## 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.<sup>1</sup> 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%).<sup>2</sup> None of the healthy control group in this study had evidence of viral particles in their musclethis 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 atrophy<sup>3</sup>; 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.<sup>4</sup> 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),<sup>5</sup> and Bakheit et al (an upregulation of hypothalamic 5HT receptors using a buspirone challenge).<sup>6</sup> 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.'

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 de-bilitating and distressing condition',<sup>8</sup> 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.

> CHARLES SHEPHERD ME Association, Friars Cottage Surgery, Queens Square, Chalford Hill, Gloucester GL6 8EH

- Vereker MI. Chronic fatigue syndrome: a joint paediatric-psychiatric approach. Arch Dis Child 1992;67:550-5.
- 1992;67:550-5.
   Gow JW, Behan WMH, Clements GB, et al. Enteroviral RNA sequences detected by polymerase chain reaction in muscles of patients with postviral fatigue syndrome. *BMJ* 1991;302: 692-6.
   Behan WMH, More IAR, Behan PO. Mitochen and the postviral fatigue formalita in the postviral fatigue formation.
- chondrial abnormalities in the postviral fatigue syndrome. Acta Neuropathol (Berl) 1991;83: 61-5.
- 4 Buchwald D, Cheyne PR, Peterson DL, et al. A chronic illness characterised by fatigue, neurologic and immunologic disorders, and
- neurologic and immunologic disorders, and active human herpes type 6 infection. Ann Intern Med 1992;116:103–13.
  5 Demitrack MA, Dale JK, Straus SE, et al. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab 1991;73:1224–34.
  6 Bokheit AMO. Behop PO. Dinon TG. et al.
- 6 Bakheit AMO, Behan PO, Dinan TG, et al. Possible upregulation of hypothalamic 5hydroxytryptamine receptors in patients with

- postviral fatigue syndrome. BMJ 1992;304: 1010-2.
  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).
- (Hansard).

## Atrial natriuretic peptide

SIR,-Experimental data suggest that atrial natriuretic peptide (ANP) has pulmonary vasodilator activity.<sup>1-3</sup> 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.<sup>4</sup> 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 (PaO<sub>2</sub>) 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 Pao<sub>2</sub> 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.<sup>3</sup> In this group plasma ANP rose to around 3600

Clinical measurements during ANP infusions

| Day 1:<br>Central venous           | Preinfusion | End of<br>infusion | Minutes after end of infusion |       |      |
|------------------------------------|-------------|--------------------|-------------------------------|-------|------|
|                                    |             |                    | 40                            | 90    | 230  |
| pressure (mm Hg)<br>Blood pressure | 8           | 8                  | 8                             | 8     | 9    |
| (mm Hg)                            | 56          | 48                 | 40                            | 48    | 59   |
| Heart rate/min                     | 178         | 199                | 190                           | 204   | 182  |
| Pao <sub>2</sub> (kPa)             | 6.79        | 6.53               | 7.0                           | 17.26 | 8·23 |
| Day 2:                             |             |                    | 45                            | 90    | 180  |
| Central venous                     |             |                    |                               |       |      |
| pressure (mm Hg)                   | 6           | 6                  | 6                             | 5     | 7    |
| (mm Hg)                            | 54          | 52                 | 52                            | 45    | 45   |
| Heart rate/min                     | 175         | 177                | 197                           | 170   | 170  |
| $PaO_2$ (kPa)                      | 5.7         | 7.43               | 6.54                          | 6.46  | 6.78 |