Letters to the Editor

Chronic fatigue syndrome

Sir,

De Lorenzo and colleagues¹ report a previously undefined relationship between chronic fatigue syndrome (CFS) and phosphate diabetes. They also report that mean serum phosphate concentration was found to be significantly lower in CFS patients than in control subjects. They explain their findings by the hypothesis that CFS patients have a metabolic defect that is secondary to their chronic underutilisation of skeletal muscle. Another hypothesis can, however, be proposed.

Hypophosphataemia in sepsis has been recently reported to be associated with high levels of tumour necrosis factor- α and interleukin-6.² However, these inflammatory cytokines are also produced to excess in both CFS patients³ and hypocortisolaemic subjects.⁴ De Lorenzo and colleagues' findings,¹ therefore, may simply reflect the hypocortisolism of CFS patients,⁵ which is one of the 20 features that CFS shares with Addison's disease.⁵

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- 1 De Lorenzo F, Hargreaves J, Kakkar VV. Phosphate diabetes in patients with chronic fatigue syndrome. *Postgrad Med J* 1998;74:229-32.
- 2 Barak V, Schwartz A, Kalickman I, Nisman B, Gurman G, Shoenfeld Y. Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. *Am J Med* 1998;104:40-7.
- 3 Chao CC, Janoff EN, Hu S, et al. Altered cytokine release in peripheral blood mononuclear cell cultures from patients with the chronic fatigue syndrome. *Cytokine* 1991;3:292-8.
- 4 Papanicolaou DA, Tsigos C, Oldfield EH, Chrousos GP. Acute glucocorticoid deficiency is associated with plasma elevations of interleukin-6: does the latter participate in the symptomatology of the steroid withdrawal syndrome and adrenal insufficiency? *J Clin Endocrinol Metab* 1996;81:2303-6.
- 5 Baschetti R. Similarity of symptoms in chronic fatigue syndrome and Addison's disease. *Eur J Clin Invest* 1997;27:1061.

Asymptomatic murmurs

Sir,

I read with interest the article entitled 'Asymptomatic murmurs' by Biggart and Coltart.¹ Although the patient was eventually diagnosed to have an unruptured aneurysm of the sinus of Valsalva, the murmur was due to the coexistent aortic stenosis. It was by chance that echocardiogram, which was performed for assessment of the systolic murmur and showed mild aortic stenosis, revealed a bizarre right atrial echo. The latter, in combination with a large calcified mass in the region of the right atrium, led to the clinical suspicion of a calcified aneurysm of the sinus of Valsalva, which was confirmed by ascending aortography.

It should be emphasized that unruptured aneurysms of sinus of Valsalva are usually asymptomatic and do not produce any heart murmurs. As was cited as reference 4 in the article, my colleagues in China and I² reported the value of three-dimensional transoesophageal echocardiography in making the

diagnosis of an unruptured aneurysm of sinus of Valsalva and in distinguishing it from an atrial myxoma.

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- 1 Biggart SA, Coltart DJ. Asymptomatic murmurs. *Postgrad Med J* 1997;73:597-8.
- 2 Wang X-F, Li Z-A, Cheng TO, et al. Clinical application of three-dimensional transoesophageal echocardiography. *Am Heart J* 1994;128:380-8.

The use of the Internet amongst gastroenterology out-patients

Sir,

The Internet is becoming a widely available source of knowledge and is being used to disseminate information to a large audience.¹ The rapid growth of the Internet has been associated with the development of many on-line services for patients. In the USA there are a number of web pages devoted to patient education.² In addition to those provided by the National Institute of Health and various university departments of gastroenterology, there are a number of on-line magazines such as *The Old Crohnie*, *Keith's Crohn's Chronicle* and the *IBD Newsletter*.

As the Internet is increasing in its accessibility, we undertook a pilot postal questionnaire study to assess how many of our gastroenterology out-patients had accessed the Internet and actively used this facility to obtain information about their disease. We were also interested to know whether they felt that the Internet would play a larger role in the future. Forty-four patients were asked to complete a postal questionnaire which was confidential and anonymous. The questionnaire asked patients if they had access to a computer (and the Internet) and if they had used the Internet to seek information about their disease. It also asked patients if they felt that the Internet would play a larger role in the future with respect to obtaining information about hospitals, their treatment and their condition. Reasons of patient confidentiality and anonymity prevented us from carrying out a second mailing.

Of the 23 patients who replied, only six had access to a computer and of these only two patients had used the Internet. Neither had sought information on their disease. However, 65% of patients believe that it will become very important in the future, particularly in providing information about their treatment and the best hospitals to provide this (69%). Patients also felt it would enable them to check on their doctors' treatments (61%).

At present the Internet appears to have little place in the education of gastroenterology patients in Britain. This largely reflects the limited availability of the Internet to most of our patients, but the Internet community is rapidly expanding and it will gain more influence over time. Indeed, the majority of patients believe its role will grow, and it will provide an important check on the quality of the treatment that they receive.

Many of the web pages that patients access are unstructured and are not subject to the usual peer review process afforded by medical journals.³ Several user groups devoted to Crohn's disease and ulcerative colitis have an active information exchange programme.⁴ On reviewing these sources of information it is obvious that there is a widespread need for better quality information. It is therefore critical that doctors become actively involved in the development of information on the Internet and respond to the needs of patients who post questions to the user groups. Only by doing this may we increase the caliber of information that is available to our patients. Failure to do so may well stimulate the growth of poor quality information which could act as a stimulus to inappropriate litigation.

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- 1 Soetikno RM, Provenzale D, Lenert LA. Studying ulcerative colitis over the World Wide Web. *Am J Gastroenterol* 1997;92:457-60.
- 2 Mackenburger M, Hobbie C. Patient education on the Web. *J Pediatr Health Care* 1997;11:89-91.
- 3 Kipp DE, Radel JD, Hogue JA. The Internet and the nutritional scientist. *Am J Clin Nutr* 1996;64:659-62.
- 4 Widman LE, Tong DA. Requests for medical advice from patients and families to health care providers who publish on the World Wide Web. *Arch Intern Med* 1997;157:209-12.

Compression syndromes caused by substernal goitres

Sir,

We read the article by Anders¹ on compression syndromes caused by substernal goitres with interest. We would like to comment on some of the statements of the author.

First, Anders stated that dysphagia is the most frequent oesophageal symptom of substernal goitre. In our initial publication,² we reported dysphagia as a presenting symptom in only 26% of our patients. This percentage has now dropped to 15%, according to our more recent data.

Secondly, the author quoted our paper³ about recurrent transient ischaemic attacks related to thyrocervical 'steal' by an increased thyroid blood flow. In fact, in the case we reported, the transient ischaemic attacks (right hemiplegia) were most probably caused by the association of two causes: first, a cerebrovascular circulation 'steal' syndrome secondary to the development of a left voluminous retrotracheal goitre resulting in the enlargement of the inferior thyroid artery (which did not arise from the thyrocervical trunk of the subclavian artery but as a collateral branch of the common carotid artery at the level of its bifurcation) with subsequent decrease in left carotid blood flow, and secondly the presence of a congenital left atretic vertebral artery limiting collateral blood flow into the circle of Willis. Our review of the literature disclosed a similar case of cerebrovascular circulation 'steal'

syndrome in extensive haemangioma of the tongue and lip in a newborn infant.⁴

Thirdly, the substernal goitres reported in the literature have not been uniformly defined in relation to the proportion of the thyroid gland within the thorax. Therefore, it is rather difficult to compare the sizes and the results of reported series of substernal goitres. For the last decade, we and others⁵ have chosen to refer to any goitre in which more than 50% of its mass is inferior to the thoracic inlet as substernal.

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- 1 Anders HJ. Compression syndromes caused by substernal goitres. *Postgrad Med J* 1998;74:327-9.
- 2 Michel LA, Bradpiece HA. Surgical management of substernal goitre. *Br J Surg* 1988;75:565-9.
- 3 Gadisseux P, Minette P, Trigaux JP, Michel L. Cerebrovascular circulation 'steal' syndrome secondary to a voluminous retrotracheal goiter. *Int Surg* 1986;71:107-9.
- 4 Ismagalov MF. The cerebrovascular circulation 'steal' syndrome in extensive hemangioma of the tongue and lip in a newborn infant. *Pediatrics* 1983;74:64-5.
- 5 Katic MR, Grillo HC, Wang CC. Substernal goitre. *Ann Thorac Surg* 1985;99:391-9.

Anaphylactoid reaction to hydroxycobalamin with tolerance of cyanocobalamin

Sir,

A patient with an anaphylactoid reaction to hydroxycobalamin but good tolerance of cyanocobalamin is described, which emphasizes the usefulness of challenge tests in cases of allergic or pseudoallergic reactions.

A 33-year-old woman with a history of Crohn's disease developed subacute combined degeneration of the spinal cord due to vitamin B12 deficiency. Replacement therapy with hydroxycobalamin was established at a dose of 10 mg intramuscularly every month with no problems for more than a year. Unexpectedly, 2 hours after a dose, the patient developed generalised urticaria and angioedema with involvement of the upper airway. Prick and intradermal tests performed with 5 mg/ml and 100 µg/ml of hydroxycobalamin, respectively, were negative. Under in-hospital observation the patient was given 2500 µg of hydroxycobalamin by the intramuscular route; 20 min later, she experienced pruritus on her palms, shortly followed by generalised urticaria, prominent lip and palpebral oedema, hoarseness and chest tightness. The patient was treated with epinephrine, methylprednisolone and chlorpheniramine with total recovery in 2 hours. A challenge test with benzyl alcohol, added as preservative, was carried out with no reaction. On the basis that the neurologic manifestations would progress without adequate replacement treatment, a desensitisation protocol was developed. Increasing doses of hydroxycobalamin, beginning with 0.05 µg, were administered every 15 min by the intramuscular route. Ten minutes after the injection of 125 µg of hydroxycobalamin, the same allergic reaction appeared. Premedication with antihistamines did not provide reliably effective protection from the hydroxycobalamin-induced reaction in the

patient. However, intramuscular challenge tests with cyanocobalamin up to 10 mg, performed on three different occasions, were followed by no reaction. At present, the patient receives 10 mg of cyanocobalamin monthly without problems.

Cobalamin is an organometallic vitamin which cannot be synthesized in the human body and must be supplied in the diet. The minimum daily requirement is about 2.5 µg. In patients with disease of the distal small intestine such as Crohn's disease, cobalamin deficiency may develop. In order to avoid clinical features of cobalamin deficiency, especially neurologic manifestations, replacement therapy is suggested. Because oral absorption is inadequate, replacement must be administered parenterally. The vitamin preparations which are used therapeutically are cyanocobalamin and hydroxycobalamin (both also called vitamin B12) given intramuscularly at monthly periods and maintained indefinitely. Allergic reactions to vitamin B12 are rare but can be observed even after several years of treatment.¹ James and Warin reported one patient with dyspnoea and urticaria in the course of a treatment with cyanocobalamin and hydroxycobalamin in which specific IgE could not be showed, suggesting an anaphylactoid reaction rather than a real allergic mechanism.² Recognising that a reaction is caused by direct histamine release may be important since treatment can generally be continued by lowering the dose of the drug. In the patient reported here, the immediate response obtained with low doses of hydroxycobalamin (125 µg) on rechallenge, the tolerance of previous doses of this drug (sensitisation period), together with the perfect tolerance of therapeutic doses of cyanocobalamin suggests an allergic mechanism even in the presence of negative skin tests. Even though the reaction developed only at or above a dose of 125 µg, it is difficult to explain this as an anaphylactoid mechanism, since the capacity of hydroxycobalamin and cyanocobalamin to induce direct release of histamine is quite similar. A reaction to an excipient rather than to the drug itself was ruled out because the only preservative in the formulation was benzyl alcohol (provided by the manufacturer) which was well tolerated by the patient on challenge. Up to now, positive skin tests with hydroxycobalamin have been described in only two patients.³⁻⁴ Accordingly, cyanocobalamin may be tried as an alternative in patients with a history of systemic reactions to hydroxycobalamin.

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- 1 Ugwu CN, Gibbins FJ. Anaphylactic reaction to vitamin B12 appearing after several years of treatment. *Age Ageing* 1981;10:196-7.
- 2 James J, Warin RP. Sensitivity to cyanocobalamin and hydroxycobalamin. *BMJ* 1971;2:262.
- 3 De Blay F, Sager MF, Hirth C, et al. IgE-mediated reaction to hydroxycobalamin injection in patient with pernicious anaemia. *Lancet* 1992;339:1535-6.
- 4 Branco-Ferreira M, Clode MH, Pereira-Barbosa MA, Palma-Carlos AG. Anaphylactic reaction to hydroxycobalamin. *Allergy* 1997;52:118-9.

Salvage angioplasty following failed thrombolysis

Sir,

Drs Mahy and Jennings are correct to point out the dilemmas facing physicians responsible for the further management of patients with acute myocardial infarction and apparent failure to respond to thrombolytic therapy.¹ The lack of evidence supporting any particular management strategy is surprising given that up to 50% of patients fail to respond to thrombolytic therapy in the first few hours and that persistent ST segment elevation following acute myocardial infarction (AMI) is clearly associated with poor outcome. Purcell *et al.*² demonstrated a mortality of 18.2% in unselected patients with AMI and <50% resolution of ST segment elevation in the worst lead 60 minutes after the initiation of thrombolytic therapy. A substudy³ of the INJECT trial revealed a mortality of 17.5% in patients with ≤30% resolution of the summed ST segment elevation in leads reflecting the infarct zone. Even though it is frequently stated that such electrocardiographic (ECG) features are not 100% sensitive or specific for persistent arterial occlusion, the presence of such features must alert us to a patient who is at high risk of further adverse events. Salvage angioplasty has only been examined in one large prospective randomised study against conservative therapy.⁴ Despite a statistically significant reduction in the incidence of death or severe heart failure, this strategy has not been widely adopted nor examined further in the modern angioplasty era. This is surprising, given that this study probably underestimated the benefit of salvage angioplasty for a number of reasons. Firstly, high-risk patients, including those with a previous myocardial infarction who are perhaps more likely to benefit from attempts to open a second vessel, were excluded. Secondly, patients in this trial were taken on for salvage angioplasty relatively late after the onset of chest pain. Thirdly, intra-aortic balloon counterpulsation was rarely used, but is now known to reduce the risk of arterial occlusion following salvage angioplasty.⁵ Fourthly, the trial was performed without modern glycoprotein IIb/IIIa inhibitors, such as abciximab (Reopro®). These agents have been shown to be beneficial in high-risk angioplasty without increased risk of haemorrhage.⁶ Lastly, and most importantly, this trial was performed in the early 1990s before the modern coronary artery stent era. It is undoubtedly the case that the availability of coronary artery stents allows angioplasty in the context of AMI to be performed with greater success. We would go so far as to say that the results of the trials of immediate angioplasty following thrombolytic therapy, which universally demonstrated unfavourable outcomes with this strategy, have no relevance in the modern stent era. This is an area which commands further study. Our policy of performing salvage angioplasty in the context of <50% ST segment resolution in the worst lead 2 hours after the initiation of thrombolytic therapy has produced favourable results, especially if the patient presents promptly, receives thrombolysis promptly and the 2-hour ECG is scrupulously reviewed. Our experience is that this policy can reduce mortality from an expected 17-20% to 5%. Thus, patients with persistent ST elevation following thrombolytic therapy should be considered early for