, potentials of short duration and low voltage, sometimes polyphasic, occurred; the interference pattern appeared fairly early. On relaxation there was persistence of the electrical activity. Percussion gave rise to prolonged myotonic discharges.

The activity of the respiratory muscles was recorded at the level of the seventh right intercostal space. When the needle was inserted, myotonic discharges of slow positive potentials, rapid potentials, or these types superimposed were observed (Fig. 1B). The respiratory activity produced poor tracings consisting of small-size and short-duration potentials (5–6 ms), often polyphasic. Coughing and forced breathing increased the EMG activity only slightly. A myotonic discharge was recorded from right rectus abdominis (Fig. 1C).

**RESPIRATORY FUNCTION TESTS** (Tables 1 and 2) The spirometric data were obtained with the patient seated using a Pulmotest Godard closed circuit apparatus; residual volume and flow resistance were recorded with Pulmorex volumetric body plethysmograph. The gas analysis values of arterial blood were determined using a Radiometer blood microsystem apparatus.

Spirometry revealed severe ventilatory insufficiency of a primarily restrictive type. In particular, there was a marked reduction of the vital capacity (51% of predicted, according to Baldwin), the total lung capacity (2750 ml) and the maximum breathing capacity (24% of predicted according to Baldwin). There were only moderate signs of airway obstruction (percent vital capacity: 64; airway resistance: mean 3.6 cm H₂O/l/s).

Arterial gas analysis during quiet wakefulness showed marked hypoxia and hypercapnia with respiratory acidosis.

Ventilatory response to CO₂ (rebreathing) was slight and drug stimulation of the respiratory centre with crotethamide and cropropamide (Micoren) proved ineffective.

**POLYGRAPHIC STUDIES** A 24 hour polygraphic recording was made with simultaneous recording of

**FIG. 1** A: an EMG recorded from the seventh right intercostal space during quiet respiration shows reduced activity consisting of short duration potentials. B: myotonic discharge on insertion of the needle into the seventh intercostal space. C: myotonic discharge consisting of slow positive potentials, recorded from the rectus abdominis.

**TABLE 1**

<table>
<thead>
<tr>
<th><strong>LUNG FUNCTION TESTS</strong></th>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td><strong>Height</strong></td>
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<td><strong>Weight</strong></td>
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<tr>
<td><strong>Respiratory rate</strong></td>
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<tr>
<td><strong>Tidal volume</strong></td>
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<tr>
<td><strong>Resting ventilation</strong></td>
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<td><strong>Resting ventilation/m²</strong></td>
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<tr>
<td><strong>Ventilatory equivalent for O₂</strong></td>
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<tr>
<td><strong>Inspiratory reserve volume</strong></td>
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<tr>
<td><strong>Expiratory reserve volume</strong></td>
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<tr>
<td><strong>Vital capacity</strong></td>
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<tr>
<td><strong>Vital capacity (percentage of predicted value)</strong></td>
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<tr>
<td><strong>Inspiratory capacity</strong></td>
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<tr>
<td><strong>Functional residual capacity</strong></td>
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<tr>
<td><strong>Total lung capacity</strong></td>
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<tr>
<td><strong>Residual volume</strong></td>
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<tr>
<td><strong>Residual volume x 100</strong></td>
</tr>
<tr>
<td><strong>Total lung capacity</strong></td>
</tr>
<tr>
<td><strong>Maximum expiratory volume/s</strong></td>
</tr>
<tr>
<td><strong>Maximum breathing capacity</strong></td>
</tr>
<tr>
<td><strong>Maximum breathing capacity</strong> (percentage of predicted value)</td>
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<tr>
<td><strong>Airway resistance</strong></td>
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<tr>
<td><strong>Dynamic lung compliance</strong></td>
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<tr>
<td><strong>Viscous work (inspiratory)</strong></td>
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<tr>
<td><strong>Elastic work</strong></td>
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<tr>
<td><strong>Red cell count</strong></td>
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<tr>
<td><strong>Haematocrit</strong></td>
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<tr>
<td><strong>PaCO₂</strong></td>
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<tr>
<td><strong>PaO₂</strong></td>
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<tr>
<td><strong>SaO₂</strong></td>
</tr>
<tr>
<td><strong>pH</strong></td>
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the EEG, horizontal oculogram, EMG of the mylohyoid muscle, and thoracic respirogram. The recordings were carried out using a Galileo polygraph model PF 146 placed in a room beside the bedroom. Sleep stages were scored according to Dement and Kleitman (1957) but stages 3 and 4 were considered together. For the diurnal recording the patient sat in a comfortable armchair where he could read or eat; the doors to the room were kept open so that the patient was not isolated from normal background noise; periodically he was allowed to get up and walk in the corridors for a short time.

The patient was relatively uncooperative throughout the recording period and repeatedly asked to have the electrodes removed from his head: for this reason we believe that he slept considerably less in the laboratory than he usually did in the ward. In the course of the day he had repeated episodes of sleep lasting from 20 min to more than an hour. His nocturnal sleep was disturbed by numerous prolonged awakenings during which the patient continued to ask that the recording be terminated. In 24 hours the patient slept a total of nine hours; of these 19.25% was stage 1, 25.28% stage 2, 20% stages 3–4 and 35.47% rapid eye movement stage (REM). During both diurnal and nocturnal sleep we observed several episodes of falling directly into REM sleep. The morphological alterations of the wakefulness EEG tracing were reflected in the sleep tracing: in fact, the scarcity of spindles and K-complexes made it difficult to distinguish between the different slow waves of sleep.

A subsequent nocturnal polygraphic recording was made during which the systemic and pulmonary arterial pressure and the oral and nasal respirogram were also recorded. For the oral and nasal respirogram two thermocouples were placed in front of the mouth and in one nostril respectively. The pulmonary arterial pressure was recorded continuously by means of a Grandjean micro-catheter introduced through an antecubital vein of the left arm pushed into the pulmonary artery (Grandjean, 1967). The systemic arterial pressure was recorded using an Abbocath Teflon needle introduced percutaneously into the left radial artery. The catheter and the Teflon needle were connected to Statham P 23 Db transducers which were, in turn, connected to manometric pre-amplifiers of the polygraph. Through a three-way stopcock, the recording could be interrupted periodically to allow perfusion of the needle and the catheter with heparinized saline solution and periodic sampling of the arterial blood for gas analysis determinations. The analyses were performed immediately after sampling.

During sleep the breathing became substantially more irregular than during wakefulness: there were long periods in which the breathing gradually shallowed culminating in the onset of true central apnoeas lasting from a few to 20 seconds. In stage REM the shallow respiratory excursions and apnoeas were more prolonged than in the other stages; occasionally the apnoeas had the character of obstructive apnoeas—that is, with persistence of the thoracic movements during the oral and nasal apnoea.

The alveolar hypoventilation worsened notably throughout slow wave sleep and deteriorated further in REM sleep. Both the systemic and the pulmonary arterial pressures rose progressively from stage 1 though stage 4 with a final increase in stage REM (Fig. 2 and Table 3).

The patient was transferred to a cardiology ward where he underwent treatment with an intermittent positive pressure breathing apparatus (IPPB). After seven days of therapy the alveolar ventilation during wakefulness had improved greatly (pH: 7.28; PaO₂: 6.5 kPa (49 mmHg); PaCO₂: 7.7 kPa (58 mmHg) and right heart catheterization was performed; the pressure values of the atrium, right ventricle and the pulmonary artery were much lower (RA = 6/0 mmHg, mean: 2; RV = 27/0–5 mmHg; PA = 42/15 mmHg, mean 22; mean wedge pressure: 8.6/6.1 mmHg).
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FIG. 2 Polygraphic recording during spontaneous nocturnal sleep (11 April 1974). The pulmonary arterial pressure (Pulm. Art. Press.) is already high during wakefulness (73/40 mmHg), it increases during slow sleep (st. 3) and undergoes a further rise in REM sleep, reaching values of 96/53 mmHg. The systemic arterial pressure (Arter. Press.), normal during wakefulness, increases only slightly during sleep (EEG: first two channels; OCULOG.: horizontal electro-oculogram; EMG: electromyogram of mylohyoid muscle).

TABLE 3

<table>
<thead>
<tr>
<th>Sleep stages:</th>
<th>11 April 1974</th>
<th>6 June 1974</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wa</td>
<td>St. 1</td>
</tr>
<tr>
<td>Systemic arterial pressure (mmHg)</td>
<td>137/70 146/78 146/80 142/73 150/79 142/79</td>
<td>116/61 121/66 127/67 119/63 145/72 114/58</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mmHg)</td>
<td>72/40 78/46 81/45 80/44 94/58 73/41</td>
<td>48/16 50/16 51/19 48/16 76/33 44/11</td>
</tr>
<tr>
<td>(mean)</td>
<td>(51) (59) (59) (57) (69) (55)</td>
<td>(28) (28) (53) (25)</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>8.2 9.3 — 9.7 10.6 9.0</td>
<td>6.2 — — 7.8 9.2 8.6</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>5.9 5.3 — 4.7 3.7 5.6</td>
<td>6.3 — — 6.5 4.1 6.8</td>
</tr>
<tr>
<td>O2 saturation (%)</td>
<td>70 62 — 53.6 39 64</td>
<td>77 — — 77.2 47 79</td>
</tr>
<tr>
<td>pH</td>
<td>7.26 7.23 — 7.23 7.21 7.24</td>
<td>7.30 — — 7.27 7.23 7.27</td>
</tr>
</tbody>
</table>

Wa: Values during quiet wakefulness before sleep.
Wb: Values three minutes after reawakening in the morning.
9 mmHg). The pulmonary arteriolar resistances were high—190 dyne/s/cm$^5$ (19 MPa·s·m$^{-5}$).

The cardiac output was within normal limits (cardiac index: 3.5 l·m$^{-2}$). During IPPB respiration with 100% $O_2$ the mean pulmonary pressure went from 22 to 17 mmHg while the $PaO_2$ in the pulmonary artery rose from 4.7 to 5.3 kPa (35 to 40 mmHg) and the $PaCO_2$ dropped from 10.1 to 6.7 kPa (76 to 50 mmHg). Mechanical respiration was continued for 20 more days. During this period the $PaCO_2$ values fell as low as 6.5 to 7.0 kPa (49–53 mmHg); the pH ranged between 7.31 and 7.34 and the $PaO_2$ between 6.4 and 6.9 kPa (48 and 52 mmHg).

The haematocrit had dropped to 54–57%. The patient was then transferred back to our clinic. Although the cyanosis was considerably reduced, the diurnal somnolence persisted: the nurses often found the patient sleeping at any hour of the day. His neurological condition remained unchanged.

### POLYGRAPHIC RECORDINGS

A new 24 hour polygraphic recording demonstrated that numerous sleep episodes persisted during the day. The patient slept for a total of 11 hours and 45 minutes in 24 hours. He spent 17.67% of this sleep in stage 1, 19% in stage 2, 33% in stages 3-4, and 30% in REM sleep.

On two occasions REM stages appeared a few minutes after dozing off. The morphology of the EEG tracing had become normal: in wakefulness there was regular stable alpha activity at 9 Hz with sporadic bilateral theta activity; during sleep there were abundant spindle and K-complexes.

The polygraphic recording with simultaneous recording of the pulmonary and systemic arterial pressures was also repeated. During wakefulness both the systemic arterial pressure and, in particular, the pulmonary were greatly diminished with respect to the previous recording; some degree of alveolar hypoventilation persisted. During light slow wave

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**FIG. 3 Polygraphic recording during spontaneous nocturnal sleep obtained after clinical improvement of the patient (6 June 1974).** In wakefulness both the systemic and the pulmonary arterial pressures are clearly reduced with respect to the previous recording. They do not undergo significant changes during slow sleep (st. 3) but during REM sleep both rise substantially. The pulmonary pressure increases from 50/20 mmHg during wakefulness to 86/35 mmHg during REM sleep.
sleep (stages 1 and 2) respiratory irregularities and apnoeas persisted, while during deep slow wave sleep the breathing was regular. During the REM stages the apnoeas were more frequent and in this stage alone there was a substantial worsening of the gas analysis values and a substantial increase in the systemic and pulmonary arterial pressures (Fig. 3 and Table 3).

The patient was discharged with a prescription for procainamide (3 g per day) and a respiratory analeptic crotethamide and cromopropamide (Micoren). Four months after discharge the spontaneous myotonia was much reduced; there was no cyanosis, but a certain tendency to fall asleep persisted. The patient refused any further follow-up examination.

DISCUSSION

The patient entered our clinic presenting severe hypersomnia and marked alveolar hypoventilation with secondary increase of blood cells. The hypersomnia could easily have been attributed to carbonarcosis, but further inquiry disclosed that the hypersomnia had existed before the appearance of the clinical signs of myopathy and, moreover, it persisted even after treatment when the PaCO₂ had returned to nearly normal values.

The diminished diaphragmatic motility indicated by fluoroscopy and the EMG finding of myotonia of the intercostal muscles demonstrated that the respiratory muscles were affected by myopathy. The alveolar hypoventilation worsened during sleep, especially REM sleep, and the patient was observed to fall asleep directly into a REM stage during both diurnal and nocturnal episodes of sleep.

ORIGIN OF THE ALVEOLAR HYPVENTILATION

The hypothesis that alveolar hypoventilation arising in the course of myotonic dystrophy may be due to the extension of the myopathy to the respiratory muscles is supported by our observation.

As it is not easy to explain why these patients are more likely to encounter alveolar hypoventilation than those with non-myotonic muscular dystrophy, it has been suggested that the myotonic phenomenon itself and/or a concomitant hypoexcitability of the respiratory centre facilitate the onset of alveolar hypoventilation (Kilburn et al., 1959). In the patients of Kilburn et al., the existence of a hyposensitivity of the respiratory centre was confirmed by a diminished ventilatory response to CO₂ and the aggravation of the hypoventilation produced by inhalation of pure O₂. Gillam et al. (1964) did not observe a diminished response to CO₂ but found, instead, that thiopentone administration provoked a marked respiratory depression in some of their patients. However, in their cases, contrary to those of Kilburn et al. (1959), alveolar hypoventilation was not present. On the basis of these findings, it may be concluded that a central respiratory depression exists in some cases of myotonic dystrophy; nevertheless, we cannot exclude the possibility that this is secondary to the hypercapnia produced by hypoventilation.

Our data demonstrate that sleep, and especially REM sleep, has negative effects on the alveolar ventilation and pulmonary pressure. If we admit the existence of a latent primary hyposensitivity of the respiratory centre to CO₂, it is possible that the alveolar hypoventilation arises initially only during sleep due to an exaggeration of the physiological tendency to breathe periodically and to hypoventilate (Bulow, 1963). Chronic hypercapnia during sleep would thus lead to a further progressive diminution in the excitability of the respiratory centre, with the consequent appearance of alveolar hypoventilation even during wakefulness. We have proposed an analogous pathogenetic hypothesis to explain the chronic hypoventilation produced by obstructive apnoeas in the Pickwickian syndrome (Lugasèi et al., 1972).

ORIGIN OF THE HYPERSOMNIA

With regard to the origin of the hypersomnia our case must be grouped with those of Phemister and Small (1961), Gillam et al. (1964), and Kilburn et al. (1959a) in which the sleep disturbance cannot be imputed to carbonarcosis.

The hypothesis that hypercapnia resulting from hypoventilation progressively depresses not only the respiratory centre, but also the CO₂ sensitive reticular activating substance (Bonvallet et al., 1955), offers a plausible explanation for the hypersomnia but does not explain why this disturbance may set in before (or independently of) alveolar hypoventilation.

The presence of hypersomnia in myotonic
dystrophy may also be explained by the theory that the condition is primary and of central origin (Phemister and Small, 1961; Kilburn et al. 1959b) or that it is caused by a reduction in the proprioceptive impulses originating in the respiratory muscles. These impulses have a stimulatory effect on alertness as well as on the respiratory centre (Kilburn et al., 1959a; Gillam et al., 1964).

The hypothesis of a primary central disturbance of sleep regulation would also serve to clarify some anomalies in sleep structure, such as the abundance and precocity of the REM stages which we discovered in our case and which were probably present in the patient of Kilburn et al. (1959a) who reported frequent dreams and episodes of sleep paralysis.

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