only about one-fifth fulfil the specific criteria required for CFS [5]. Clinical similarities apart, there are biological differences between the two; for example, cerebrospinal fluid levels of substance P are elevated in FMS but not in CFS patients [6], and cardiovascular responses to postural challenge are characteristic of many CFS patients but are not apparent in those with FMS [7].

Our group has previously demonstrated that CFS patients have a significantly increased microcirculatory blood flow response to the endothelium-dependent vasodilator acetylcholine (ACh) [8] but not to the endothelium-independent vasodilator sodium nitroprusside (SNP)—a unique phenomenon that we believe may be related to a disturbance of endothelial acetylcholinesterase expression in these patients [9]. Similar experiments carried out by us on patients with FMS [10] and matched control subjects failed to demonstrate any significant difference in either the ACh or SNP responses, nor did these patients show increased baseline vasoconstriction, but the FMS patients did have a significantly elevated resting blood pressure compared with their matched controls.

As part of an investigation into specific vascular risk factors in CFS, we have recently completed a study in our Vascular Diseases Research Unit on 47 patients who, on clinical examination, fulfilled the Centre for Disease Control 1994 criteria for CFS [11], and 34 age- and sex-matched healthy controls. The local ethics committee approved the study and all subjects gave written, informed consent. Supine blood pressure measurements were obtained after a standard rest period of 20 min. ET-1 levels were measured from a morning blood sample, collected in EDTA (ethylenediamine tetraacetate), kept on ice and then centrifuged at 4°C within 5 min. Plasma was separated, aliquoted and stored at –70°C until assayed for ET-1 levels by ELISA (enzyme-linked immunosorbent assay) (R&D Systems, Oxford, UK).

No differences in plasma ET-1 levels were found between CFS patients and their control group ($P = 0.30$, unpaired t test). CFS patients had a mean ET-1 level of 0.49 pg/ml (range 0.11–1.02) and the control group had a mean ET-1 level of 0.44 pg/ml (range 0.16–0.92). We also found no differences in blood pressure between CFS patients and control subjects. The mean and range for systolic blood pressure were 125 mmHg (90–198) in CFS patients and 123 mmHg (100–180) in controls ($P = 0.50$); for diastolic blood pressure the results for CFS patients and control subjects were 74 mmHg (50–108) and 72 mmHg (50–88) respectively ($P = 0.36$).

Taken together, these experimental data challenge the concept that CFS and FMS are part of the same spectrum of illness. Normal ET-1 levels in CFS patients in conjunction with an enhanced endothelial response to ACh may predispose these patients to abnormal cardiovascular responses to orthostatic challenge. While there have been reports of impaired activation of the hypothalamic–pituitary–adrenal (HPA) axis in both CFS and FMS patients that is clearly dissimilar to that seen in depression [12], caution is required about assuming that FMS and CFS are aetiologically analogous disorders of the stress response axis. Our results show no elevation of ET-1 in CFS, in contrast to the data of Pache *et al.*

The authors have declared no conflicts of interest.

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1. Pache M, Ochs J, Genth E, Mierau R, Kube T, Flammer J. Increased plasma endothelin-1 levels in fibromyalgia syndrome. Rheumatology 2003;42:493–4.
2. White KP, Speechley M, Harth M, Ostbye T. Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population: A controlled study. Scand J Rheumatol 2000;29:44–51.
3. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160:221–7.
4. Buchwald D. Fibromyalgia and chronic fatigue syndrome: similarities and differences. Rheum Dis Clin North Am 1996;22:219–43.
5. Nørregaard J, Bülow PM, Prescott E, Jacobsen S, Danneskiold-Samsøe B. A four-year follow-up study in fibromyalgia. Relationship to chronic fatigue syndrome. Scand J Rheumatol 1993;22:35–8.
6. Evengard B, Nilsson CG, Lindh G *et al.* Chronic fatigue syndrome differs from fibromyalgia. No evidence for elevated substance P levels in cerebrospinal fluid of patients with chronic fatigue syndrome. Pain 1998;78:153–5.
7. Naschitz JE, Rozenbaum M, Rosner I *et al.* Cardiovascular response to upright tilt in fibromyalgia differs from that in chronic fatigue syndrome. J Rheumatol 2001;28:1356–60.
8. Spence VA, Khan F, Belch JJF. Enhanced sensitivity of the peripheral cholinergic vascular response in patients with chronic fatigue syndrome. Am J Med 2000;108:736–9
9. Khan F, Kennedy G, Spence VA, Belch JJF. Prolonged acetylcholine-induced vasodilatation in chronic fatigue syndrome. Clin Physiol, in press.
10. Al-Allaf AW, Khan F, Moreland J, Belch JJF. Investigation of cutaneous microvascular activity and flare response in patients with fibromyalgia syndrome. Rheumatology 2001;40:1097–1.
11. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953–9.
12. Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic–pituitary–adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Ann NY Acad Sci 1998;840:684–97.

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Reply

Sir, we appreciate the comments by Dr Kennedy and colleagues regarding our report [1] about plasma endothelin-1 levels in fibromyalgia syndrome. The aim of our study was to measure endothelin-1 (ET-1) plasma levels in patients with fibromyalgia syndrome (FMS), and to compare the results with those for healthy controls matched for sex and age. Using a specific radioimmunoassay [2], we found plasma ET-1 levels to be significantly increased in FMS patients when compared with controls (2.74 ± 0.76 pg/ml, range 1.68–3.95 *vs* 1.4 ± 0.23 pg/ml, range 0.9–1.86; $P < 0.0001$).

Dr Kennedy and colleagues measured plasma ET-1 levels in patients with chronic fatigue syndrome (CFS) by means of ELISA and found the ET-1 levels to be unaltered in their patients. They conclude that 'these data challenge the concept that CFS and FMS are part of the same spectrum of illness'. Their finding is indeed interesting, but it remains unclear to us why these data are 'in contrast to' our data, as we measured plasma ET-1 levels in FMS and not in CFS patients. Moreover, in the Introduction of our report we pointed out a clinical, but not an aetiological, overlap between FMS and CFS.

The results of Dr Kennedy and colleagues lend additional support to the hypothesis that FMS and CFS are aetiologically distinct. However, further research in this field is necessary before firm conclusions can be drawn.

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1. Pache M, Ochs J, Genth E, Mierau R, Kube T, Flammer J. Increased plasma endothelin-1 levels in fibromyalgia syndrome. Rheumatology 2003;42:493–4.
2. Moreau P, Takase H, Kung CF, Shaw S, Luscher TF. Blood pressure and vascular effects of endothelin blockade in chronic nitric oxide-deficient hypertension. Hypertension 1997;29:763–9.

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Systemic juvenile idiopathic arthritis, Kikuchi's disease and haemophagocytic lymphohistiocytosis

Sir, I read with interest the case report of a 1-yr-old girl with systemic juvenile idiopathic arthritis and Kikuchi's disease, who later developed haemophagocytic lymphohistiocytosis (HLH), and its successful management [1]. Diagnostic criteria for HLH were published in 1991 [2]. The diagnosis of HLH requires the presence of all five criteria (fever $>38.5^{\circ}$C for 7 or more days, palpable splenomegaly, cytopenia involving two or more cell lines, hypertriglyceridaemia or hypofibrinogenaemia and haemophagocytosis). The case reported by Ramanan *et al.* [1] satisfies the diagnostic criteria.

In a recent study of 122 children with HLH enrolled from 11 countries, the rate of parental consanguinity was 24% and there was a positive family history in 49% of cases [3]. Ramanan *et al.* have not commented on the parental consanguinity and the family history of their patient.

The prognosis of HLH has improved significantly since the advent of the HLH-94 protocol from the Histiocyte Society [3]. The protocol includes induction with dexamethasone and etoposide and intrathecal methotrexate in selected cases, followed by continuous treatment with cyclosporin along with pulses of dexamethasone and etoposide for 1 yr. However, haematopoietic cell transplantation appears to provide the best cure rate, of about 60% [4]. The 40-page HLH-94 protocol can be obtained from the Histiocytosis Association of America through their website (http://www.histio.org/society/protocols/trials-protocols.shtml). However, treating physicians and potential patients must be registered before the protocol can be released.

Epstein–Barr virus and parvovirus B19 infections can be associated with both HLH and Kikuchi's disease [5–7]. Ramanan *et al.* do not mention whether their patient was tested for these infections.

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1. Ramanan AV, Wynn RF, Kelsey A, Baildam EM. Systemic juvenile idiopathic arthritis, Kikuchi's disease and haemophagocytic lymphohistiocytosis—is there a link? Case report and literature review. Rheumatology 2003;42:596–8.
2. Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol 1991;18:29–33.
3. Arico M, Janka G, Fischer A *et al.* Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia 1996;10:197–203.
4. Henter JI, Samuelsson-Horne A, Arico M *et al.* Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002;100:2367–73.
5. McClain K, Gehrz R, Grierson H, Purtilo D, Filipovich A. Virus-associated histiocytic proliferations in children. Frequent association with Epstein–Barr virus and congenital or acquired immunodeficiencies. Am J Pediatr Hematol Oncol 1988;10:196–205.
6. Yen A, Fearneyhough P, Raimer SS, Hudnall SD. EBV-associated Kikuchi's histiocytic necrotizing lymphadenitis with cutaneous manifestations. J Am Acad Dermatol 1997;36:342–6.
7. Yufu Y, Matsumoto M, Miyamura T, Nishimura J, Nawata H, Ohshima K. Parvovirus B19-associated haemophagocytic syndrome with lymphadenopathy resembling histiocytic necrotizing lymphadenitis (Kikuchi's disease). Br J Haematol 1997;96:868–71.

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Reply

Sir, We thank Dr Jawad for his comments and his interest in our paper [1]. To address the issues raised by the author, there was no family history of haemophagocytic lymphohistiocytosis (HLH) or of consanguinity. We did do serology for Epstein–Barr virus (EBV) and parvovirus, both of which were negative (we mentioned in our paper that the viral serology was negative, although we did not specify the viruses checked).

As for his comments on the diagnostic criteria, these are beset with problems. The criteria were designed primarily for the diagnosis of primary HLH, but many clinicians in practice use the criteria for secondary HLH and for HLH associated with rheumatic disease. Henter *et al.* [2], in their criteria, acknowledge the fact that not all patients will fulfil the criteria and that clinical decisions regarding therapy need to be made even when patients do not satisfy the diagnostic criteria.

There are certain problems with the existing criteria. Low haemoglobin concentration, raised white cell count and raised platelet count are characteristic of active systemic disease in systemic onset juvenile idiopathic arthritis (SoJIA). Hence, relative cytopenia may enable earlier diagnosis of HLH compared with the absolute cytopenia in the present criteria.

One of the major problems with the existing criteria for HLH is the need for tissue demonstration of haemophagocytosis. It is well recognized that bone marrow aspirate or biopsy may not always show haemophagocytosis; furthermore, haemophagocytosis is not always demonstrable at onset [3, 4]. In one series of 27 children with primary HLH, autopsy studies revealed haemophagocytosis in the bone marrow in only 39% (9/23). On the contrary, 71 and 74% showed haemophagocytosis in the spleen and lymph nodes respectively [4]. Whilst this demonstrates that biopsies of the spleen and lymph nodes have higher yields, they constitute a much greater risk in the face of active coagulopathy. There is a need for criteria that take these difficulties into account, yet provide a robust framework for early diagnosis and treatment.

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