LETTERS TO THE EDITOR

Chronic fatigue syndrome: a joint paediatric-psychiatric approach

SIR,—While agreeing that physical, psychological, and social factors must all be taken into account in the management of this complex and controversial syndrome I would disagree with Dr Margaret Vereker's statement that no organic pathology can be detected to account for any of the symptoms.¹ This conclusion has been made without reference to a number of research papers describing persisting viral infection, neuromuscular abnormalities in both structure and function, and immune system dysfunction.

Gow *et al* using polymerase chain reaction techniques, have been able to demonstrate the presence of enteroviral genome in muscle biopsies from a significant number of patients (53%) compared with controls (15%).² None of the healthy control group in this study had evidence of viral particles in their muscle—this was only found in those with colonic or breast malignancies. Precisely what cytopathological effect this intracellular virus is having within muscle remains open to debate. However, Behan *et al* have published electron microscopic evidence of structural damage to the muscle mitochondria along with type II fibre atrophy³; this is a finding which is not normally considered to be consistent with simple disuse.

Equally, it is now accepted that a large number of common viral infections (for example herpes, measles, mumps, and enteroviruses) are all capable of entering, persisting, and multiplying within the central nervous system, often without producing any detectable cytopathological damage. Their effect is on cell function rather than structure, and they particularly affect neurotransmitter activity in areas such as the limbic system and hypothalamus.

Details of objective central nervous system pathology have recently begun to emerge from research groups in both the United Kingdom and the United States. Buchwald *et al* have produced evidence of immune dysfunction (a significantly increased CD4/CD8 lymphocyte ratio), reactivation of human herpes virus type 6, and structural CNS abnormalities in a group of well over 200 patients.⁴ The magnetic resonance imaging (MRI) brain scans revealed punctate, subcortical areas of high signal intensity consistent with oedema or demyelination in 78%. The authors of this multicentre study concluded that the patients were experiencing a chronic, immunologically mediated inflammatory process in the central nervous system after a viral infection. Furthermore, in a personal communication, Professor Anthony Komaroff, from Harvard, has stated that he believes that these MRI studies indicate central nervous system inflammation.

Evidence of hypothalamic dysfunction has come from both Demitrack *et al* (lowered concentrations of blood cortisol consistent with inadequate hypothalamic-pituitary axis stimulation),⁵ and Bakheit *et al* (an upregulation of hypothalamic 5HT receptors using a buspirone challenge).⁶ As far as symptomatology is concerned these latter findings may well be significant in view of the often marked disturbances in sleep pattern, appetite, and

thermoregulation described in both adults and children with postviral fatigue syndrome.

On behalf of the ME Association could 'also correct the author's statement that we regard physical exercise as being 'harmful' and something that 'must be avoided'. My own guidelines on the management of children state quite clearly that... 'A period of bed rest may well be beneficial in the early stages, but following this, rest and exercise need to be carefully balanced. On the one hand there is a very real danger that prolonged immobility will result in further weakness, wasting and even contractures. On the other there is no doubt that when children do start to recover, there is a great temptation to start suddenly doing too much and precipitate relapse. If children learn to pace themselves, both physically and mentally, they should be able to build on progress, which in turn will have a very beneficial effect on self-confidence.'⁷

Unfortunately, the ME Association continues to attract a great deal of misinformed criticism. Despite this we have established a research fund of nearly £250 000; persuaded the Department of Health to recognise postviral fatigue syndrome (ME/CFS) as 'a debilitating and distressing condition',⁸ and vigorously exposed the quack remedies that many patients turn to when orthodox medicine rejects or trivialises their suffering. Although the author is clearly concerned about parents being 'exposed' to our views I would once again emphasise that we recognise that social and psychological factors may well play an important part in this syndrome, especially in children.

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7 Shepherd CB. *Living with ME*. London: Heinemann Cedar, 1992:233-8.

8 Dorrell S. (Secretary of State for Health) House of Commons Debate 13.11.92 col 582W (Hansard).

Atrial natriuretic peptide

SIR,—Experimental data suggest that atrial natriuretic peptide (ANP) has pulmonary vasodilator activity.¹⁻³ We postulated that ANP might have therapeutic potential in severe persistent pulmonary hypertension of the newborn (PPHN).

A boy born at 41 weeks' gestation developed severe PPHN in association with meconium aspiration and perinatal asphyxia. By 5 days of age the hypoxaemia was unresponsive to high dose intravenous prostacyclin (maximum infusion rate 40 ng/kg/min) and aggressive conventional ventilation using an SLE 2000. The alveolar-arterial oxygen difference was 80 kPa (600 mm Hg), which is predictive of a poor outcome.⁴ With parental consent, ANP (Shire Pharmaceuticals) was infused in incremental doses, each over 30 minutes, of 10, 20, 40, 80, and 160 ng/kg/min and on the next day of 80, 160, and 320 ng/kg/min. Serial measurements were made of plasma ANP, urine cyclic guanosine monophosphate (cGMP), mean blood pressure, central venous pressure, heart rate, and arterial blood gases.

Mean preinfusion serum ANP concentrations on the two days were 215 and 128 pg/ml; peak plasma ANP was 5929 and 7632 pg/ml. Preinfusion cGMP excretion rates of 0.4-1 nmol/kg/hour increased to 4 nmol/kg/hour and remained raised for two hours. The table shows the clinical measurements preinfusion, at the end of the infusion, and at 40/45, 90, and 230/180 minutes after the end of the infusion.

Blood pressure showed a clinically relevant fall after the end of the infusion on both days. Central venous pressure remained essentially unchanged. Preductal arterial oxygen tension (Pao₂) fell slightly by the end of the infusion on day 1 but 90 minutes later had risen to 17.26 kPa, then falling to 8.23 kPa by 230 minutes. On the second day of infusion Pao₂ rose by 1.73 kPa during the infusion and 180 minutes later remained 1.08 kPa above the preinfusion value. The baby survived to go home.

There has been some experience of ANP infusion in adults but no previous report of ANP infusion in a neonate. Adnot *et al* reported a reduction in pulmonary artery pressure after ANP infusion up to 100 ng/kg/min in adults with pulmonary hypertension secondary to chronic obstructive lung disease.³ In this group plasma ANP rose to around 3600

Clinical measurements during ANP infusions

	Preinfusion	End of infusion	Minutes after end of infusion		
			40	90	230
Day 1:					
Central venous pressure (mm Hg)	8	8	8	8	9
Blood pressure (mm Hg)	56	48	40	48	59
Heart rate/min	178	199	190	204	182
Pao ₂ (kPa)	6.79	6.23	7.0	17.26	8.23
Day 2:			45	90	180
Central venous pressure (mm Hg)	6	6	6	5	7
Blood pressure (mm Hg)	54	53	52	45	65
Heart rate/min	175	177	187	170	170
Pao ₂ (kPa)	5.7	7.43	6.54	6.46	6.78

pg/ml (compared with 2556 and 2888 pg/ml after infusion at 80 ng/kg/min in the neonate reported here). The same workers found ANP infusion to attenuate the pulmonary response to hypoxia in pigs.¹

On the first day of infusion the infant showed a slight fall in PaO₂ at the end of the infusion followed, 90 minutes later, by an appreciable rise that lasted for approximately two hours. The initial fall might be explained by increased perfusion of poorly ventilated lung units³ but the late rise is difficult to explain, though the cGMP excretion rate did remain raised for two hours. A dose dependent relaxation of pulmonary arteries, induced by ANP, has been shown in bovine arterial rings² but in our case ANP concentration returned to baseline by around 23 minutes.

In this infant high dose ANP infusion was relatively well tolerated. Although we do not claim that this child's satisfactory outcome was related to treatment with ANP, we do believe that ANP should be added to the list of therapeutic options in the management of persistent pulmonary hypertension of the newborn that require further study.

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- 1 Adnot S, Chabrier PE, Brun-Buisson C, Viossat I, Braquet P. Atrial natriuretic factor attenuates the pulmonary pressor response to hypoxia. *J Appl Physiol* 1988;65:1975-83.
- 2 Ignarro LJ, Wood KS, Harbison RG, Kadowitz PJ. Atriopeptin II relaxes and elevates cGMP in bovine pulmonary artery but not vein. *J Appl Physiol* 1986;60:1128-33.
- 3 Adnot S, Andrivet P, Chabrier PE, et al. Atrial natriuretic factor in chronic obstructive lung disease with pulmonary hypertension. *J Clin Invest* 1989;83:986-93.
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An indirect calorimetry system for ventilator dependent very low birthweight infants

SIR,—While the need for measurement of energy expenditure and nutrient utilisation in sick ventilator dependent infants is undisputed, we have several reservations about the indirect calorimetry system described by Forsyth and Crighton.¹ On p316 is $\dot{V}_E$ the inspired or expired minute ventilation? The equations given appear to take these to be equal, even though this amounts to assuming that the respiratory quotient (RQ) is 1. If instead the inspired and expired volumes of inert gas are assumed equal the oxygen consumption ($\dot{V}_{O_2}$) can be found as

$$\dot{V}_{O_2} = \dot{V}_{\text{inspired}} \left\{ \frac{F_{IO_2} - F_{EO_2} - F_{IO_2} \cdot F_{ECO_2}}{1 - F_{EO_2} - F_{ECO_2}} \right\};$$

a similar expression exists for carbon dioxide production. When $F_{IO_2} = 0.4$ the equations in the paper underestimate $\dot{V}_{O_2}$ by 12% if RQ = 0.7 and overestimate it by 8% if RQ = 1.2; calculated values of RQ will be biased towards

1,² with true RQs of 0.7 and 1.2 being computed as 0.80 and 1.11 respectively.

In the gas infusion studies reported in table 1 it is unclear how to assess the values calculated for $\dot{V}_{O_2}$ when nitrogen is infused into the system. This part of the study calculates $\dot{V}_{O_2}$ as if the results were from a patient; the first equation on p318 then allows the calculated $\dot{V}_{O_2}$ to be checked in terms of nitrogen flow rate and F_{IO_2} . If $\dot{V}_{O_2}$ is calculated correctly then this check equation is

$$\dot{V}_{O_2} = \frac{\dot{W}_{N_2} \cdot F_{IO_2}}{1 - F_{IO_2}};$$

if the equations on p316 are used then this becomes:

$$\dot{V}_{O_2} = \frac{\dot{V}_{\text{inspired}} \dot{W}_{N_2} \cdot F_{IO_2}}{\dot{V}_{\text{inspired}} + \dot{W}_{N_2}} \cong \dot{W}_{N_2} \cdot F_{IO_2}.$$

For the nitrogen flow rates given in table 1 (10.10, 14.10 ml/min) and F_{IO_2} is 0.40, the expected values of $\dot{V}_{O_2}$ would be, from the first equation, 6.73, 9.40 ml/min and from the approximate version of the second equation, 4.04, 5.64 ml/min. From the results for the higher nitrogen flow rate it would appear that the second equation has been used (as would be consistent with the earlier part of the paper) but the agreement is poor at the lower flow rate.

Finally, we were disappointed that gas infusion studies were performed using only one ventilator setting. Increasing the inspired oxygen concentration (while keeping $\dot{V}_{O_2}$ constant) causes a reduction in the inspired-expired oxygen difference ($F_{IO_2} - F_{EO_2}$). Thus as $F_{IO_2} - F_{EO_2}$ decreases, the error sensitivity in the measurement of $\dot{V}_{O_2}$ is magnified.³ It is not uncommon for sick ventilated infants to need F_{IO_2} up to 1.00. The errors in the measurement of energy expenditure at high oxygen concentrations will be markedly increased and this must be acknowledged.

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- 1 Forsyth JS, Crighton A. An indirect calorimetry system for ventilator dependent very low birthweight infants. *Arch Dis Child* 1992;67: 315-9.
- 2 Ferrannini E. The theoretical basis of indirect calorimetry: a review. *Metabolism* 1988;37: 287-301.
- 3 Ultman JS, Bursztein S. Analysis of error in the determination of respiratory gas exchange at varying F_{IO_2} . *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology* 1981;50:210-6.

Dr Forsyth comments:

Although the general principles of indirect calorimetry may apply to all systems and subjects, there are some features which require specific consideration depending upon the nature of the system and the size of the subject being studied. In our system for ventilated low birthweight infants,¹ there are at least two important aspects which differ from adult systems, first the effect of changes in RQ on expiratory flow volume ($\dot{V}_E$) and second, the validity of excluding F_{ICO_2} from the calorimetry calculations.

Adult calorimetry systems commonly use an inspiratory flow volume ($\dot{V}_I$) in the region of 40 l/min, and for a 70 kg individual with an oxygen consumption ($\dot{V}_{O_2}$) of 320 ml/min and RQ of 0.7, the difference between $\dot{V}_I$ and $\dot{V}_E$

will be 96 ml (0.24% of $\dot{V}_I$). In our system $\dot{V}_I$ is 6 l/min (inspiratory flow from the ventilator), and for a 1500 g ventilated infant with a $\dot{V}_{O_2}$ of 9 ml/min and RQ of 0.7, the difference between $\dot{V}_I$ and $\dot{V}_E$ is 2.7 ml, that is 0.045% of $\dot{V}_I$. In order to correct for this difference, Drs Matthews and Matthews offer a formula based on adult data,² and which involves the values of four different measurements. Not only is there a risk that the overall error of these measurements may exceed the error induced by the difference in the $\dot{V}_I$ and $\dot{V}_E$ flow volumes but their equation is not valid for our system. If it is applied to the 1500 g infant, the 'corrected' $\dot{V}_{O_2}$ will be 7.79 ml/min compared with the actual $\dot{V}_{O_2}$ of 9.0 ml/min (an underestimate of 13.3%). This underestimate is constant, and not limited to the margins of RQ. Using our simpler equation the calculated $\dot{V}_{O_2}$ at RQ 0.7 is 7.9 ml/min (underestimate 12%), but this error reduces to 0% as the RQ approaches 1.0. The large persistent error with the Matthews' equation is due to the omission of F_{ICO_2} . In adults this is usually less than 1% of F_{ECO_2} and commonly ignored, but for a low birthweight infant in our system the F_{ICO_2} can account for up to 22% of F_{ECO_2} . The formula should therefore be corrected to

$$\dot{V}_{O_2} = \dot{V}_I \cdot \left\{ \frac{F_{IO_2} - F_{EO_2} - F_{IO_2} \cdot F_{ECO_2} + F_{EO_2} \cdot F_{ICO_2}}{1 - F_{EO_2} - F_{ECO_2}} \right\}$$

A simpler and potentially more accurate adjustment is the traditional Haldane correction, $\dot{V}_I = \dot{V}_E \cdot F_{EN_2} / F_{IN_2}$, and as our system is continually measuring inspiratory and expiratory nitrogen this can be easily accommodated.

During the nitrogen infusion study the mean F_{IO_2} was 0.421 and $\dot{V}_E$ 5.257 l/min. By using the measured values for $\dot{V}_E$, F_{IO_2} , and F_{EO_2} the predicted $\dot{W}_{N_2}$ were compared with the actual $\dot{W}_{N_2}$, and using our last equation the actual oxygen consumption as opposed to the simulated $\dot{V}_{O_2}$ was confirmed to be zero. The $\dot{V}_{O_2}$ data reported with the nitrogen infusions were calculated as for an infant study using the described software calculations and were included, albeit with the limitations as discussed above, to relate the infusion data to actual levels of $\dot{V}_{O_2}$ which are seen in low birthweight infants. Unfortunately we did transcribe the wrong data point for the $\dot{V}_{O_2}$ for the nitrogen infusion of 10.1 ml/min and this should have been 4.20 (0.22) ml/min. We are grateful for this being drawn to our attention.

Although we will shortly be providing clinical and technical data on the use of our system with higher levels of F_{IO_2} , it is our experience that in the present surfactant era considerably fewer babies are requiring a very high F_{IO_2} for a long period of time. We realise that some babies do require an F_{IO_2} as high as 1.0, but we believe that for those babies there are more urgent priorities than a measurement of energy expenditure.

- 1 Forsyth JS, Crighton A. An indirect calorimetry system for ventilator dependent very low birthweight infants. *Arch Dis Child* 1992;67: 315-9.
- 2 Ferrannini E. The theoretical basis of indirect calorimetry: a review. *Metabolism* 1988;37: 287-301.

Imposed upper airway obstruction and covert video surveillance

SIR,—Covert video surveillance (CVS) may be extremely useful and is often the only method to prove that some cases of apparent life threatening events (ALTE) are caused by imposed upper airway obstruction. Samuels