Aerobic work capacity in patients with chronic fatigue syndrome

Marshall S Riley, Charles J O'Brien, David R McCluskey, Noel P Bell, David P Nicholls

Abstract

***Objective*—To determine the aerobic work capacity of patients with the chronic fatigue syndrome and compare it with that of two control groups, and to assess the patients' perception of their level of activity before and during illness.**

***Design*—A symptom limited exercise treadmill test with on line gas analysis and blood sampling was used. Subjects were assessed by one investigator, who was blind to the group which they were in.**

***Setting*—Department of medicine, Royal Victoria Hospital, Belfast.**

***Subjects*—13 Patients (10 women, three men) who fulfilled the diagnostic criteria for chronic fatigue syndrome. Two control groups of similar age, sex, and body weight: 13 normal subjects (10 women, three men) and seven patients (five women, two men) with the irritable bowel syndrome.**

***Main outcome measures*—Aerobic work capacity as assessed by several variables such as length of time on treadmill, heart rate, and biochemical measurements; Borg score; and visual analogue scores of perceived level of physical activity.**

***Results*—The patients with the chronic fatigue syndrome had a reduced exercise capacity compared with that of the other subjects, spending a significantly shorter time on the treadmill. They had a significantly higher heart rate at submaximal levels of exertion and at stage III exertion had significantly higher blood lactate concentrations. Using a Borg score, they showed a significantly altered perception of their degree of physical exertion with a mean score of 8·2 compared with 6·6 and 5·3 for the normal subjects and patients with the irritable bowel syndrome respectively. Using a visual analogue scale they indicated that they had a greater capacity for activity before illness than had the patients with the irritable bowel syndrome, but the scores were not significantly different between the two groups. Both groups of patients indicated reduced activity at the time of testing. Normal controls and patients with the irritable bowel syndrome aspired to a greater level of activity than their current level, but the patients with the chronic fatigue syndrome aspired to a level similar to that which they had had before their illness.**

***Conclusions*—Patients with the chronic fatigue syndrome have reduced aerobic work capacity compared with normal subjects and patients with the irritable bowel syndrome. They also have an altered perception of their degree of exertion and their premorbid level of physical activity.**

Department of Medicine, Royal Victoria Hospital, Belfast BT12 6BJ
Marshall S Riley, MRCP, *research fellow*
Charles J O'Brien, MRCP, *registrar*
David R McCluskey, FRCPED, *consultant immunologist*
David P Nicholls, MRCP, *consultant physician*

Department of Medicine, Queen's University of Belfast, Belfast
Noel P Bell, MSC, *scientific officer*

Correspondence to:
Dr McCluskey.

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Introduction

The chronic fatigue syndrome (also known as myalgic encephalomyelitis, Royal Free disease, and the post-viral fatigue syndrome) is characterised by unexplained weakness, lethargy, and fatigue after exercise together with many other symptoms that often include neuropsychiatric features.[1] The onset of symptoms usually occurs after an acute viral illness in the form of either an upper respiratory infection or gastroenteritis. Patients complain of flu-like symptoms for many months or years for which no definite cause can be found.

Enteroviruses, particularly the coxsackie and herpes groups, have been regarded as the putative agents.[2] The most prominent and consistent symptom is muscle fatigue, which results in limited exercise capacity and profound weakness and tiredness after exercise. Using an exercise treadmill, we measured the aerobic work capacity of patients with the chronic fatigue syndrome. We also tried to determine whether their response to exercise was abnormal compared with that of healthy subjects and patients with the irritable bowel syndrome.

Subjects and methods

We studied three groups of subjects aged 20-40 and of average body weight; each group had a similar ratio of males to females (table I). Subjects were excluded if they had any medical condition other than the chronic fatigue syndrome or the irritable bowel syndrome or were taking drugs known to affect performance of work.

TABLE I—*Demographic details of patients with chronic fatigue syndrome and controls. Figures are means (SD)*

	No	Age (years)	Weight (kg)
Patients with chronic fatigue syndrome	13	34 (6·1)	64 (11·2)
Normal controls	13	34 (4·8)	65 (13·8)
Patients with irritable bowel syndrome	7	28 (6·7)	60 (9·9)

Patients with the chronic fatigue syndrome—As there is no definitive laboratory test for the chronic fatigue syndrome it was diagnosed by exclusion of other organic disorders and from the clinical history. Thirteen patients (three men and 10 women) attending an immunology clinic who met the Centers for Disease Control criteria for the syndrome were randomly selected for study.[3] The two main criteria were (1) the onset of persistent or relapsing debilitating fatigue or early fatigability, in a person who did not have a history of similar symptoms, that failed to resolve with bed rest and was severe enough to reduce average daily activity to below half of the patient's premorbid activity for at least six months; (2) exclusion of other clinical conditions that may produce similar symptoms by thorough evaluation. The minor criteria comprised 11 symptoms, and the three physical criteria were fever, lymphadenopathy, and non-exudative pharyngitis. For a diagnosis of the chronic fatigue syndrome both of the major criteria had to be present plus either eight minor or six minor and two physical criteria. All

patients had had symptoms for six months or more (mean 31 months, range 6-78) with onset after an acute fever.

Normal controls—Thirteen healthy subjects (10 women and three men) were selected from the general population. They comprised nine hospital staff, three relatives of staff, and one relative of a patient.

Patients with the irritable bowel syndrome—Five women and two men attending the gastroenterology clinic of the Royal Victoria Hospital who fulfilled the diagnostic criteria for the irritable bowel syndrome were selected.[4]

Exercise testing—After an initial exercise test for familiarisation about one week before the study all subjects reported to the laboratory two to three hours after a light meal. A Teflon cannula was inserted into an antecubital vein, and after 15 minutes' supine rest samples of blood were withdrawn for measurement of resting lactate, phosphate, and glucose concentrations and creatine kinase activity. Subjects then performed a symptom limited treadmill exercise test to a Bruce protocol[5] modified by the addition of an initial stage at a 5% gradient with on line measurement of respiratory gas exchange. They were encouraged to exercise until they were unable to continue. During peak exercise blood was again withdrawn for measurement of lactate, phosphate, and glucose concentrations and creatine kinase activity. In addition, during the final minute of each stage of exercise and after three minutes' recovery after exercise a sample was withdrawn for measurement of lactate concentration. After the test subjects were asked to indicate the degree of subjective difficulty at peak exertion on a Borg score.[6] All exercise testing was done by the same investigator (MR), who was blind to the experimental group of the subject.

Activity score—Subjects were asked to indicate on a visual analogue scale their overall capacity for physical activity just before their illness, when appropriate, and before the exercise testing. They were also asked to indicate the level of activity to which they reasonably aspired.

Measurement of gas exchange—Minute ventilation was measured with a vane turbine placed on the inspiratory side of a non-rebreathing respiratory valve circuit (dead space 88 ml) in conjunction with a Ventilometer (P K Morgan). Expired oxygen and carbon dioxide concentrations were determined by paramagnetic and infrared analysis respectively and minute O_2 consumption and CO_2 production calculated on line by a microcomputer (Ericsson). Details of this method have been reported.[7] The respiratory exchange ratio was calculated as minute O_2 consumption/minute CO_2 production. It rises with increasing lactic acidosis as buffering occurs because of increased elimination of CO_2 and thus serves as a non-invasive indication of the extent of anaerobic metabolism.[8,9] End tidal CO_2 tension was measured with an end tidal analyser (Engstrom, Sweden), expired air being sampled with a fine bore tube inserted into the mouthpiece just in front of the mouth.

TABLE II—*Responses at peak exertion in patients with chronic fatigue syndrome and controls. Figures are means (SD)*

	Patients with chronic fatigue (n=13)	Normal controls (n=13)	Patients with irritable bowel (n=7)
Time on treadmill (s)	672 (109)**	849 (52)	901 (91)
Minute O_2 consumption (ml/min/kg)	31·8 (5·3)*	37·9 (5·1)	42·6 (7·0)
Respiratory exchange ratio	1·14 (0·1)	1·19 (0·1)	1·13 (0·05)
Peak heart rate (beats/min)	177 (18)	182 (7)	189 (5)
Borg score	8·2 (1·9)*	6·6 (0·8)	5·3 (1·3)
Peak lactate (mmol/l)	4·25 (1·5)	5·37 (1·2)	5·73 (0·9)
End tidal CO_2 (mm Hg):			
At rest	34·8 (4·4)	35·8 (5·2)	32·1 (5·0)
At peak exercise	34·9 (5·3)	36·3 (5·4)	33·6 (4·5)

*p<0·05, **p<0·01 Compared with values in normal controls.

Statistical analysis—Variation among groups was tested by analysis of variance. When repeated measures were taken over time a repeated measures two way analysis of variance was used. When appropriate, further comparisons between groups were made with the Tukey test.

Blood sampling and assays—The venous cannula was flushed with 0·9% saline. Lactate samples were precipitated immediately in 8% perchloric acid and the supernatant assayed by an enzymatic colorimetric method (Sigma). Blood glucose concentration, creatine kinase activity, and phosphate concentration were measured with a nephelometer (Cobas Bio; Roche Diagnostica).

Results

All subjects completed the exercise tests uneventfully. Of those with the chronic fatigue syndrome, 12 stopped because of fatigue and one because of dyspnoea. Ten of the normal controls stopped because of fatigue and three because of dyspnoea. Of those with the irritable bowel syndrome, five stopped because of fatigue, one developed chest tightness without electrocardiographic changes, and one stopped because of light headedness (blood pressure remained normal).

The patients with the chronic fatigue syndrome were on the treadmill for a shorter time and had a lower peak O_2 consumption than the subjects in either of the two control groups. Despite this their score for perceived exertion was higher than that of the two other groups (table II) and no differences were seen in the peak respiratory exchange ratios among the groups. No significant differences in these variables were found between the normal controls and those with the irritable bowel syndrome. Peak heart rate and lactate concentrations were also similar in these two groups. End tidal CO_2 tensions both at rest and during exercise were similar in all groups.

HEART RATE AND LACTATE CONCENTRATION

Table III shows the heart rate, whole blood lactate concentration, and minute O_2 consumption at rest and during and after exercise. The first three stages of exercise were completed by all subjects and therefore were used to compare responses at equal absolute workloads. Heart rate showed a different pattern of response with exercise in the patients with the chronic fatigue syndrome ($p<0·05$); this was apparent as a trend to higher heart rates at rest and significant increases at submaximal exertion. Lactate concentration also showed a trend to higher values at submaximal exertion, although this was significant only at stage III ($p<0·05$). No differences in submaximal minute O_2 consumption were seen. During recovery from exercise lactate concentration and minute O_2 consumption were higher in the patients with the irritable bowel syndrome, reflecting the greater workload achieved.

GLUCOSE CONCENTRATION

No significant differences in glucose concentration were apparent among the groups either before or during peak exercise (table IV). No group showed any significant change in blood glucose concentration with exercise.

CREATINE KINASE ACTIVITY

No significant differences in creatine kinase activity were seen among the groups (table IV), and there was no significant change after exercise.

ACTIVITY SCALE

Using a visual analogue score, the patients with the chronic fatigue syndrome indicated that they had had a greater capacity for activity before the start of their

TABLE III—*Heart rate, blood lactate concentration, and minute oxygen consumption in patients with chronic fatigue syndrome and controls at various stages of exercise. Figures are means (95% confidence intervals)*

	Stage of exercise testing					
	At rest	Stage I	Stage II	Stage III	Peak exercise	Recovery
			Heart rate (beats/min)			
Chronic fatigue syndrome	99·8 (90·3 to 109·4)	123·0* (110·0 to 136·0)	136·8* (122·9 to 150·6)	160·2* (149·8 to 180·0)	176·6 (166·0 to 187·2)	122·2 (110·6 to 133·9)
Normal controls	86·4 (78·4 to 94·3)	104·1 (97·6 to 110·6)	118·5 (112·7 to 124·2)	142·2 (133·1 to 151·2)	181·9 (177·6 to 186·2)	116·0 (110·2 to 121·8)
Irritable bowel syndrome	86·6 (81·1 to 92·1)	105·7 (96·4 to 115·0)	119·9 (107·0 to 132·8)	147·4 (129·9 to 165·0)	188·9 (184·2 to 193·6)	119·1 (105·6 to 132·7)
			Lactates (mmol/l)			
Chronic fatigue syndrome	0·95 (0·77 to 1·13)	1·12 (0·95 to 1·30)	1·59 (1·19 to 2·00)	2·01*† (1·66 to 2·35)	4·25 (3·33 to 5·16)	5·03† (3·90 to 6·16)
Normal controls	0·88 (0·70 to 1·05)	1·14 (0·72 to 1·56)	1·05 (0·60 to 1·49)	1·19 (0·85 to 1·53)	5·37 (4·63 to 6·10)	6·49 (5·41 to 7·58)
Irritable bowel syndrome	0·79 (0·65 to 0·92)	0·98 (0·72 to 1·24)	1·36 (0·64 to 2·07)	1·17 (0·71 to 1·64)	5·73 (4·93 to 6·52)	7·61 (6·06 to 9·17)
			Minute O_2 consumption (ml/min/kg)			
Chronic fatigue syndrome	4·67 (4·34 to 5·00)	16·13 (14·58 to 17·69)	19·42 (17·96 to 20·87)	24·54 (23·43 to 25·65)	31·7*† (28·58 to 34·96)	6·89*† (6·04 to 7·67)
Normal controls	4·93 (4·47 to 5·39)	14·07 (13·37 to 14·78)	17·92 (16·95 to 18·90)	23·73 (22·56 to 24·90)	37·88 (34·79 to 40·98)	8·52 (7·93 to 9·12)
Irritable bowel syndrome	5·13 (4·14 to 6·12)	14·98 (14·30 to 15·67)	19·42 (18·53 to 20·31)	26·00 (23·66 to 28·34)	42·57 (36·10 to 49·05)	9·15 (8·64 to 9·66)

*p<0·05 For patients with chronic fatigue syndrome *v* normal controls.
†p<0·05 For patients with chronic fatigue syndrome *v* patients with irritable bowel syndrome.

TABLE IV—*Blood glucose concentration and creatine kinase activity at various stages of exercise testing in patients with chronic fatigue syndrome and controls. Figures are means (SD)*

	Patients with chronic fatigue syndrome	Normal controls	Patients with irritable bowel syndrome
Glucose (mmol/l):			
At rest	5·1 (1·0)	4·9 (1·2)	4·9 (1·0)
At peak exercise	5·2 (0·9)	5·3 (1·1)	5·5 (1·0)
Creatine kinase (U/l):			
At rest	58·9 (18·7)	92·1 (40·3)	91·0 (74·7)
At peak exercise	66·5 (21·6)	103·9 (52·4)	70·5 (22·7)
18 Hours after exercise	65·8 (22·7)		

TABLE V—*Exercise capacity of patients with chronic fatigue syndrome and controls at three stages indicated by visual analogue score*

	Patients with chronic fatigue syndrome	Normal controls	Patients with irritable bowel syndrome
Before illness	7·8 (2·0)‡		6·5 (2·0)
Current level	2·3 (1·6)*	5·7 (1·5)	3·4 (1·1)*
Level aspired to	7·9 (1·5)	7·3 (1·1)†	7·9 (1·8)†

*p<0·05 Compared with value in normal controls.
†p<0·05 Compared with original state.
‡p<0·05 Compared with current level in normal controls.

illness than had the patients with the irritable bowel syndrome, but the scores were not significantly different between the two groups (table V). Both groups of patients indicated reduced activity at the time of testing. The normal controls and patients with the irritable bowel syndrome aspired to a greater level of activity than their current level, but the patients with the chronic fatigue syndrome aspired to a level similar to that which they had had before their illness.

Discussion

We found that patients with the chronic fatigue syndrome have a lower exercise tolerance than either normal subjects or patients with the irritable bowel syndrome. The reduction in peak O_2 consumption indicates that this is due to a decreased aerobic work capacity and not simply to decreased efficiency at walking on the treadmill. The main reason for the impaired exercise performance seems not to be diminished motivation, as no significant differences were noted in peak heart rate or respiratory exchange ratio among the groups.

Significant differences in submaximal heart rate and lactate concentrations were seen among the groups. Comparisons made at the same absolute workloads on the treadmill (stages I-III) showed a significant trend to higher lactate concentrations and heart rates in the patients with the chronic fatigue syndrome, after the pattern observed in deconditioned subjects.[10 11] Unlike Montague *et al*, we did not find a tendency for impaired heart rate responses.[12] Previous studies have shown biochemical and structural abnormalities of muscle in patients with the chronic fatigue syndrome.[13-15] Many of these studies were uncontrolled, and their findings may partly be the consequence of deconditioning.

Many muscle disorders result in abnormalities of muscle enzymes in the serum that are often exacerbated by exercise.[16] We found no such abnormalities in creatine kinase activities.

The stable blood glucose concentration before and at peak exertion indicates that this is not a limiting factor for exercise. Our finding of a normal end tidal CO_2 concentration both at rest and at peak exercise indicates that patients with the chronic fatigue syndrome do not hyperventilate; hyperventilation has been suggested to contribute to their symptoms.[17]

The patients with chronic fatigue syndrome perceived the workload at peak exercise to be significantly greater than did those in the other groups (table II). Objectively, their relative exertion was not greater as shown by the similar peak heart rate responses, respiratory exchange ratios, and whole blood lactate concentrations in the group. A possible explanation could be that γ afferents from muscle end plates are overactive, resulting in greater perception of stretch,[18 19] or a difference in perception of exercise at a higher cerebral level. The activity scores cast an interesting light on the patients' perception of their capacity for exercise. In general the scores did not relate to objective measures of exercise capacity such as time on the treadmill or peak O_2 consumption. Patients with the chronic fatigue syndrome invariably indicated a high previous level of activity and a reduced current level with an aspiration to return to the previous level. Interestingly, the patients with the irritable bowel syndrome also claimed a reduced exercise capacity, but their objective measurements on testing were similar to those of the normal controls. Both the normal controls and the patients with the irritable bowel syndrome aspired to exercise levels greater than they had had before. Our data suggest either that the patients with the chronic fatigue syndrome were extremely fit before their illness or that they had an altered perception of their premorbid activity level.

In summary, patients with the chronic fatigue syndrome show impaired capacity for exercise despite an increased perception of their exertion. We found no evidence for a deficient cardiovascular response or peripheral muscle function other than that which would be expected as a result of deconditioning. Other mechanisms, however, such as atrophy of muscle fibre or depletion of muscle enzymes may result in similar findings and merit further investigation.

1 Behan PO, Behan WHM, Bell EJ. The post-viral fatigue syndrome—an analysis of findings in 50 cases. *J Infect* 1985;**10**:211-22.
2 Bell EJ, McCartney RA, Riding MH. Coxsackie B viruses and mylagic encephalomyelitis. *J R Soc Med* 1988;**81**:329-31.
3 Holmes GP, Kaplan JE, Gantz NM, *et al.* Chronic fatigue syndrome; a working case definition. *Ann Intern Med* 1988;**108**:387-9.
4 Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br Med J* 1978;ii:653-4.
5 Bruce RA. Exercise testing of patients with coronary artery disease. *Annals of Clinical Research* 1971;**3**:323-32.
6 Borg GAV. Psychophysical basis of perceived exertion. *Med Sci Sports Exerc* 1982;**14**:377-81.
7 Elborn JS, Stanford CF, Nicholls DP. Reproducibility of cardiopulmonary parameters during exercise in patients with chronic cardiac failure. The need for a preliminary test. *European Journal of Cardiology* 1990;**11**:75-81.
8 Clode M, Campbell EJM. The relationship between gas exchange and changes in blood lactate concentrations during exercise. *Clin Sci* 1969;**37**:263-72.
9 Jones NL. *Clinical exercise testing.* 3rd ed. Philadelphia: W B Saunders, 1988:213-30.
10 Saltin B, Blomqvist B, Mitchell JH, Johnston RL, Wildenthal K, Chapman CB. Response to submaximal and maximal exercise after bedrest and training. *Circulation* 1968;**38** (suppl 7):1-78.
11 Holloszy JO, Booth FW. Biochemical adaptations to endurance exercise in muscle. *Annu Rev Physiol* 1976;**38**:263-91.
12 Montague TJ, Marrie TJ, Klassen GA, Bewick DJ, Horacek BM. Cardiac function at rest and with exercise in the chronic fatigue syndrome. *Chest* 1989;**95**:779-84.
13 Arnold DL, Radda GK, Bore PJ, Styles P, Taylor DJ. Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a post-viral exhaustion/fatigue syndrome. *Lancet* 1984;i:1367-9.
14 Archard LC, Bowles NE, Behan PO, Bell EJ, Doyle D. Post viral fatigue syndrome: persistence of enteroviral RNA in skeletal muscle and elevated creatine kinase. *J R Soc Med* 1988;**81**:326-9.
15 Byrne E, Trounce I. Chronic fatigue and myalgic syndrome: mitochondrial and glycolytic studies in skeletal muscle. *J Neurol Neurosurg Psychiatry* 1987;**50**:743-6.
16 Beaudet AL. The glycogen storage of diseases. In: Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, Fauci AS, eds. *Harrison's principles of internal medicine.* 11th ed. New York: McGraw-Hill, 1987:1648.
17 McEvedy CP, Beard AW. Royal Free epidemic of 1955: a reconsideration. *Br Med J* 1970;i:7-11.
18 Woods JJ, Furbush F, Bigland-Ritchie B. Evidence for a fatigue-induced reflex inhibition of motorneuron firing rates. *J Neurophysiol* 1987;**58**:125-37.
19 Stokes MJ, Cooper RG, Edwards RHT. Normal muscle strength and fatigability in patients with effort syndromes. *Br Med J* 1988;**297**:1014-7.

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Five year prospective study of HIV infection in the Edinburgh haemophiliac cohort

R J G Cuthbert, C A Ludlam, J Tucker, C M Steel, D Beatson, S Rebus, J F Peutherer

Department of Haematology, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW
R J G Cuthbert, MRCP, *lecturer*
C A Ludlam, FRCPATH, *consultant*
J Tucker, MRCPATH, *senior registrar*

MRC Human Genetics Unit, Western General Hospital, Edinburgh EH4 2XU
C M Steel, FRCP, *assistant director*
D Beatson, FIMLS, *medical laboratory scientific officer*

Department of Bacteriology, University of Edinburgh, Edinburgh
S Rebus, BSC, *medical laboratory scientific officer*
J F Peutherer, FRCPATH, *senior lecturer*

Correspondence to: Dr R J G Cuthbert, Department of Haematology, City Hospital, Nottingham NG5 1PB.

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Abstract

***Objective*—To identify measures of immune state that reflect the course of HIV related disease in order to predict deterioration of symptoms and assess response to treatment.**

***Design*—Five year longitudinal clinical and laboratory study.**

***Setting*—Regional haemophilia centre, university virology laboratory, and Medical Research Council laboratory.**

***Patients*—32 Patients with haemophilia A exposed to a single batch of HIV contaminated factor VIII concentrate from the Scottish National Blood Transfusion Service in 1984 who were followed up regularly in Edinburgh (31) or abroad (one).**

***Main outcome measures*—Counts of circulating T cell subsets (CD4 and CD8); plasma β_2 microglobulin, neopterin, and IgA concentrations; and delayed type hypersensitivity to multiple skin test antigens.**

***Results*—18 Patients who seroconverted after exposure had received significantly more contaminated factor VIII than the 14 who did not (mean 43 (range 9-109) *v* 15 (3-30) phials, $p<0.01$). The two groups were not distinguishable by other criteria before exposure. The group that seroconverted subsequently showed a progressive fall in mean circulating CD4 lymphocytes and an increase in plasma β_2 microglobulin and neopterin concentrations. From 1987 patients in this group also showed an increase in mean circulating CD8 lymphocytes and in plasma IgA concentration, neither of which was seen in patients who did not seroconvert. Patients with HIV antibody who developed Centers for Disease Control category IV symptoms within five years after infection showed more extreme changes in all measures, except CD8 lymphocyte count, than those whose symptoms remained in categories II and III. Skin test reactivity declined to barely detectable levels in all patients positive for HIV antibody.**

***Conclusions*—Serial estimates of circulating CD4 lymphocytes and of plasma β_2 microglobulin concentration are the most reliable measures of disease progression; of these, β_2 microglobulin concentration seems to be the better predictor of impending serious symptoms. High IgA concentrations reflect rather than predict disease state. Individual variation in most measures is such that a wide range of measurements should be used in assessing the effects of trial treatment in HIV infected patients without symptoms.**

Introduction

The early identification of individual patients who have a poor prognosis for HIV disease is an important objective. It may, for example, permit initiation of antiviral treatment at a stage before serious clinical deterioration and has therefore been a goal of many cohort studies of HIV infection.[1] Among the prognostic variables identified in some or all of these reports have been age at seroconversion[2,3]; declining CD4 cell counts[2-8] and rising CD8 cell counts[4,5]; rising plasma β_2 microglobulin,[5,8] neopterin,[8,9] and IgA[5-8] concentrations; and altered delayed type hypersensitivity responses.[10,11] Though there is universal agreement on the value of serial CD4 cell counts to track the course of infection, there is no consensus on which additional variable or combination of variables might be useful for early detection of those patients at greatest risk of rapid progression to symptomatic disease.[1] One difficulty common to virtually all published studies is that the times of onset and the sources of infection are very heterogeneous. We previously described a unique group of haemophiliac patients infected with HIV from a single batch of factor VIII concentrate used between March and May 1984.[12] This led inadvertently to the establishment of a cohort of individual patients with a common source of infection, whose times of HIV seroconversion were clearly recorded. Since that report three further seroconversions have occurred among members of the cohort. In this study we reanalyse the data on seroconversion and describe