Fortnightly Review

Sleep studies of respiratory function and home respiratory support

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Breathing differs when we are awake and asleep. Cortical stimulation of the respiratory centres wanes with the onset of sleep, resulting in a decrease in chemosensitivity to carbon dioxide and oxygen tensions; a reduction in upper airway, intercostal, and accessory muscle tone, particularly in rapid eye movement sleep; altered responses to elastic and resistive respiratory loads; and a reduction in metabolic rate.¹ Failure to adapt to these physiological processes in predisposed subjects sets the scene for the development of sleep disordered breathing, in the form of the sleep apnoea syndromes and nocturnal hypoventilation (fig 1). Night time and daytime respiratory function is linked in that although obstructive apnoeas occur only during sleep, these can ultimately lead to diurnal abnormalities of breathing. Nocturnal hypoventilation either accompanies or heralds the development of diurnal respiratory failure.

FIG 1—Links between sleep disordered breathing conditions

Sleep disordered breathing

OBSTRUCTIVE SLEEP APNOEA/HYPOPNOEA SYNDROME

This syndrome is characterised by snoring and repeated episodes of complete or partial obstruction of the upper airway which cause sleep fragmentation, fluctuations in arterial oxygen saturation, and daytime somnolence. There is no satisfactory definition of the syndrome, as a spectrum exists which ranges from normal breathing through snoring to severe effects. It is also clear that some snorers, in the absence of apnoeic episodes, may also suffer from disrupted sleep (the upper airway resistance syndrome).² For diagnostic purposes the occurrence of 15 or more episodes of apnoea or hypopnoea per hour (apnoea/hypopnoea index) is usually considered abnormal. In each person the severity of the condition can be expressed by the apnoea/hypopnoea index, but it is the consequences of these events in terms of degree of desaturation, sleep fragmentation, and cardiovascular abnormalities such as hypertension and dysrhythmias which are crucial. The effects of untreated obstructive sleep apnoea/hypopnoea syndrome are listed in the box.

Early surveys of the prevalence of this syndrome

Long term effects of untreated obstructive sleep apnoea

- Premature death³
- Increased incidence of vascular events, including myocardial infarction and stroke⁴
- Impaired daytime performance leading to increase in road traffic accidents and poor work performance
- Stress on personal relationships caused by snoring and personality change

Summary points

- Sleep disordered breathing is common and has previously been underdiagnosed. Obstructive sleep apnoea affects up to 4% of men and 2% of women
- Facilities for the investigation and treatment of sleep disordered breathing need to be expanded to meet this need. Training in respiratory sleep medicine should be increased
- Full polysomnography is unnecessary in all patients referred for sleep studies. Screening sleep studies should be subject to continued assessment and audit
- Home ventilation improves quality of life and reduces morbidity and mortality in patients with hypercapnic respiratory failure due to chest wall disorders and stable neuromuscular disease. Selected patients with chronic airflow obstruction and progressive neuromuscular conditions may benefit. Nasal intermittent positive airway pressure ventilation is the non-invasive method of choice
- Health purchasers should make adequate provision for funding the investigation and treatment of patients with sleep disordered breathing

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suggested a figure of around 1% in men, with the condition being rare in premenopausal women. A recent large study in the United States, however, has shown that 9% of men and 4% of women of working age have an apnoea/hypopnoea index of 15 or more.⁵ Four per cent of the men and 2% of the women studied had symptoms related to their sleep disordered breathing. These figures indicate that the obstructive sleep apnoea/hypopnoea syndrome is a public health problem of major proportions which has previously been seriously underestimated.

CENTRAL SLEEP APNOEA

In contrast, central sleep apnoea is rare. It can be divided into two forms: hypercapnic and non-hypercapnic. In the non-hypercapnic variety central apnoeas occur in the presence of normal ventilatory function during the day. Affected people show ventilatory instability at the onset of sleep, leading to a periodic pattern of breathing—for example, Cheyne-Stokes respiration in cardiac failure. Here, the response to changes in arterial partial pressure of carbon dioxide occur at a different rate to changes in partial pressure of oxygen because of a combination

of delayed circulation time and high central chemosensitivity. As with the obstructive sleep apnoea/hypopnoea syndrome, central apnoeas may fragment sleep. In addition to cardiac failure, periodic breathing occurs at altitude, in frontal lobe diseases, and in other forms of cerebral injury.

The hypercapnic form of central apnoea is part of the spectrum of nocturnal hypoventilation syndromes and is associated with defective ventilatory responses to hypercapnia and hypoxia (see below). These patients form the overlap group between central sleep apnoea and the hypoventilation syndromes in figure 1.

NOCTURNAL HYPOVENTILATION

This is confirmed by arterial desaturation and carbon dioxide retention, which is most distinct during rapid eye movement sleep. Nocturnal hypoventilation is seen in patients with primary or acquired central drive disorders, neuromuscular and chest wall disorders, and severe airflow obstruction.

Diagnosis and monitoring

All forms of sleep disordered breathing are readily diagnosed by monitoring of ventilation during sleep. The key questions to ask are, who needs a sleep study and what type of monitoring should be carried out?

WHO NEEDS A SLEEP STUDY?

Obstructive sleep apnoea/upper airway resistance syndrome

To increase the yield of sleep studies with positive results several authors have examined the predictive power of clinical features in the diagnosis of the obstructive sleep apnoea/hypopnoea syndrome. Hoffstein and Szalai showed that in patients with this syndrome, snoring is almost universal (an important exception being patients who have undergone upper airway surgery); nocturnal choking is experienced by 73%, apnoeas were witnessed by partners in 75%, and hypersomnolence was present in 57%.⁶ A prevalence study in the United Kingdom has shown that neck circumference, alcohol consumption, age, and obesity are independent risk factors for the syndrome.⁷

Therefore patients who snore and have a history of witnessed apnoeas, nocturnal choking, and daytime somnolence have a high probability of the obstructive sleep apnoea/hypopnoea syndrome. An outpatient consultation should include questions on weight gain and change in collar size, alcohol consumption, family history of snoring or this syndrome, and nasal blockage. It should be noted that symptoms of this syndrome in female patients may sometimes differ from those in males.⁸ If it is due to adenotonsillar hypertrophy in children it may present as hyperactivity, learning problems, and failure to thrive.⁹ Daytime somnolence in adults can be quantified by using the Stanford or Epworth sleepiness scale or multiple sleep latency time.¹⁰ Clinical examination

should include viewing the upper airway and a full cardiorespiratory assessment.

Nocturnal hypoventilation

The commonest symptoms of nocturnal hypoventilation are morning headache, daytime fatigue, and a reduction in exercise tolerance. Symptoms can be non-specific and often develop insidiously. For this reason "at risk" groups with restrictive and obstructive lung disorders should be identified and followed as outpatients. These include patients with idiopathic scoliosis and a vital capacity of less than half predicted, those with congenital or early onset scoliosis, those with high thoracic curves, and patients with weakness of the respiratory muscles. Bye *et al* have shown that in subjects with neuromuscular disease, minimum oxygen saturation during sleep correlated with vital capacity and fall in supine vital capacity.¹¹ Daytime hypercapnia is associated with an inspiratory muscle strength of less than 30% predicted.

In chronic obstructive pulmonary disease the best guide to the degree of nocturnal desaturation is oxygen saturation when awake. The presence of additional pathology such as obstructive sleep apnoea/hypopnoea syndrome may cause a nocturnal fall in oxygen saturation that is disproportionate to daytime levels; this possibility should be considered in patients with chronic obstructive pulmonary disease in whom daytime arterial blood gas tensions are worse than expected. With the exception of this subgroup, most such patients who fulfil criteria for long term oxygen therapy tolerate this without unacceptable nocturnal or diurnal hypercapnia. Routine sleep studies are therefore not required in these patients.

MONITORING OF RESPIRATION DURING SLEEP

Polysomnography is the conventional method of studying sleep/wake disorders and has previously acted as the yardstick with which other techniques are compared (box). It is the recommended investigation for all forms of sleep disordered breathing in the policy guidelines of a number of organisations, including the American Thoracic Society.¹²

Although polysomnography has been immensely helpful in the development of sleep medicine and has aided standardisation of monitoring, it has several limitations. Importantly, it is costly in equipment and staff time. Owing to the limited number of sleep laboratories in the United Kingdom full polysomnography on all current referrals would be an impossibility, and referral rates are likely to rise. In addition, conventional sleep staging¹³ may not detect micro-arousals, so the diagnosis of the upper airway resistance syndrome and the true degree of sleep fragmentation can be missed.

To meet the needs of all patients with possible sleep/wake disorders alternative monitoring strategies have been developed. These include simpler screening studies that can be carried out unattended in hospital or at home, and split night studies. Few of these methods have been validated against polysomnography, but they offer a pragmatic solution which should be subject to further investigation and audit.

SCREENING SLEEP STUDIES FOR OBSTRUCTIVE SLEEP APNOEA/HYPOPNOEA SYNDROME

Oximetry—Pulse oximeters are widely available and many have facilities for data storage and printout. If samples are taken about every 5 seconds, changes in arterial oxygen saturation are accurately followed and characteristic patterns of desaturation in severe obstructive sleep apnoea/hypopnoea syndrome and hypoventilation can be recognised. Although oximeters are inexpensive and can be used in the home, oximetry alone is not an ideal screening method as it

Polysomnography

Channel	Data
Electroencephalogram (EEG)	Arousals
Electro-oculogram (EOG)	Sleep stages: non rapid-eye movement 1-4
Electromyogram (EMG)	rapid eye movement awake
Pulse oximetry	Arterial oxygen saturation Heart rate
Airflow at nose and mouth plus ribcage and abdominal movement	Characterisation of apnoeas Apnoea/hypopnoea index
Microphone/decibel meter	Snoring
Position monitor	Posture in bed
Leg movement	Periodic leg movement

cannot reliably exclude the diagnosis of the syndrome. Two recent studies comparing oximetry with polysomnography showed that oximetry predicted an apnoea/hypopnoea index of >15 with a sensitivity of only 40%.^{14,15} This is unacceptable as a considerable number of subjects with this syndrome and minimal or no desaturation will be missed. False positive diagnoses of the obstructive sleep apnoea/hypopnoea syndrome can also be a problem¹⁶ and can be caused by artefacts on the trace or desaturation in patients with chronic lung disease. To facilitate interpretation of data the overnight trace should always be available for scrutiny.¹⁶

Multichannel screening systems—An ever expanding range of equipment is available, including the Mesam IV, Edentech, Densa Pneumograph 600, and CNS Poly G systems. Many of these include pulse oximetry, thermistors to measure oronasal airflow, chest and abdominal movement sensors, and a body position

FIG 2—Multichannel screening system (Densa pneumograph 600) showing from top to bottom line: incidence of apnoeas and hypopnoeas, arterial oxygen saturation, body position, paradox phase angle between chest and abdominal movement and snoring (L-loud, Q-quiet) over a two hour period in patient with moderate obstructive sleep apnoea/hypopnoea syndrome

FIG 3—Arterial oxygen saturation, oronasal airflow, chest wall movement, and abdominal movement from polysomnography recording (Poly) compared with data in bottom chart from Mesam IV screening system in patient with the obstructive sleep apnoea/hypopnoea syndrome

FIG 4—Top graph: overnight monitoring of oxygen saturation (—) and transcutaneous carbon dioxide (---) in young man with Duchenne muscular dystrophy showing nocturnal hypoventilation. Bottom graph: same patient on subsequent night being treated with nasal intermittent positive pressure ventilation

monitor (see figs 2 and 3). The combination of video recording plus oximetry is also popular and allows examination of respiratory pattern, body position, and movement. A video camera may be particularly helpful in documenting other problems such as sleep terrors, nocturnal epilepsy, periodic leg movements, and sleep induced laryngospasm. As snoring is the presenting feature in many patients it is important that an attempt is made to confirm the presence of snoring and assess its severity by using a microphone or decibel meter. Software algorithms calculate an apnoea/hypopnoea index on the basis of oximetry, airflow, and detection of chest movement. Electroencephalogram, electro-oculogram, and electromyogram channels are not usually included in these portable systems so that it is impossible to quantify sleep. Evidence suggests however, that it is unnecessary to document formally the presence of sleep and that sleep staging does not add considerably to the ability to detect the obstructive sleep apnoea/hypopnoea syndrome.¹⁴ A disadvantage is that data on arousals and sleep disruption are lost, and these are key determinants of daytime somnolence.¹⁷ Fortunately recent work indicates that arousals may be usefully assessed by autonomic phenomena such as changes in the heart rate or fluctuations in blood pressure.¹⁸

Transcutaneous/end tidal carbon dioxide tension—Whereas nocturnal hypercapnia is a late feature of obstructive sleep apnoea/hypopnoea syndrome, it is inevitable in the hypoventilation syndromes. Hence monitoring of partial pressure of carbon dioxide is not required routinely in the obstructive sleep apnoea/hypopnoea syndrome but is advisable if hypoventilation is suspected. Monitoring of partial pressure of carbon dioxide is also helpful in patients who have features of the obstructive sleep apnoea syndrome on a background of chronic lung disease, severe obesity, or muscle weakness (these patients fall into the overlap category between the syndrome and nocturnal hypoventilation in fig 1). Transcutaneous or end tidal measurement of carbon dioxide is vital to assess the efficiency of ventilatory treatment (see fig 5) or the effects of oxygen therapy in a hypercapnic patient. The response time of the monitor for the transcutaneous partial pressure of carbon dioxide is much slower than oximetry or end tidal measurement, but it can track changes with reasonable accuracy.

Home versus hospital studies—Home monitoring offers the potential advantages of a representative night's sleep for the subject and cost savings. This economic gain is offset if a technician has to travel to the patient's home to set up the equipment and retrieve it the next morning. The Mesam IV is suitable for application to the patient in hospitals who then returns it the next day. Home studies are popular with patients and particularly valuable in children and in disabled subjects so that the stress and disruption of an overnight admission is avoided. These advantages need to be weighed against an inevitable degradation in the quality of the results and greater likelihood of having to repeat the study because of loss of data. Studies looking at the validity, cost effectiveness, and outcome of home monitoring are underway.

Split night studies—In obvious case of sleep disordered breathing the diagnosis may be confirmed after a short period of monitoring and treatment (for example, continuous positive airway pressure or assisted ventilation) titrated to the patient for the remainder for the study. This saves time, but equipment titration studies may need to be repeated because of poor acclimatisation to treatment, and short studies or daytime nap studies are too insensitive for screening low risk patients.

Which sleep study?

The choice of sleep study remains controversial. A recent European consensus document¹⁹ and a Royal College of Physicians report²⁰ have emphasised a practical approach which balances patient outcome against demand on sleep laboratories and cost. The scheme outlined in the box is now followed by several centres in the United Kingdom and the rest of Europe. It should be emphasised that in this fast moving topic it is essential to maintain flexibility and resist the development of rigid guidelines.²⁰

Respiratory support in the home

The chief forms of respiratory support in the home (excluding oxygen therapy and nebulisers) are continuous positive airway pressure treatment and assisted ventilation. Other ventilatory devices such as the rocking bed and pneumobelt have a limited application.

CONTINUOUS POSITIVE AIRWAY PRESSURE

Nasal continuous positive airway pressure, developed by Sullivan *et al*, is an effective treatment for

the obstructive sleep apnoea/hypopnoea syndrome and the upper airway resistance syndrome.²¹ Resolution of daytime symptoms is immediate, and morbidity and mortality are reduced.³ The delivery of a constant positive pressure via nasal mask or facemask works as a pneumatic splint to maintain patency of the collapsible upper airway during sleep. Treatment needs to be continued indefinitely unless reversible features (for example, obesity, thyroid dysfunction, acromegaly) are contributing.

A range of machines is marketed with little to choose between them in terms of performance. Cost is the key factor, with prices of around £425-£700. The mask is often a source of discomfort and needs to be carefully fitted; nasal symptoms and claustrophobia are other common complaints. Compliance with this treatment in patients with the obstructive sleep apnoea/hypopnoea syndrome is reported to be around 60-70%, but the average duration of use may be as low as four to five hours a night.²² Some subjects find this period is sufficient to relieve daytime symptoms, but it is unclear whether limited use at night will reduce the long term risk of cardiac and vascular complications. Compliance rates may be improved by accurate titration of the setting to obstructive events by using "smart" machines. Better mask design and the easy availability of advice and home support should also help acclimatisation to treatment.

The bilevel positive pressure device (BiPAP, Respirationics) can be used on subjects with the obstructive sleep apnoea/hypopnoea syndrome associated with moderate or severe hypercapnia. This system enhances minute ventilation, thereby improving carbon dioxide clearance, while providing a background of positive pressure which can be varied in inspiration and expiration.

HOME VENTILATION

A rapid increase in the number of patients being treated with assisted ventilation in the home has occurred over the past decade. Up to 1000 subjects in the United Kingdom now receive home ventilation, most of whom require only nocturnal respiratory support. Worldwide domiciliary ventilatory activity and the mechanisms of action of treatment have recently been reviewed.²³ Factors contributing to the expansion of home ventilation are the recognition that nocturnal respiratory support can improve diurnal function in patients with hypercapnic respiratory failure due to a variety of causes; a renewed interest in negative pressure ventilation; and the emergence of nasal intermittent positive pressure ventilation. The last two are both non-invasive methods of ventilatory support which are preferred for home use, providing the patient has adequate bulbar function and can breathe spontaneously for most of the day. Invasive intermittent positive pressure ventilation via tracheostomy is usually required for those with bulbar insufficiency, excessive bronchial secretions, or a high ventilatory dependence (more than 16 hours a day).

INTERMITTENT POSITIVE PRESSURE VENTILATION WITH TRACHEOSTOMY

The number of patients receiving this form of home ventilation has remained fairly constant, the main indications being lesions of the cervical spinal cord and severe neuromuscular disease. The complexity of care needed for these immobile patients is far greater than for those using non-invasive methods and will include suction facilities, mobility aids, and back up ventilatory support. The outcome depends on the prognosis of the underlying medical condition, but there is considerable morbidity and mortality associated with the stoma itself.²⁴

Which type of sleep study?

Category	Monitoring
High probability obstructive sleep apnoea	*Multichannel screening study; if negative result proceed to polysomnography
Low probability obstructive sleep apnoea	Multichannel screening study at hospital or home
Possibility of non-respiratory sleep/wake disorder (for example, narcolepsy) or equivocal result in screening study	Polysomnography
At risk patient Nocturnal hypoventilation	Oximetry and transcutaneous carbon dioxide monitoring or multichannel screening study, or both
Titration of continuous positive airway pressure treatment	Multichannel screening study at hospital or home or "smart" continuous positive airway pressure
Titration of assisted ventilation/oxygen therapy	Oximetry and transcutaneous carbon dioxide

*Multichannel screening system=combinations of pulse oximetry/monitoring of airflow, chest and abdominal movement, and snoring or video and oximetry system

NEGATIVE PRESSURE VENTILATION

Negative pressure can be applied to the chest wall either by using a cabinet type device which encloses the entire body below the neck (iron lung) or by using the more compact cuirass or jacket devices.²⁵ Negative pressure ventilation works well in patients with neuromuscular and chest wall disorders and has an important application in very young children who cannot tolerate a mask. It has, however, proved unsuccessful in reducing dyspnoea and improving arterial blood gas tensions in patients with severe chronic obstructive pulmonary disease.²⁶ Here and in other conditions negative pressure ventilation provokes upper airway obstruction—an induced form of the obstructive sleep apnoea/hypopnoea syndrome which reduces the efficiency of treatment. Skill in negative pressure ventilation is available in only a few centres in the United Kingdom and provision is patchy throughout Europe. This, coupled with the fact that the equipment is not particularly user friendly and is difficult to transport, has led to a trend towards nasal ventilation.

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION

Nasal intermittent positive pressure ventilation (fig 4) was first introduced in the United Kingdom in 1986, and there has been a swift uptake of this technique for domiciliary use, inpatient treatment of acute ventilatory failure, and weaning. Commercial silicone masks or full face masks (Respironics; Sullivan bubble mask, ResCare) are used, though some centres prefer customised facepieces. Nasal pillows (Puritan Bennett) are also available. Ventilators suitable for home ventilation include the Lifecare PLV-100, BiPAP, Monnal D, Pneupac, and Nippy models, which cost between £3000 and £6000. Flexibility, reliability, portability, and simplicity of use are important considerations when matching ventilatory performance to the patient's respiratory needs.²⁷ Face-mask ventilation can be used in children as young as 2 years. The main disadvantages are discomfort, rhinitis, and mouth leaks. Mouthpiece ventilation is available in the United States and in France, especially for the treatment of patients after polio. It is used infrequently in the United Kingdom.

SELECTION OF PATIENTS FOR HOME VENTILATION

Conditions which have been shown to benefit from home ventilation are listed in the box. Patients with chronic hypercapnic respiratory failure who fail to respond to standard treatment should be considered for home ventilation, with the aim of controlling symptoms, improving quality of life, and reducing mortality. Nocturnal ventilatory support is advisable in symptomatic patients when oxygen saturation is below 90% for most of the night and partial pressure of carbon dioxide exceeds 7 kPa (fig 5), although the decision to start treatment should be strongly influenced by the level of symptoms, underlying prognosis, and patient's preference. On the basis of figures from France it was estimated conservatively that the number of patients requiring home ventilation in the United Kingdom is around double the number currently receiving it (excluding patients with chronic obstructive pulmonary disease).

In patients with restrictive disorders who use nasal intermittent positive pressure ventilation the five year survival is in excess of 90% in patients with previous poliomyelitis and around 80% in those after tuberculous lung and chest wall disease.²⁸ Improved quality of life and reduction in hospital admissions are also reported. Many patients are able to return to full employment.²⁷ Similar results have been found in a smaller study of patients receiving negative pressure ventilation.

Indications for home ventilation

Treatment of hypercapnic respiratory failure due to

- Chest wall disease:
 - Scoliosis
 - Thoracoplasty
 - Fibrothorax
- Respiratory muscle disorders:
 - Old poliomyelitis
 - Myopathies
 - Muscular dystrophies
- Neurological disorders:
 - Primary alveolar hypoventilation
 - Central sleep apnoea
 - Brainstem lesions
 - Cervical spinal cord injury
 - Phrenic nerve lesions
 - Polynuropathy

Possible indications (see text):

- Chronic obstructive pulmonary disease
- Bronchiectasis
- Rapidly progressive neuromuscular disease

A proportion of patients with hypercapnic respiratory failure due to severe chronic obstructive pulmonary disease, who are unable to tolerate long term oxygen therapy, may benefit from nasal intermittent positive pressure ventilation as it is more mechanically efficient than negative pressure ventilation and not associated with upper airway obstruction. The relative benefits of long term oxygen therapy and nasal intermittent positive pressure ventilation are currently being assessed in a European multicentre trial.

Non-invasive nocturnal ventilation may offer relief of symptoms to selected patients with respiratory muscle weakness due to progressive neuromuscular disease such as Duchenne muscular dystrophy, although it is unlikely to have a widespread application in these disorders. Life expectancy is increased,²⁷ but the issue of an inevitable increase in ventilatory dependence needs to be discussed with the patient and family at the start of treatment.

PROVISION OF SERVICES

The Royal College of Physicians' report on sleep apnoea and related conditions recommends that there should be one specialist respiratory sleep centre per three million of the population.²⁰ This will require an expansion to around 18 such centres in the United Kingdom. Training programmes are needed not only to staff these centres but also to increase awareness of sleep apnoea in the general public and medical profession. It is envisaged that specialist respiratory centres will provide polysomnography for the indications given in the box detailing types of sleep study, while other centres may carry out screening sleep studies and refer patients as necessary.

Specialist respiratory centres are also needed to provide skills in home ventilation. This should include a comprehensive back up system of medical and technical advice, servicing and repair of ventilators, plus family support and education. In France the provision of home ventilatory care is centrally funded and organised through the Association Nationale pour le traitement à domicile de l'insuffisance respiratoire chronique (ANTADIR) network. In the United Kingdom a register of home ventilation is being set up as an initiative of the British Thoracic Society. Health purchasers need to be aware of the availability of treatment for sleep disordered breathing to ensure adequate funding of sleep studies and continuous positive airway pressure or ventilatory support equipment.

Conclusions

The obstructive sleep apnoea/hypopnoea syndrome and nocturnal hypoventilation are conditions which are easily diagnosed and both respond to treatment which improves quality of life and reduces morbidity and mortality. Research is required on several fronts—to investigate the basic mechanisms of sleep disordered breathing and its consequences, to assess the value of surgical intervention in snoring and mild obstructive sleep apnoea/hypopnoea syndrome, and to improve mechanical treatments. The immediate practical challenge is to provide sufficient facilities and equipment to investigate and treat appropriately all patients with sleep disordered breathing.

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Inventing a new diagnostic test for vaginal infection

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Bacterial vaginosis, which is underdiagnosed in clinical practice, has a characteristic fishy smell because of production of diamines. This smell is the basis of a visual rapid diagnostic test that is technically simple to perform. The test has been patented in Europe and America, and a licence agreement has been negotiated. This paper describes the process from idea to invention to patenting and licensing. The combined costs of research and patenting were met by a multinational company in return for rights to exploit the patented invention. The process has taken nine years and has needed clinical, scientific, legal, and commercial input to get the test to the marketplace.

About 5000 patents a year are registered by British inventors, but the Japanese company Hitachi registers 20 000 patents a year. Yet Japanese research shows that in the past few decades half the economically valuable inventions around the world originated in Britain.¹ Since the withdrawal of the British Technology Group's monopoly of exploiting university research in 1986 many universities have accepted the responsibility of exploiting their own intellectual property. They now realise the commercial value of their intellectual property, and most have established offices of technology transfer, which focus on opportunities for industrial exploitation. The government's recent white paper on science and technology *Realising our Potential* further emphasises the importance of developing new technologies and discusses the various methods by which industry and academia might collaborate for the

benefit of the economy.² It is becoming more common for university research to lead to commercial products that have been exploited through the establishment of licence agreements or have formed the basis for a new company. In this paper we describe our experience of inventing a rapid diagnostic test in response to a clinical need and taking it to the market.

The diagnostic test

CLINICAL NEED FOR TEST

Vaginal symptoms are a common and recurring problem that affects about one in 10 women who present to a general practitioner. Vaginal symptoms are often assumed to be due to thrush, but bacterial vaginosis has been found to be associated with up to half of patients with vaginal symptoms.³ Bacterial vaginosis has the clinical features of a grey homogeneous malodorous vaginal discharge with higher than normal pH of 5.0-5.5 and minimal inflammation.⁴ There is increasing evidence of the virulence of bacterial vaginosis: it has been associated with pelvic inflammatory disease after abortion,⁵ endometritis after caesarean section,⁶ amniotic fluid infections,⁷ and preterm or low birth weight delivery.^{8,9}

Despite this, bacterial vaginosis is not commonly diagnosed. The clinical history gives useful pointers, and diagnosis can be made by means of microscopy because of the presence of "clue cells," which are vaginal epithelial cells dotted with coccobacilli. Microscopy is, however, a rare skill in clinical practice. Thus bacterial vaginosis is a common condition that is

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