The biochemistry of runners in a 1600 km ultramarathon

K E Fallon, G Sivyer, K Sivyer, A Dare

Abstract
Objective—To investigate biochemical changes related to muscle breakdown, hepatic damage, hyponatraemia, and a number of other variables in the serum of participants in a 1600 km ultramarathon run.
Methods—Blood samples were obtained from nine participants (seven men, two women) in a 1600 km foot race before, after 4 and 11 days of running, and at the conclusion of the event. Samples were analysed by standard methods and results corrected, where appropriate, for changes in plasma volume.
Results—Significant (p<0.05) increases in the following variables were found during or at the conclusion of the event: plasma volume, sodium, chloride, urea, alkaline phosphatase, γ-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, bilirubin, total protein, albumin, glucose, calcium, and phosphate. Significant (p<0.05) decreases in the following variables were found during or at the conclusion of the event: globulin, uric acid, and cholesterol. No change occurred in serum potassium, bicarbonate, creatinine, and triglycerides.
Conclusion—A wide range of biochemical perturbations occur during ultramarathon running but a number of variables remain within normal limits despite severe physical stress. Large increases in plasma volume occur, and hyponatraemia is rare in events of this duration. The time course of increases in enzymic indicators of muscle damage indicates that duration of running is not the sole determinant of such increases. This study provides indirect evidence of possible hepatic damage during prolonged exercise and an increase in serum calcium both of which warrant further investigation.
(*Br J Sports Med* 1999;**33**:264–269)

A significant amount of biochemical data has accumulated during studies of marathons and ultramarathons but little information is available on very long distance running events. In view of the unusual distance of this event, this study was conducted to document a wide range of biochemical changes and in particular to attempt to clarify a series of issues related to ultraendurance sport, specifically the incidence of hyponatraemia, the time course of changes in indicators of skeletal muscle breakdown, and possible hepatic damage.

Hyponatraemia is a significant medical problem in ultraendurance events, being reported in 20% of finishers in the Hawaiian Iron Man triathlon.[1] Concentrations of sodium have been found to be significantly elevated after a 100 km run,[2 3] but no change was found after a 160 km run[4] or after 10 days of a 20 day 500 km stage race.[5] It has been hypothesised that hyponatraemia would not occur in an ultramarathon of this duration because of significant intake of solid food and utilisation of glucose-electrolyte drinks.

Few studies on the effect of repeated daily training or running on creatine kinase (CK) are available, but in army personnel undergoing a 24 day intensive training course, CK was higher in the early than in the later part of the programme,[6] and Dressendorfer and Wade[7] found a continuing increase in CK over the first eight days of a 500 km run. Noakes[8] has suggested that the increase in muscle enzymes, particularly CK, is related to both intensity and duration of exercise, with duration having the dominant effect such that the largest increases are found after very prolonged exercise but that each athlete possibly shows a maximum increase in serum enzyme activity which may be achieved by running for four to six hours. The second postulate of this study was therefore that enzymic indicators of muscle damage would have their highest levels early in the event and that duration of exercise would not be the primary determinant of enzyme increases.

It is not known if hepatic damage occurs during prolonged exercise. However, whereas lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are found in both liver and muscle cells and therefore increases in these enzymes cannot specifically indicate liver cell damage, Nagel *et al*[9] have suggested that a decrease in CK and AST after the third day of running that is not accompanied by a decrease in ALT may indicate reduction of skeletal muscle damage with continuing hepatic cell injury. The third hypothesis was therefore that changes in these enzymes would be similar in this event to those in the study of Nagel *et al* and that this would support a further study in which liver-specific enzymes would be measured.

Methods

Before commencement of this study, approval was obtained from the ethics committee of the South Queensland Regional Health Authority.

Department of Sports Medicine, Australian Institute of Sport, Canberra, Australia
K E Fallon

Private Practice, Parkwood, Queensland, Australia
G Sivyer
K Sivyer

Queensland Medical Laboratory, Gold Coast, Queensland, Australia
A Dare

Correspondence to:
Dr K Fallon, Australian Institute of Sport, PO Box 176, Belconnen, ACT, Australia 2616.

Table 1   Subject characteristics

Variable	Mean	SD	Range
Age (years)	53	11.2	41–76
Training distance (km/week)	194	212	50–650
Years of running	20	12	6–40
Previous ultramarathons	34	34	6–100
Previous marathons	19	17	1–50
Best marathon time (hours)	3.26	0.55	2.5–4.3

Table 2   Performance data for each of the runners

Runner	Time (days)	Distance (km)	Rate (km/day)	Day 4 (km)	Day 11 (km)
A	11.45	1600	118.8	490.2	1306.5
B	11.79	1600	115.7	520.8	1317.8
C	14.44	1600	110.8	520.4	1249.4
D	14.95	1600	107.8	498.7	1231.7
E	11.49	1364	118.7	545.4	1308.9
F	16	1346	85.5	409.3	1019.5
G	16	1146	71.6	297	785.3
H	16	1138	71.1	327	802.6
I	14.89	1044	70.1	329.6	782.9
Mean	14.11	1382	96.7	437.6	1089.4
SD	1.98	229	21.7	97.7	241.6

All procedures conformed to the National Health and Medical Research Council guidelines for experimentation with human subjects and all subjects gave their informed written consent before participation.

Seven male and two female experienced ultramarathon runners participating in the 1600 km ultramarathon in Nanango, Australia volunteered for this study. The data for those who completed at least 1000 km were included in the analysis. The ultramarathon was a continuous event, the object being to cover 1600 km (1000 miles) in the shortest possible time. Runners competed on a 400 m oval grass track, the surface of which changed progressively to dirt after the first three days of the event. Temperature range during the 16 days of the event was 11.0–31.8°C, and the relative humidity 17–100%. The runners were allowed free intake of their usual diets before and during a race. A medical and training history was obtained before the start of the race. Four of the runners completed 1600 km in less than 16 days, three completed 16 days of running but did not complete 1600 km, and two completed shorter distances (1364 km and 1044 km) in less than 16 days.

Blood (25 ml) was withdrawn from an antecubital vein, using a sterile technique, about 30 minutes before the start. Further samples were obtained between 9 and 10 am on days 4 and 11 and at the conclusion of the run. The mean delay in sampling after the event was less than 30 minutes. Each sample was obtained with the subject in the seated position and was taken within 30 seconds of the

subject being seated. All specimens were refrigerated and transported to the laboratory within six hours of venepuncture.

Estimation of electrolytes, urea, creatinine, glucose, urate, total bilirubin, alkaline phosphatase (AP), ALT, AST, γ-glutamyltransferase (GGT), LDH, calcium, phosphate, total protein, albumin, cholesterol, triglycerides, and CK was performed on an Olympus AU 800 autoanalyser using trace reagents. Haptoglobin was measured on an Hitachi 917 analyser using Boehringer Mannheim reagents. Haemoglobin and packed cell volume were measured on a Coulter Stack "S" autoanalyser. Plasma volume changes were derived from changes in haemoglobin and packed cell volume.[10] All results were corrected for changes in plasma volume unless specifically indicated.

Statistical significance of paired differences in means and standard deviations of the metabolic alterations from baseline values were calculated by Student's *t* test. The level of significance was set at p<0.05.

Results

Table 1 presents a summary of the characteristics of the subjects of this study.

Table 2 gives the performance data for each of the runners. Four of them completed 1600 km, three completed shorter distances in the 16 day period of the event, and one completed over 1000 km in almost 15 days of running.

Table 3 gives means (SD) for electrolytes, indicators of renal function, and changes in plasma volume. Serum sodium remained within normal limits throughout the event, except for one runner in whom it reached a level of 130 mmol/l on day 11. No significant changes occurred in serum potassium, and all individual values remained within normal limits. Serum chloride was significantly increased only at the end of the event. No significant changes occurred in serum bicarbonate or serum creatinine, and all individual values for chloride, bicarbonate, and creatinine concentration remained within normal limits. Urea was significantly increased at 4 and 11 days and at the end of the run.

Table 4 gives the means (SD) for serum enzymes. AP activity was significantly elevated above baseline at day 4 and 11 and at the end of the run. GGT was increased on day 4 and at the conclusion of the run. All mean values for AP and GGT remained within normal limits. ALT was significantly increased at day 4 and was not significantly different to the day 4 level on day 11 and at the end of the run. AST levels were significantly elevated at day 4 and decreased significantly from this value on day 11; however, both the day 11 value and that at the end of the run remained significantly increased compared with the level before the race. LDH was significantly increased at day 4 and was not different to the day 4 level on day 11 and at the end of the run. CK had increased significantly by day 4, decreased between days 4 and 11 and between day 11 and the end of the race, but the value at the end of the race remained above that measured before. The

Table 3   Concentrations of electrolytes and indicators of renal function and changes in plasma volume during the ultramarathon race

Variable	Before the race	Day 4	Day 11	After the race
Sodium (mmol/l)	138 (2)	141 (4)★	137 (3)	141 (2)★
Potassium (mmol/l)	4.4 (0.5)	4.4 (0.3)	4.4 (0.3)	4.4 (0.5)
Chloride (mmol/l)	102 (2)	101 (4)	99 (4)	105 (2)★
Bicarbonate (mmol/l)	28 (2)	27 (2)	28 (1)	29 (2)
Urea (mmol/l)	5.7 (1.1)	9.3 (2.0)★	8.6 (2.0)★	8.8 (1.5)★
Creatinine (μmol/l)	0.09 (0.01)	0.09 (0.01)	0.09 (0.02)	0.09 (0.01)
Plasma volume (% change)		13.4 (4.3)★	21.6 (19.2)★	12.6 (9.8)★

Values are mean (SD).
★p<0.05 *v* pre-race value.

Table 4 Serum enzyme activity during the ultramarathon race

Enzyme	Before the race	Day 4	Day 11	After the race
AP	62 (16)	85 (22)★	88 (25)★	91 (21)★
GGT	22 (8)	24 (8)★	26 (8)	35 (14)★
ALT	25 (9)	107 (63)★	100 (59)★	87 (41)★
AST	24 (5)	162 (99)★	107 (61)★†	63 (22)★‡
LDH	161 (17)	465 (161)★	482 (212)★	430 (161)★
CK	123 (64)	2656 (2130)★	1565 (1105)★†	567 (297)★‡

Results are expressed as U/l and are mean (SD).
AP, alkaline phosphatase; GGT, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase.
★p<0.05 *v* pre-race value; †p<0.05 day 4 *v* day 11 value; ‡p<0.05 day 11 *v* post-race value.

Table 5 Other biochemical variables measured throughout the ultramarathon race

Variable	Before the race	Day 4	Day 11	After the race
Bilirubin (μmol/l)	13 (7)	22 (17)★	10 (5)	10 (3)
Haptoglobin (mg/dl)	181 (73)	341 (89)★	390 (64)★	412 (119)★
Total protein (g/l)	75 (5)	79 (6)★	75 (8)	77 (8)
Albumin (g/l)	41 (3)	48 (4)★	43 (5)	46 (5)★
Globulin (g/l)	34 (4)	31 (3)★	31 (3)★	32 (4)
Glucose (mmol/l)	5.4 (0.9)	6.5 (1.3)	6.6 (0.9)★	5.8 (0.4)
Uric acid (mmol/l)	0.28 (0.07)	0.26 (0.12)	0.23 (0.11)★	0.28 (0.14)
Cholesterol (mmol/l)	5.1 (0.4)	4.9 (0.5)★	4.7 (0.7)	5.0 (0.4)
Triglycerides (mmol/l)	1.9 (0.9)	0.9 (0.4)	1.7 (0.7)	1.7 (0.4)
Calcium (mmol/l)	2.38 (0.06)	2.70 (0.11)★	2.66 (0.24)★	2.62 (0.21)★
Phosphate (mmol/l)	1.1 (0.1)	1.3 (0.2)★	1.3 (0.2)★	1.3 (0.2)★

Values are mean (SD).
★p<0.05 *v* pre-race value.

mean values for ALT, AST, and LDH were above the normal range on days 4 and 11 and at the end of the run.

Table 5 gives the means (SD) for other biochemical variables. Serum bilirubin, total protein, and cholesterol were increased on day 4 only. Serum albumin was increased on day 4 and at the end of the race. Serum globulin levels were elevated on days 4 and 11. Glucose was increased and uric acid decreased on day 11 only. Serum haptoglobin, calcium, and phosphate were increased on days 4 and 11 and at the end of the race. There was no significant change in serum triglyceride. Only serum bilirubin on day 4 and serum calcium on days 4 and 11 were above the normal range.

Discussion

Caution needs to be exercised in the interpretation of the end of race data in this study as they represent a number of end points which include completion of 1600 km, 16 days of running, and early retirement. However, it should be noted that each of four runners completed 1600 km, three of the others finished on the 16th day, and the runner who finished on day 12 had completed 1364 km.

ELECTROLYTES AND MEASURES OF RENAL FUNCTION

In an attempt to identify hyponatraemia and other electrolyte abnormalities, serum electrolytes were not corrected for changes in plasma volume. Serum sodium remained within normal limits throughout the event except for in one runner in whom a level of 130 mmol/l was reached on day 11. The runner was asymptomatic at the time, which is consistent with other cases of exercise related hyponatraemia, symptoms generally not occurring until serum sodium concentration falls below 125 mmol/l.[11] Serum sodium was increased above the baseline value on both day 4 and at the conclusion of the event but was not significantly different from the baseline level on day 11. This finding is consistent with other studies of ultramarathon runners.[2–5]

The cause of hyponatraemia in athletes remains controversial, but several mechanisms have been postulated. The first is that a significant total body sodium loss occurs as the result of prolonged increased sweating,[12] the second that hypervolaemic hyponatraemia occurs because of the consumption of large volumes of hypotonic solutions,[13] and the third that sodium may be translocated into a third space which may be the gastrointestinal tract.[13] As no large weight changes were noted during or at the conclusion of the event, indicating that significant dehydration and overhydration were unlikely to have occurred, it is understandable that serum sodium concentrations did not change. Each of the runners was also noted to use carbohydrate-electrolyte drinks as their predominant fluid replacement, which is at variance with the finding of a recent study of runners in a 100 km event.[14] This and the use of solid food may have assisted in maintenance of adequate sodium intake. In future studies assessment of urinary electrolytes and osmolality in addition to hormones related to fluid homoeostasis may assist in clarification of the mechanisms involved in maintenance of normal serum sodium.

As in this study, serum potassium has previously been found to be unchanged after a standard marathon,[15] a 56 km run,[16] and long course triathlons.[17] No significant changes occurred in serum creatinine, and all individual values remained within normal limits. A significant (60%) increase in creatinine after a 100 km run has been described,[3] and increases have been documented after a 160 km run[4] and a 24 hour event.[18] Reduced renal blood flow, reduced glomerular filtration rate, and hypovolaemia have been postulated to lead to increases in creatinine in these shorter events. In the 1600 km race, the work rate is considerably lower than in these shorter events and therefore these renal changes are unlikely. The opportunity to maintain hydration is also enhanced and significant dehydration is rare.

Urea was significantly increased above baseline values at 4 and 11 days and at the end of the run, and this is similar to an increase documented after runs of 56 km,[16] 100 km,[3] 160 km,[4] and 24 hours,[18] and after a 400 km staged road race over 15 days.[19] Such increases are suggestive of a catabolic state, not unexpected when increases in muscle enzymes, indicative of muscle damage, are considered. It is unlikely that this increase indicates a decrease in renal function, as suggested by Rama *et al*[3], as serum creatinine remained unchanged.

LIVER FUNCTION TESTS AND INDICATORS OF MUSCLE CELL DAMAGE

Changes in serum enzyme concentrations are consistent with those previously reported for ultramarathon events. An elevation of GGT activity, which remained within the normal reference range, has been previously reported after a 100 km run,[9] and both AST and ALT

were found to be increased after a 67 km run.[20] Increases in serum LDH have been described after marathons[15] and ultramarathons,[21] and both AST and LDH were increased after a long course triathlon[17] and 100 mile foot races.[4 22] AP has also been shown to be increased after a 160 km run.[4]

In a study of runners who completed 1000 km in 20 days, Nagel *et al*[9] showed a continuous increase in AP from day 1 to day 19, a rise in AST on day 3 followed by a gradual fall, a rise in ALT to a maximum on day 6 which was then maintained, and no change in GGT and LDH. The results from this study are similar for AP, ALT, and AST but the increase in GGT at the end of the race and significant increases in LDH during and after the race are different. It was, however, noted in the 1000 km run study that large short term increases occurred in both these enzymes from day to day in more than half the runners. The discrepancy may be explained by the greater distance in this study and subsequent increase in muscle damage and the manner in which the distance was covered in the 1000 km run. In that event the average daily distance was 50 km, which would have allowed long rest periods, whereas in the present study the 1600 km was covered in a semicontinuous fashion in as short a time as possible and the mean daily distance was 95 km.

LDH, ALT, and AST are found in both liver and muscle cells and therefore increases in these enzymes cannot specifically indicate liver cell damage. LDH may also be increased in cases of haemolysis, and this is explored in the section in which bilirubin and haptoglobin are discussed. Nagel *et al*,[9] however, suggest that a decrease in CK and AST after the third day of running, which is not accompanied by a decrease in ALT, may indicate reduction in skeletal muscle damage with continuing hepatic cell injury. In this study, CK and AST decreased progressively after day 4 and ALT remained increased. This finding parallels that of Nagel *et al* and may indicate liver injury. More specific to the liver is GGT, and, although mean values remained within normal limits, a significant increase at the conclusion of the event adds to the suspicion of liver damage, albeit mild, from very long distance running. The predominant tissue sources of AP are liver, bone, and intestine.[8] Ischaemic damage to the gut is unlikely in long ultramarathons as the work rate is relatively low and hydration is usually well maintained. However, significant bone stress occurs in these events, and a study in which isoenzymes of AP are assayed will be required to determine if AP can be used to indicate hepatic cell damage from prolonged running. Clearly a study based on measurement of liver-specific enzymes and isoenzymes is warranted.

A number of studies have shown that long distance running produces elevated CK activity,[4 7 8] and this is considered to be an indicator of muscle breakdown. Analysis of isoenzymes indicates that the origin of increased CK is predominantly skeletal muscle.[23] The peak mean increase in this study (2343 U/l) was found on day 4, and it is considerably higher than that described during a 20 day 500 km stage run, which included a 70 hour rest period during days 11 and 12,[7] and the value found one day after a 15 day 400 km run.[19] It is, however, similar to the value (1778 U/l) found immediately after a 160 km run[4] and a 160 km triathlon[24] (2000 U/l) but lower than that found after 100 km running races (2843 U/l[3] and 6368 U/l).[21] The discrepancy between this study and others may lie in the time of sampling. As the first sample was taken on day 4, an earlier peak may have been missed. Another possibility is the absence of downhill running and therefore eccentric muscle activity (thought to be more injurious to muscle) during a track as opposed to a road race.

Noakes[8] indicates that increases in muscle enzymes during exercise are more related to duration rather than intensity such that the largest increases are found after very prolonged exercise but that each runner possibly shows a maximum increase in serum enzyme activity which may be achieved by running for four to six hours. This study in part supports this somewhat contradictory assertion, in that the value at the conclusion of the event and indeed that at day 11 were significantly lower than the peak value despite continued daily strenuous running.

An explanation for the early peak and subsequent decrease in CK despite continuing activity is multifactorial. As serum CK is an indicator of the balance between production and clearance of this enzyme, a decrease in production or an increase in clearance are possible explanations. A progressive decrease in the daily distance run is a likely major factor in decreased CK production, and decreased muscle damage may occur as the result of assumption of a more shuffling gait, involving less eccentric contraction, which is commonly seen in ultramarathon runners as the distance run increases. Increased clearance may be an adaptation to continued exercise, and most studies indicate that lower levels of CK are encountered after a training programme,[8] but it is a matter of speculation whether such an adaptation could become effective during a prolonged running event. It is of interest that LDH, an enzyme that may also indicate muscle damage, showed an increase on day 4 and then remained not significantly different from that level on days 11 and at the conclusion of the run.

BILIRUBIN AND HAPTOGLOBIN

Bilirubin had increased from the initial value on day 4, when it was above the normal range. After a 160, km run a significant increase in bilirubin was found, which, when broken down into direct and indirect types, suggested intravascular haemolysis.[4] Although no change was found after a 1000 km 20 day run, a significant increase was seen on day 3, a similar pattern to that of the present study.[5] Although only total bilirubin has been measured in these studies, if taken in conjunction with low haptoglobin levels on day 3 of the 1000 km run, it is possible that this indicates maximum haemolysis during

the early stage of the event. This is consistent with the hypothesis that footstrike is the causative factor of haemolysis, as runners in ultramarathons typically adopt a shuffling gait as the event progresses and this is likely to be accompanied by a lower force of footstrike and therefore potentially less damage to red blood cells. Another possible explanation for maximum haemolysis in the early stage of the event is that, as older red cells are more fragile, those most vulnerable may be damaged early, and once these are removed from the circulation a steady state is reached.[5] In this study a significant increase in haptoglobin had occurred by day 4, most likely as part of an acute phase response, and therefore measurement of this variable was not useful as an indicator of haemolysis.

OTHER BIOCHEMICAL PARAMETERS
As previously described, plasma volume was increased by 13.4% on day 4, 16.6% on day 11, and 12.6% at the end of the run.[25]

Serum albumin was significantly above the pre-race level on day 4 and at the end of the race but not different on day 11. All mean values remained within normal limits. No change was found after a 56 km run,[16] but increases in serum albumin have been described after marathon running[15] and 100 km[26] and 160 km[4] runs. This response is unusual in that albumin is said to be a negative acute phase reactant and a decrease may have been expected. Total protein increased significantly by day 4, but was not different to baseline values on day 11 and at the conclusion of the event. In an 1100 km event run over 20 days, total protein levels were unchanged at day 4 but were significantly lower by the end of the run.[27] Plasma proteins are thought to play an important role in maintaining plasma volume during exercise.[26] Increases in plasma volume in this study are consistent with maintenance of intravascular albumin and total protein during the race. Calculations based on the method of Rocker *et al*[28] indicate that a net influx of proteins into the intravascular space occurred during the event and this had increased considerably after the run. Serum globulin decreased on days 4 and 11.

On day 11, serum uric acid concentration was significantly lower than before the race, and a significant increase occurred between day 11 and the end of the run, the final value being not significantly different from the pre-race level. No change in uric acid was seen after a 56 km run,[16] but Noakes and Carter[4] found a significant increase after a 160 km run. It is not surprising to find no change in serum uric acid after exercise performed at the intensity of a 1600 km run. Exercise intensity is a critical factor in increases in serum uric acid concentration,[29] the rise in which during exercise is thought to be related to degradation of purine nucleotides.

Serum calcium was significantly higher than the baseline value on days 4 and 11 and at the end of the run. Serum phosphate was significantly higher than the pre-race value on days 4 and 11 and at the end of the run. The effect of endurance exercise on serum calcium has rarely been investigated, but a significant increase has been found after a long course triathlon[7] and no change after a 160 km run.[4] The mechanism and significance of this increase may be elucidated by future measurement of parathyroid hormone and urinary levels of calcium and phosphate. A significant increase in phosphate has been documented after a 160 km run,[4] but the reason for this increase is not known.

CONCLUSION
This study has documented a range of biochemical variables during a continuous 1600 km foot race. There appear to be a number of differences in biochemical responses between staged and continuous races over similar long distances. These may be related to the population studied, the total distance covered, intensity of exercise, rest periods, differences in the acute phase response to musculoskeletal tissue damage, or failure to consider the effects of plasma volume changes. The three hypotheses proposed have been supported by the findings of this study. Hyponatraemia was not a consistent finding, and, although other factors may be important, it is likely that intake of solid food, utilisation of glucose-electrolyte drinks, and avoidance of large weight increases are protective factors. The time course of plasma indicators of muscle damage has been clarified, and the postulate that enzymic indicators of muscle damage would peak early in the event and that duration of exercise would not be the primary determinant of such increases has been supported. Indirect evidence for possible hepatic damage has been provided but definitive evidence for such damage will only be found by studying liver-specific enzymes. The significance of a number of the findings such as increases in serum calcium and phosphate is currently not known and warrants further investigation.

1 Hiller WDB, O'Toole ML, Laird RH, *et al*. Electrolyte and glucose changes in endurance and ultraendurance exercise: results and medical implications. *Med Sci Sports Exerc* 1988;**18**:S62.
2 Reinhart WH, Staubli M, Werner Straub P. Impaired red cell filterability with elimination of old red blood cells during a 100 km race. *J Appl Physiol* 1983;**54**:827–30.
3 Rama R, Ibanez J, Riera M, *et al*. Haematological, electrolyte and biochemical alterations after a 100 km run. *Can J Appl Physiol* 1994;**19**:411–20.
4 Noakes TD, Carter JW. Bochemical parameters in athletes before and after having run 160 kilometers. *S Afr Med J* 1976;**50**:1562–6.
5 Wade CE, Hill LC, Hunt MH, *et al*. Plasma aldosterone and renal function during a 20 day road race. *Eur J Appl Physiol* 1985;**54**:456–60.
6 Ross, JH, Attwood, EC, Atkin GE, *et al*. A study of the effects of severe repetetive exercise on serum myoglobin, creatine kinase, transaminases and lactate dehydrogenase. *QJM* 1983;**206**:268–79.
7 Dressendorfer RH, Wade CE. The muscular overuse syndrome in long distance runners. *Physician and Sportsmedicine* 1983;**11**:116–30.
8 Noakes TD. Effect of exercise on serum enzyme activities in humans. *Sports Med* 1987;**4**:245–67.
9 Nagel D, Seiler D, Franz H, *et al*. Ultra-long-distance running and the liver. *Int J Sports Med* 1990;**11**:441–5.

10 Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma and red cells in dehydration. *J Appl Physiol* 1974;**37**:247–8.

11 Barr SI, Costill DL. Water: can the endurance athlete get too much of a good thing? *J Am Diet Assoc* 1989;**89**:1629–35.

12 Surgenor S, Uphold RE. Acute hyponatraemia in ultra-endurance athletes. *Am J Emerg Med* 1994;**12**:441–4.

13 Noakes TD. The hyponatraemia of exercise. *Int J Sport Nutr* 1992;**2**:205–28.

14 Fallon KE, Broad E, Thompson MW, *et al*. Nutritional and fluid intake in a 100 km ultramarathon. *Int J Sport Nutr* 1998;**8**:24–35.

15 Krebs PS, Scully BC, Zinkgraf SA. The acute and prolonged effects of marathon running on 20 blood parameters. *Physician and Sportsmedicine* 1983;**11**:66–73.

16 Irving RA, Noakes TD, Buck R, *et al*. Evaluation of renal function and fluid homeostasis during recovery from exercise induced hyponatraemia. *J Appl Physiol* 1991;**70**:342–8.

17 Van Rensberg JP, Kielblock AJ, Van der Linde A. Physiologic and biochemical changes during a triathlon competition. *Int J Sports Med* 1986;**7**:30–5.

18 Nagel D, Seiler D, Franz H. Biochemical, haematological and endocrinological parameters during repeated intense short-term running in comparison to ultra-long-distance running. *Int J Sports Med* 1992;**13**:337–43.

19 Dressendorfer RH, Wade CE, Amsterdam EA. Development of pseudoanaemia in marathon runners during a 20 day road race. *JAMA* 1981;**246**:1215–18.

20 Rehrer NH, Brouns F, Beckers EJ, *et al*. Physiological changes and gastro-intestinal symptoms as a result of ultra-endurance running. *Eur J Appl Physiol* 1992;**64**:1–8.

21 Kanter MM, Kaminsky LA, Laham-Saeger J, *et al*. Serum enzyme levels and lipid peroxidation in ultramarathon runners. *Ann Sports Med* 1986;**3**:39–4.

22 Superko HR, Catlin MJ, Smith, JL. Serum enzyme changes in prolonged endurance competition. *Med Sci Sports Exerc* 1979;**11**:89.

23 Noakes TD, Kotzenberg G, McArthur PS, *et al*. Elevated serum creatine kinase MB and creatine kinase BB-isoenzyme fractions after ultramarathon running. *Eur J Appl Physiol* 1983;**52**:75–9.

24 Taylor C, Rogers G, Goodman C, *et al*. Hematologic, iron related and acute-phase protein responses to susutained strenuous exercise. *J Appl Physiol* 1987;**62**:464–9.

25 Fallon KE, Sivyer G, Sivyer K, *et al*. Changes in haematological parameters and iron metabolism associated with a 1600 kilometre ultramarathon. *Br J Sports Med* 1999;**33**:27–32.

26 Poortmans JR, Haralambie G. Biochemical changes in a 100 km run: proteins in serum and urine. *Eur J Appl Physiol* 1979;**40**:245–54.

27 Schriewer H, Jung K, Gunnewig V, *et al*. Serum lipids and lipoproteins during a twenty day run of 1100 km. *Annals of Sports Medicine* 1984;**1**:71–4.

28 Rocker L, Kirsch KA, Heyduck B, *et al*. Influence of prolonged physical exercise on plasma volume, plasma proteins, electrolytes and fluid regulating hormones. *Int J Sports Med* 1989;**10**:270–4.

29 Green HJ, Fraser, IG. Differential effects of exercise intensity on serum uric acid concentration. *Med Sci Sports Exerc* 1988;**20**:55–9.

Take home message

"Within normal limits" is a medical term which brings reassurance to patients and doctors alike. To avoid fruitless investigation and unnecessary concern, the normal biochemical changes associated with ultramarathon running should be known to those involved in coverage of these events.