another, and this obviously facilitates meta-analysis and makes systematic review feasible. Pre-clinical animal trials entail testing specific effects on particular measures of physiological function while seeking to control all other possible variables. Ethical imperatives limit the number of animals used to the minimum and require that previously published studies are not simply repeated. Moreover, because of the systematic nature of the research, each experiment necessarily differs in its precise design, method, and dependent variables from those that have gone before making it much more difficult to combine data from different studies.

What we need is critical review, rather than systematic review, of all the evidence before human trials commence. A critical review compiles and evaluates the different sources of experimental evidence on a qualitative basis. A difficulty with systematic reviews is that attempts to meet precise inclusion criteria often mean useful information is excluded. The reliability and validity of each animal model needs to be assessed on its merits and its relevance to the particular clinical application. While seeking to identify and protect against major problems at the early stage of development, no model is perfect and may still miss effects that are rare or species specific, and which can be revealed only in subsequent human trials of the new treatment. Partial information, while never perfect, is better than no information.

Finally, the close association of basic and clinical science is an essential requirement for successful translation. This must include a critical appreciation of what experimental science has to offer in terms of a solution to the clinical problem.

Roger Lemon *professor*

Institute of Neurology, London WC1N 3BG (rlemon@ion.ucl.ac.uk)

Stephen B Dunnett *professor*

School of Biosciences, Cardiff University, Cardiff CF10 3US

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Childhood obstructive sleep apnoea

Serious neurobehavioural sequelae have prompted interest in diagnosis and management

Obstructive sleep apnoea is characterised by oxygen desaturation and reduced oro-nasal air flow despite preserved thoracic and abdominal respiratory effort.[1] It occurs in 1-2% of children and is more common in prematurely born infants and in black and Hispanic children.[2] As our knowledge of this condition has grown, so has concern about it among parents and clinicians. How is it best diagnosed and managed?

Habitual snoring, breathing through the mouth, periods of observed apnoea, restless sleep, urinary incontinence, inattentiveness, daytime hyperactivity, mood swings, and failure to thrive are the most common clinical manifestations of childhood obstructive sleep apnoea. How loudly a child snores is not correlated to the presence or severity of sleep disordered breathing. The most common predisposing factors are adenotonsillar hypertrophy, neuromuscular disorders, and craniofacial anomalies associated with maxillary hypoplasia, retrognathia, or macroglossia. The local release of proinflammatory cytokines such as C reactive protein, tumour necrosis factor α, and interleukin 6 might also play a part in exacerbating mucosal swelling and airway narrowing.[3]

The neuropsychological sequelae of classic childhood obstructive sleep apnoea have now been firmly established. O'Brien et al recently described 35 children with obstructive sleep apnoea (mean age 6.7 years) and 35 closely matched controls.[4] The children with sleep apnoea had notable deficits in attention span, executive function, phonological processing, visual attention, and general conceptual ability compared with the controls. The deficit in phonological processing is worrying since this serves as a basic building block in the development of reading skills.

Nocturnal polysomnographic observations in paediatric obstructive sleep apnoea were first made by Guilleminault et al in 1975.[5] Polysomnography consists of the simultaneous recording of cardiorespiratory, electromyographical, and electroencephalographic variables. The threshold of oxygen desaturation that should be used for scoring respiratory events during polysomnography remains unresolved. Federal guidelines in the United States (Medicare) stipulate a 4% oxygen drop from the baseline during respiratory events, whereas the Cleveland heart health study[2] applied a 3% desaturation threshold. These disparities are not trivial and can lead to inconsistencies from one sleep laboratory to another in diagnosing obstructive sleep apnoea. Standardisation of sleep monitoring techniques and the universal application of validated criteria for diagnosing childhood obstructive sleep apnoea remain a priority.

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Though nocturnal polysomnography is the accepted gold standard for diagnosing childhood obstructive sleep apnoea, it is expensive and not widely available. The small number of sleep centres with trained paediatric staff coupled with increasing public demand for childhood sleep evaluations have strained resources. Alternative methods of diagnosing childhood obstructive sleep apnoea therefore need consideration.

Goldstein et al have shown that a comprehensive clinical assessment can diagnose childhood obstructive sleep apnoea with 48% accuracy.[6] The assessment consists of a validated quality of life survey, review of an audiotape for snoring and "snort arousals" (sensitivity 88%, specificity 52%, positive predictive value 62%), evaluating the lateral neck radiograph for adenoidal hypertrophy, voice recording assessment for hypernasality, and an electrocardiogram. Though 48% accuracy is far from optimum, this assessment is nevertheless a useful tool for the general practitioner.

Another substitute for nocturnal polysomnography is physical examination combined with the inexpensive and easily available technique of nocturnal pulse oximetry. Brouillette et al from the Montreal Children's Hospital have shown that when the clinical history suggests obstructive sleep apnoea, an abnormal overnight oximetry trend graph has a 97% positive predictive value.[7] A normal overnight oximetry study does not, however, exclude mild or moderate obstructive sleep apnoea as only 93/210 (44%) of their patients with sleep apnoea proved by polysomnography showed abnormal results on oximetry.

Though adenotonsillectomy is widely used for treating childhood sleep apnoea, its benefit has not been definitively established through more evidence based research. About a fifth of patients below the age of 36 months develop dangerous postoperative airway oedema after adenotonsillectomy, so all children in this age group should be closely monitored for cardiorespiratory compromise for at least 24 hours. Positive pressure airway breathing is helpful in those with obstructive sleep apnoea that persists despite adenotonsillectomy. Weight reduction measures intuitively make sense, but again their value has not been established through randomised controlled trials. Corticosteroids such as intranasal fluticasone seem to reduce the size of adenoids and the severity of symptoms slightly[8] and serve as an adjunctive treatment.

Increased interest in childhood obstructive sleep apnoea should prompt the randomised trials that are now necessary to assess the best ways of managing the condition.

Suresh Kotagal *consultant*

Sleep Disorders Center, Division of Child Neurology, Mayo Clinic, Rochester, MN 55905, USA
(kotagal.suresh@mayo.edu)

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Radiotherapy for the future

Protons and ions hold much promise

Charged particle beams (CPB), consisting of protons or carbon ions produced in a cyclotron or synchrotron, are an important development in radiotherapy.[1] [w1] Compared with conventional x rays, charged particle beams produce excellent dose distributions to tumours and reduced doses to normal tissues. They thus hold out the promise of enhanced treatments for cancer and improved quality of life for patients being treated.

All the major technical advances in radiotherapy, such as increasing x ray energies and better target localisation have improved accuracy and outcomes,[w2] [w3] without direct evidence from randomised clinical trials. The one modern exception, conformal radiotherapy (using better shaped x ray beams to conform with tumour geometry), was tested in a randomised trial only in the United Kingdom: the reduction in serious morbidity found has led to extensive use.[w4]

Treatment with charged particle beams marks a more radical change from incremental improvements in x ray based therapy**.** Its safe implementation has been made possible by improved tumour and normal tissue imaging using spiral computed tomography and magnetic resonance imaging, rapid three dimensional dose plan computing, and the industrial manufacture of entire CPB treatment centres.

Carbon ions cause denser ionisation than protons and x rays. They theoretically offer better prospects for radio resistant tumours. Like conventional x rays, CPB cause DNA damage, but they deposit energy more selectively. As particle velocity decreases through tissue, ionisation becomes maximal at the "Bragg peak,"[w5] with none a few millimetres further beyond

P+ *Additional references w1-w13 are on bmj.com*

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