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Marathon fatigue: the role of plasma fatty acids, muscle glycogen and blood glucose

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Summary. The role of carbohydrate depletion in marathon fatigue was examined in 6 marathon runs. Four of the runs were potentially 'fast-time' marathons and culminated in fatigue. The utilization of carbohydrate, lipid and protein, and plasma concentrations of free fatty acids (FFA), glucose and lactate were measured at intervals throughout the runs. The contribution from protein to energy output was low (1—2%). The utilization of lipid was dependent upon plasma concentrations of FFA, which rose throughout the run. The utilization of carbohydrate mirrored that of FFA and thus fell throughout the run. Fatigue was characterized by a drop in running speed, a drop in carbohydrate utilization, an unchanging FFA utilization and a fall in blood glucose. The fall in blood glucose was not seen in the non-fatigued runners. These results are consistent with carbohydrate depletion being the cause of fatigue. The implications of these data are that lipid is the preferred fuel, but is rate-limiting, and that carbohydrate depletion, even though it causes fatigue, ensures an optimal-time marathon.

Key words: Human — Marathon — Fatigue — Carbohydrate depletion

Introduction

Fatigue is a regular occurrence during long distance running events; the casualty rate varies between 0.05 and 2.0% (Richards et al. 1984). The causes of long-term fatigue are many and include fatigue at the neuromuscular level, dehydration, hyperthermia and carbohydrate depletion (Nadel 1985; Newshome and Leech 1983; Sawka et al. 1985; Bergstrom et al. 1967; Hermansen et al. 1967). Hyperthermia appears to be the most common cause of fatigue in fun runs, however this may well be because temperature measurement is simple and thus is frequently performed (Richards et al. 1979; Richards and Richards 1984). The mechanism of long-term fatigue will vary between situations and also may be a combination of all the above factors.

There are three main sources of energy available to a marathon runner, carbohydrate, fat and protein. The protein contribution is no more than 5% (Plante and Houston 1984) and thus the majority of the fuel for the run must derive from carbohydrate and lipid. Carbohydrate depletion, in the form of hypoglycemia, has been demonstrated in fatigued long-distance runners (Richards et al. 1979) and in exhausted laboratory animals (Clark and Conlee 1979), and indeed was at least one of the problems of Gabriela Andersen-Schiess, who lurched and swayed to the finish of the 1984 women's Olympic marathon (Newsholme 1985). There is a sound biochemical rationale, which when taken to its logical conclusion, shows that carbohydrate depletion is a feasible cause of long-term fatigue. This rationale is briefly discussed below.

The marathon runner cannot rely on carbohydrate alone because the stores in the blood, muscle and liver are limiting. These carbohydrate stores are sufficient for only 90 min of marathon running (Newsholme and Leech 1983). Lipid stores are potentially sufficient for 80 h running (Newsholme and Leech 1983), but also cannot constitute a sole fuel source for the marathon runner for the following reasons. (a) The rate of entry of FFA[1] into the muscle cell depends upon the

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[1] The term FFA is used to describe the total pool of FFA in the plasma and includes those bound to albumin and those which are not bound, but simply dissolved in the plasma

concentration of unbound (to albumin) FFA in the plasma, (b) the concentration of unbound FFA in the plasma is restrained by solubility, and (c) the contribution by plasma and intramuscular triglycerides to energy output is acknowledged as insignificant (Newsholme and Leech 1983; Gollnick 1982)[2]. Therefore, the maximal rate of ATP production from β-oxidation in muscle cannot produce 100% of the ATP which is required each minute by the marathon runner. Marathon runners must therefore mix their fuels and use a combination of carbohydrate and fat in order to provide ATP at the required rate.

According to this scheme, the contribution from fat is always the maximum possible, and is determined by the concentration of FFA in the plasma. The contribution from carbohydrate varies according to speed and length into the run. The higher the speed, the greater the discrepancy between the required rate of ATP production and that which can be provided by β-oxidation; carbohydrate oxidation must make up the discrepancy. The greater the length into the run, the higher are the levels of total and thus unbound plasma FFA and thus the greater is the contribution from β-oxidation. The possibilities of exhausting the carbohydrate supplies are therefore significant, especially if a runner sets the pace too high early in the run when free fatty acid levels are still low. We have tested the hypothesis that carbohydrate depletion can cause fatigue by running marathon runners at a speed slightly above their 'normal' marathon speed. These runners fatigue, and the data on running speed, lipid and carbohydrate utilization, and plasma glucose, lactate and FFA concentrations are entirely consistent with carbohydrate depletion being the cause of fatigue.

Methods

Run conditions

Four male human volunteers, whose ages varied from 25—52 years, were used as subjects. None of these subjects was on a carbohydrate-loading diet. Each subject ran at least one marathon on a treadmill, in a temperature- and humidity-controlled room. The speed of the treadmill was adjusted at intervals throughout the run in either a predetermined sequence and/or in response to fatigue. Speeds ranged between 13.0 and 15.5 $km \cdot h^{-1}$ and the shortest interval at any one speed (unless interrupted by fatigue) was 20 min. The point of fatigue was defined as the time when the runner was forced to request a decrease in treadmill speed. The decreases in speed at the point of fatigue ranged from 0.5—2 $km \cdot h^{-1}$, although one (CH) did have to walk at one stage, in which case his speed dropped by 6.5 $km \cdot h^{-1}$. Six runs were studied, four resulted in fatigue and two did not. The subjects were not top competitors, therefore a 'normal' marathon time was difficult to pinpoint with an accuracy greater than 5 min. The runners who fatigued were run at the slowest pace (average pace) that the particular runner predicted they would not be able to maintain. This was in all cases about 5 min faster than their 'normal' marathon time. In these cases, if the marathon distance was completed, the actual time of the run was about 5 min longer than the 'planned' time, i.e. within the range of 'normal' time. CH-2 was run at the 'normal' marathon pace and CH-3 was an actual competitive marathon in which the second half was run faster than the first (Table 1).

Blood sampling

Blood samples (3 ml) were taken from the antecubital vein before and after the run and at hourly intervals throughout the run. To take samples during the run the treadmill was stopped for 3—4 min and the runner sat while the sample was taken. The blood was taken within one minute of the treadmill being stopped, the rest of the time being used to replace the sweat pad and to take the temperature of the runner.

Gas analysis

Oxygen (S-3A oxygen analyzer, Applied Electrochemistry Inc.) and carbon dioxide (CD-101 carbon dioxide analyzer, Datex) were measured for 5 min at 15—20 min intervals. The V_{O_2} and V_{CO_2} calculated for the 5 min sampling time was used to calculate the fuel utilization rates at those specific times. In order to determine the total amount of each fuel used, the V_{O_2} and V_{CO_2} values were assumed to represent the time interval (run at a constant speed) since the last gas analysis. The gas analysis machine was faulty during CH-2 and gas sampling was not possible during CH-3.

Nitrogen output

Urea and NH_3 were measured in blood, sweat and urine, using the Berthelot reaction (Varley et al. 1980). These concentrations were converted into g nitrogen $\cdot ml^{-1}$.

(a) Sweat. Sweat samples were taken using a sweat pad technique adapted from a method by Verde et al. (1982). Cotton wool pads (5 cm × 5 cm) surrounded by gauze, were covered by a piece of heavy gauge plastic (8 cm × 8 cm) which was

Table 1. Distance and time of each run and the time at which the runner became fatigued. The 'planned' time is in brackets in Time colum

Runner	Distance (km)	Time (h:min)	Time of fatigue
CH	42.2	3:16(3:12)	3:02
TF	42.2	3:00(2:55)	2:30
PS	42.2	2:58(2:53)	2:30
BR	32.3	2:23	1:50
CH-2	42.2	3:29	—
CH-3	42.2	3:00	—

CH-2 and CH-3 did not result in fatigue

[2] See Note added in proof

then taped firmly to the back of the runner. The sweat pads, which were preweighed in an airtight tube, were replaced each hour (during blood sampling). The pads which were removed were replaced in the tube. To remove the sweat from the pad, distilled water was added to the pad to obtain approximately a 1 in 5 dilution. After agitating the pad for several minutes to mix the sweat and the solvent, the solution was filtered (Whatman #4) to remove any cotton wool. The solution was immediately frozen in airtight tubes for later analysis.

— Sweat loss = weight before
  − weight after
  + fluid consumption
  − [CO_2(g) − O_2(g)] (gas exchange weight loss)
  − respiratory water loss.

The subject was weighed with just a towel before and after the run, using an electronic balance. All sweat was wiped from the body before weighing. The weight loss due to gas exchange is measured using the following equation:

$$\text{gas exchange weight loss} = \frac{V_{CO_2} \times \text{MWCO}_2}{\text{N}} - \frac{V_{O_2} \times \text{MWO}_2}{\text{N}}$$

MW = molecular weight.
N = volume of 1 mole of gas at STP.

The respiratory water loss (RWL) was calculated using the equation used by Mitchell et al. (1972):

$$\text{RWL} = 0.019 \times V_{O_2} (44\text{-Pa})$$

Pa = ambient water vapour pressure.

The sweat loss per hour was calculated from the total sweat loss during the run, assuming the sweating rate was constant. Once nitrogen concentration in sweat was measured, the total hourly nitrogen output in sweat could be calculated.

(b) Blood. Plasma samples were collected each hour and the nitrogen concentration measured in each. Plasma volume and thus total plasma nitrogen was determined assuming that (a) the body contains 45 ml plasma (kg body weight)$^{-1}$, and (b) that weight loss was constant between the start and the end of the run.

(c) Urine. The bladder was voided before and after the run. The nitrogen output in urine during the run was determined from the amount of nitrogen in the urine voided at the end of the run.

On the basis of urine, sweat and plasma levels, the urea output for each hour was calculated.

Total nitrogen = urine nitrogen + sweat nitrogen + Δ plasma nitrogen.

Calculation of fuel utilization

The quantity of protein utilized was calculated by assuming that 6.25 g of protein contain 1 g of nitrogen (McGilvery and Goldstein 1983).

The V_{O_2} and V_{CO_2} due to protein utilization (prV_{O_2} and prV_{CO_2}) were calculated for each time interval, assuming that for each gram of nitrogen excreted, 5.9 l of oxygen are taken up and 4.9 l of carbon dioxide are released (McGilvery and Goldstein 1983). The prV_{O_2} and prV_{CO_2} values were subtracted from the total V_{O_2} and V_{CO_2} to yield the non-protein (np) V_{O_2} and V_{CO_2}, and thus a np R value. The np R value was converted into g of fat and carbohydrate using a standard table.

Although calculation of protein oxidation using nitrogen output is a standard technique (Lemon et al. 1983), there is a degree of uncertainty in the calculations because (a) the amount of nitrogen per g of protein is estimated from an 'average' protein, and (b) nitrogen production may not accurately reflect protein oxidation (Wolfe et al. 1982). However, the data of Wolfe et al. (1982) does not necessarily reflect the oxidation of protein as a whole, and the cycling of nitrogen, which could cause a discrepancy between nitrogen production and protein oxidation, appears to be inhibited during exercise (Eller and Viru 1983). In any case, the values for protein oxidation (Table 2) are so low that they could be doubled or halved without significantly affecting the implications of the data.

Glucose, lactate and FFA

Glucose and lactate concentrations in plasma were measured in perchloric acid extracts using standard enzymatic techniques. FFA were extracted from plasma using hexane:isopropanol (3:2), methylated in CH_2Cl_2 using 0.2 M H_2SO_4 in methanol and measured by gas chromatography in a 2 m × 2 mm column of 5% EGSS-X on Chromosorb G (100—120 mesh) at 170° C. Fatty acids were quantified using a methyl heptadecanoate internal standard.

Results

Total fuel utilization

Table 2 shows the amount of each fuel used in each run. The average proportion of the total energy output accounted for by carbohydrate, lipid and protein was 59%, 40%, and 1% respectively. The contribution by protein was assumed to be constant (see Methods) at 1—2% throughout the run. The contributions by carbohydrate and lipid followed a consistent pattern throughout the runs. Carbohydrate contribution at the start of the run was always between 70% and 80% and dropped to 50%—55% at the point of fatigue. Lipid contribution started at 20%—30% and rose to 45%—50% at the point of fatigue.

Table 2. Grams of fuel used during the run and the percentage contribution of each fuel to energy output

	g fuel used (% contribution)		
	Carbohydrate	Lipid	Protein
CH	298(49)	129(48)	15(2)
TF	414(59)	121(39)	8(1)
PS	554(68)	111(31)	6(1)
BR	373(58)	118(41)	8(1)

There were no gas samples for CH-2 and CH-3 (see Methods) so these runs are not included. Percentage contributions calculated using the following caloric values: carbohydrate = 17.6 kJ · g^{-1}; lipid = 40 kJ · g^{-1}; protein = 17.6 kJ · g^{-1}

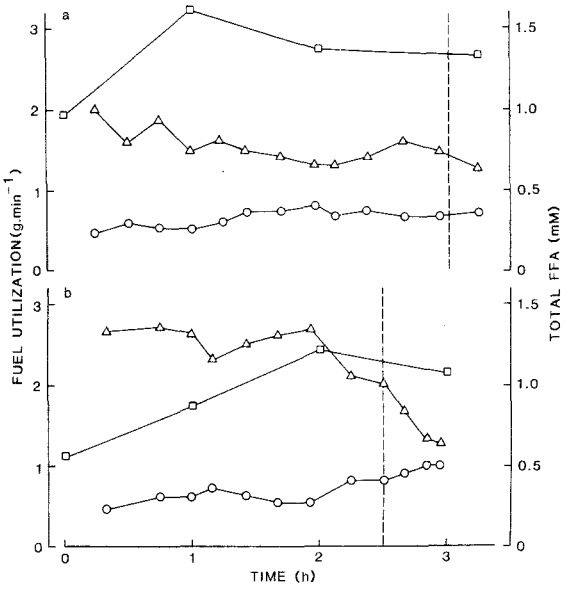

Fig. 1. Utilization rate of carbohydrate (△) and lipid (○), and concentration of total plasma FFA (□) throughout the run. The dashed lines represent the point of fatigue. a: CH; b: TF

Plasma FFA levels

Levels of FFA in plasma rose in all the fatigued runners (Figs. 1 and 2) and in CH-2 and CH-3 (not shown). There was variation in the zero time concentration and in the maximal levels, but in general the concentration increased from about 0.7 mM to 1.5 mM over the duration of the run. The lowest maximal level was that of subject BR (Fig. 2b) who fatigued very early, at 1 h 50 min (Table 1).

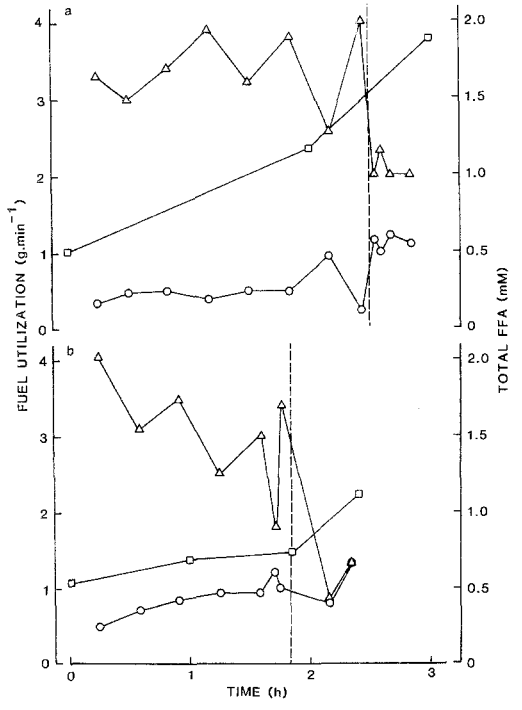

Fig. 2. Utilization rate of carbohydrate (△) and lipid (○), and concentration of total plasma FFA (□) throughout the run. The dashed lines represent the point of fatigue. a: PS; b: BR

Short-term fuel utilization

Figures 1 and 2 show the grams of carbohydrate and lipid oxidized · min^{-1}, or oxidation rate (OR). The data contain three important trends. Firstly, the OR of carbohydrate and lipid are mirror images of each other. The regular fluctuations in carbohydrate OR in the case of subjects PS and BR (Fig. 2) are due to the regular treadmill speed changes which were voluntarily requested by these two runners. Both subjects CH and TF had only one speed change before fatigue. The fluctuations in the carbohydrate OR are larger than those in the lipid OR due to the lower caloric content of the former. The large fluctuations in carbohydrate OR of PS and BR around the point of fatigue (Figs. 2a and b) are probably artifactual, due to a short gas sampling period caused by the unexpected onset of fatigue. Secondly, in all cases, the OR of lipid rises as the levels of plasma FFA rise. There is a delay in the relation in the case of subject PS (Fig. 2a), but it appears after 2 h. The apparent large decrease in fat OR in subject PS (Fig. 2a) at 2.5 h is probably artifactual, again due to the unexpected onset of fatigue which truncated the gas analysis period. Thirdly, the carbohydrate OR always drops over the immediate pre- and post-fatigue period. The lipid OR, in contrast, continues to rise as plasma FFA levels rise, and thus in all cases except subject BR (Fig. 2b), actually rises over the fatigue period. Although lipid OR drops at the point of fatigue in BR, the general trend in this case is still one of increasing lipid OR as is demonstrated by the maximal lipid OR just prior to the end of the run.

Glucose and lactate levels in plasma

The post-fatigue blood sample showed a marked decrease in glucose concentration in all of the fatigued runners (Fig. 3). In three cases the post-fatigue blood glucose level was the lowest recorded. In the case of subject BR (Fig. 3d) the post-fatigue sample was taken immediately after

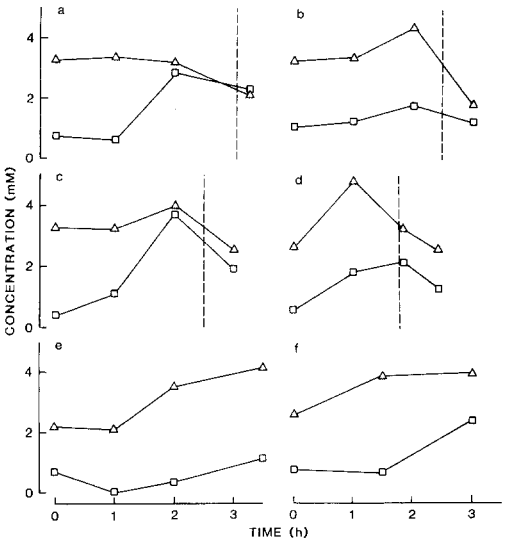

Fig. 3. Concentrations of plasma glucose (△) and lactate (□) throughout the run. The dashed lines represent the point of fatigue. a: CH; b: TF; c: PS; d: BR; e: CH-2; f: CH-3

fatigue which was unusual, and blood glucose levels did not reach their lowest value until about 20 min later. The blood glucose levels in both non-fatigued runs (Fig. 3e and f) continued to rise throughout the run. The concentration of lactate in the plasma of the fatigued runners peaked at 1.5—4.0 mM in the pre-fatigue blood sample. This was followed by a drop after fatigue. Plasma lactate levels in CH-2 and CH-3 (Fig. 3 e and f), runs which did not result in fatigue, rose continuously throughout the run.

Discussion

Protein is obviously a minor fuel source for this type of exercise and cannot be associated with fatigue. Gluconeogenesis can occur during exercise (Constable et al. 1984; Dohm et al. 1985) and amino acids could be the source of the carbon skeletons. But even if this were the case, the role of amino acids as gluconeogenic precursors would still be reflected in nitrogen output. Therefore the contribution by protein, whether as a fuel source, or as a source of gluconeogenic substrate, is small.

Both lipid and carbohydrate contribute significantly, and in some cases equally, to the total energy supply, and their contributions are initially low and high, respectively. These data are similar to those of Hall et al. (1983) and raise three questions.

1. Given the total amount of carbohydrate and lipid used during the run, is there a basis for suggesting that depletion of either store could account for fatigue? Estimates of total body carbohydrate stores vary from 400—600 g (Essen 1977; Newsholme 1983; Newsholme and Leech 1983). If one takes a middle view and assumes a total store of 500 g, 100 g in the liver and 400 g in muscle, one can calculate how much is available to the marathon runner (under conditions of no glycogen loading). If only 60% of the muscle mass is used in a marathon, then the carbohydrate available to the runner is $(60/100 \times 400) + 100 = 340$ g. Runners TF, PS, and BR would have definitely depleted their carbohydrate stores if this were the case, and those of CH would have been 88% depleted. Thus carbohydrate stores could be limiting in the runners who fatigued. Lipid stores on the other hand could not possibly be limiting. Assuming that a marathon runner consists of 5% fat, and that 10% of this is in muscle, then a 70 kg marathon runner has at least 3150 g of available lipid in adipose stores. The fatigued runners used only 4% of this amount.

2. Why are the initial contributions of carbohydrate and lipid, high and low respectively? The characteristics of lipid solubility and inter-organ and transmembrane transport provide the answer to this question. Fatty acids are the preferred fuel of muscle and this is amply demonstrated in Fig. 2a. In this case the treadmill speed was changed between 14.5 and 15.5 km · h^{-1}, every 20 min, between the 40 min mark and the 2 hr 20 min mark. These speed changes are reflected by fluctuations in the carbohydrate OR (Fig. 2a). The FFA OR in contrast, remains relatively constant, suggesting that a maximal OR of the preferred fuel is maintained despite the speed changes. The factor which limits the FFA OR, as mentioned in the introduction, is their concentration in the plasma. The results of this study clearly show that FFA concentration in the plasma is relatively low at the start of the run, and this infers that the contribution of FFA to energy output must also be relatively low. The deficit is made up by glucose, concentrations of which are 10-fold higher in blood at this time. Hence the 70% contribution by carbohydrate and 30% contribution by lipid at the start of the run. The above interpretation is also supported by the data of Hall et al. (1983) which shows that carbohydrate loading causes a decrease in FFA levels in blood which in turn results in a lower turnover of FFA during exercise.

3. Why do the contributions even out to about 50% for both carbohydrate and lipid over the

course of the run? The answer is again related to plasma FFA levels and the fact that FFA are the preferred fuel for aerobic metabolism in muscle. The results of this study show that FFA levels rise during the run, and this is a previously well documented observation (Gollnick 1977; Newsholme 1977). As the total plasma FFA levels rise, the level of unbound (to albumin) plasma FFA also rises and thus the FFA gradient across the muscle cell membrane becomes steeper. This essentially 'activates' the step which is rate limiting in the FFA oxidation process under these conditions; and so FFA OR increases. FFA are the preferred fuel, so as FFA OR increases, the carbohydrate OR decreases proportionately and the contribution by carbohydrate and lipid to total energy output falls and rises respectively. The delay in the correlation between total FFA concentration and FFA OR in runners TF and PS suggests two possibilites. Firstly, that total FFA concentration may have to reach a certain level to overcome a threshold response for FFA oxidation by muscle. Such a threshold has been observed in heart (Opie 1968) and if it exists in skeletal muscle, may vary between individuals. Secondly, that total FFA concentration may have to reach a certain level before unbound FFA levels begin to increase. This could be due to albumin having binding sites which vary in their affinity for FFA. The high affinity sites would be filled first and the lower ones last. Thus the equilibrium bound FFA ←------→ unbound FFA would favour FFA early in the run and unbound FFA later in the run, and would cause the delay in the rise of FFA OR. The delay was not observed in CH or BR. The FFA levels were initially unusually high in CH, which could be the explanation, but this was not the case in BR.

The decrease in plasma glucose concentrations in the fatigued runners during the final hour reflects the exhaustion of a carbohydrate store. Evidence from Lavoie et al. (1983) suggests that this store is muscle glycogen, as a decrease in liver glycogen does not result in hypoglycemia during a period of prolonged exercise. Muscle glycogen depletion could cause an increased uptake of plasma glucose by the muscle and hence a resultant drop in blood glucose concentration. The plasma glucose concentration for BR followed an irregular path and it could be argued that it is not a real drop in that it does not fall considerably below pre-run levels. But the important point is that a blood glucose level of 2.7 mM may have been sufficient to meet the demands of a resting body, but may not have been sufficient to meet the demands of the glycogen-depleted working muscles *and* the glucose-requiring central nervous system. In addition to this the two non-fatigued runs of CH-2 and 3 did not result in a lowered blood glucose level. Instead it continued to rise throughout the run. The assumption here is that as muscle glycogen was not depleted, no demand was placed upon blood glucose.

Lactate is often associated with fatigue in short and middle distance runners. Although there were variations in the pattern of increase in lactate levels, plasma concentrations did not rise above 4.0 mM. If lactic acid was to be considered as a cause of fatigue in any of these runners, concentrations of 10—15 mM would be expected (Hogan and Welch 1984). Runners CH, TF, PS and BR all experienced an increase in lactate concentration during the initial two thirds of the run, an observation which is common in exercise of this type (Tanaka and Matsuura 1984). But, during the final stages of the run, lactate levels dropped in these four runners. This may reflect an increased clearance of lactate from the blood during this period. If blood glucose levels were dropping, the liver may increase the rate of gluconeogenesis (perhaps through increased glucagon levels) from lactate. In the non-fatiguing runs, CH-2 and 3, there was no drop in blood glucose and similarly lactate levels did not decrease.

On the basis of these findings, it seems reasonable to suggest that the fatigued runners in this study experienced a depletion of muscle glycogen. The contracting muscle reacted by extracting more glucose from the blood which resulted in a lowering of the blood glucose concentration. This was followed by a stage when the muscle could no longer continue to use blood glucose at that rate, because of some inhibitory factor, or perhaps because the glucose supply in the local environment of the muscle became severely depleted. The only way the runner can accommodate the reduced availability of glucose is to increase the FFA OR, or to reduce the speed of running, and thus the carbohydrate OR. The FFA OR cannot be increased unless total plasma FFA levels increase, and thus the only available course is a reduction in running speed. The reduction in running speed is the point of fatigue and is characterized by *a decrease in carbohydrate OR* and *an unchanged FFA OR*.

As mentioned previously, the concept of fatigue due to carbohydrate depletion is not a new one, and there is no shortage of evidence linking decreases in glycogen stores with fatigue. The nature of depletion however, which is a continual,

gradual process, makes it difficult to prove a concrete correlation, especially when some studies even show otherwise (Costill et al. 1971). The advantage of the approach used in this study is that, for the first time, data are available which show conclusively that the onset of fatigue is associated with a decrease in carbohydrate *utilization*. A similar correlation, between speed and carbohydrate utilization, is apparent many times throughout each run as the treadmill speed is changed (Fig. 2a), the difference at the point of fatigue is that the speed drop is forced, not voluntary.

The implications of this study concern both whole body metabolic regulation, and the strategy involved in running a marathon. The data support the view that lipids are the preferred fuel for aerobically exercising muscle. The data also reemphasise the limitations lipids have as a fuel, due to their potential toxicity and their low solubility in plasma. There is an urgent need for more data on the concentration of unbound FFA in plasma and on the relation between the plasma concentrations of total and unbound FFA.

As far as a marathon strategy is concerned, the implications of the data are unexpected. Although the fatigued runners failed to run the distance in the 'planned' time, their actual time was no more than 5 min longer (Table 1). Therefore, these runners actually ran the marathon in their 'normal' time despite depleting their carbohydrate reserves. Obviously if there is muscle glycogen available at the end of the run, the runner could have run faster. Thus it is crucial, if one is to run an optimal marathon, to exhaust the muscle glycogen reserves. As it is virtually impossible for a runner to judge the pace so that glycogen reserves are depleted as the finishing line is crossed, the implication is that the safest way to ensure that all reserves are utilized is to deplete the reserves during the run. Fatigue due to carbohydrate depletion may therefore be a desirable, rather than an undesirable situation. The pace is lower after fatigue, but this is countered by the faster initial pace. There are two dangers inherent in this carbohydrate depletion strategy. Firstly, if the initial pace is at a speed which requires some anaerobic component, the efficiency of ATP generation could drop by up to an order of magnitude due to the nature of anaerobic glycolysis. Secondly, even after fatigue, the exercising muscles are still consuming carbohydrate as carbohydrate utilization is still about 10-fold higher than resting turnover rates (Figs. 1 and 2; Hall et al. 1983). Therefore, if carbohydrate depletion occurs too early, blood glucose levels could fall to dangerously low levels later in the race, as in the Gabriela Anderson-Schiess situation. A successful marathon strategy should therefore include carbohydrate depletion with the provisos that (a) there is never any anaerobic metabolic component, and (b) carbohydrate depletion occurs no earlier than 30 min before the end of the race.

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References

Bergstrom J, Hermansen L, Hultman E, Saltin B (1967) Diet, muscle glycogen and physical performance. Acta Physiol Scand 71:140—150

Clark JH, Conlee RK (1979) Muscle and liver content: diurnal variation and endurance. J Appl Physiol 47:425—428

Constable S, Young JC, Higuchi M, Holloszy JO (1984) Glycogen resynthesis in leg muscles of rats during exercise. Am J Physiol 247:R880—R883

Costill DL, Sparks K, Gregor R, Turner G (1971) Muscle glycogen utilization during exhaustive running. J Appl Physiol 31:353—356

Dohm GL, Kasperek GJ, Barakat HA (1985) Time course of changes in gluconeogenic enzyme activities during exercise and recovery. Am J Physiol 249:E6—E11

Eller AK, Viru AA (1983) Alterations of the content of free amino acids in skeletal muscle during prolonged exercise. In: Knuttgen HG, Vogel JA, Poortmans J (eds) Biochemistry of exercise. Human Kinetics Publishers, Inc. Champaign, IL, pp 363—365

Essen B (1977) Intramuscular substrate utilization during prolonged exercise. Ann NY Acad Sci 301:30—44

Gollnick PD (1982) Peripheral factors as limitations to exercise capacity. Can J Appl Spt Sci 7:14—21

Gollnick PD (1977) Free fatty acid turnover and the availability of substrates as a limiting factor in prolonged exercise. Ann NY Acad Sci 301:64—71

Hall SEH, Braaten JT, Bolton T, Vranic M, Thoden J (1983) Substrate utilization during normal and loading diet treadmill marathons. In: Knuttgen HG, Vogel, JA, Poortmans J (eds) Biochemistry of exercise. Human Kinetics Publishers, Inc. Champaign, IL, pp 536—542

Hermansen L. Hultman E, Saltin B (1967) Muscle glycogen during prolonged severe exercise. Acta Physiol Scand 71:129—139

Hogan MC, Welch HG (1984) Effect of varied lactate levels on bicycle ergometer performance. J Appl Physiol 57:507—513

Hurley BF, Nemeth PM, Martin WH, Hagberg JM, Dalsky GP, Holloszy JO (1986) Muscle triglyceride utilization during exercise: effect of training. J Appl Physiol 60:562—567

Lavoie JM, Cousineau D, Peronnet F, Provencher PJ (1983) Liver glycogen store and hypoglycemia during prolonged exercise in humans. In: Knuttgen HG, Vogel JA, Poortmans J (eds) Biochemistry of exercise. Human Kinetics Publishers, Inc. Champaign, IL, pp 297—301

Lemon PWR, Dolny DG, Sherman BA (1983) Effect of intense prolonged running on protein catabolism. In: Knuttgen HG, Vogel JA, Poortmans J (eds) Biochemistry of exercise. Human Kinetics Publishers, Inc. Champaign, IL, pp 367—372

McGilvery RW, Goldstein GW (1983) Biochemistry A Functional Approach Third edition WB Saunders Company, Philadelphia

Mitchell JW, Nadel ER, Stolwijk JAJ (1972) Respiratory weight losses during exercise. J Appl Physiol 32:474—476

Nadel ER (1985) Recent advances in temperature regulation during exercise in humans. Fed Proc 44:2286—2292

Newsholme EA (1977) The regulation of intracellular and extracellular fuel supply during sustained exercise. Ann NY Acad Sci 301:81—91

Newsholme EA (1983) Control of metabolism and the integration of fuel supply for the marathon runner. In: Knuttgen HG, Vogel IA, Poortmans J (Eds) Biochemistry of exercise, vol 13. Human Kinetics Publishers, Inc., Champaign, pp 144—150

Newsholme EA, Leech AR (1983) Biochemistry for the medical sciences. John Wiley and Sons, Chichester

Newsholme EA (1985) Personal communication

Opie (1968) Metabolism of the heart in health and disease. Part 1. Am Heart J 76:685—698

Plante RI, Houston ME (1984) Exercise and protein catabolism in women. Ann Nutr Metab 28:123—129

Richards D, Richards R, Schofiesk PJ, Ross V (1979) Biochemical and haematological changes in Sydney's The Sun City-to-Surf fun runs. Med J Aust 2:449—453

Richards R, Richards D (1984) Exertion-induced heat exhaustion and other medical aspects of the City-to-Surf fun runs, 1978—1984. Med J Aust 141:799—805

Richards R, Richards D, Whittaker R (1984) Method of predicting the number of casualties in the Sydney City-to-Surf fun runs. Med J Aust 141:805

Sawka MN, Young AJ, Cadarette L, Levine L, Pandolf KB (1985) Influence of heat stress and acclimation on maximal aerobic power. Eur J Appl Physiol 53:294—298

Tanaka K, Matsuura Y (1984) Marathon performance, anaerobic threshold, and onset of blood lactate accumulation. J Appl Physiol 57:640—643

Varley H, Gowenlock AH, Bell M (1980) Chapter VIII In: Practical clinical biochemistry. vol. 1. 5th ed. William Heinemann Medical Books Ltd, London

Verde T, Shephard RJ, Corey P, Moore R (1982) Sweat composition in exercise and in heat. J Appl Physiol 53:1540—1545

Wolfe RR, Goodenough RD, Wolfe MH, Royle GT, Nadel ER (1982) Isotopic analysis of leucine and urea metabolism in exercising humans. J Appl Physiol 52:458—466

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Note added in proof

Recent data show that muscle triglyceride is not an insignificant fuel source; in fact, the ability to use it may make the difference between fast and slow marathon times (Hurley et al. 1986). Nevertheless, plasma FFA are still the major source of lipid for the exercising muscle and the implications of the data discussed above remain unchanged.