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Fuel Utilization in Marathons: Implications for Performance

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In keeping with our yearly tradition, this Medical Grand Rounds will be presented by our chief resident. Dr. Richard Locksley will discuss fuel utilization in marathons, and its implications for performance. This is not just of academic interest to Dr. Locksley because he has run the marathon in less than 2 hours and 30 minutes himself.*

DR. LOCKSLEY:† Marathons have become increasingly popular races in the United States, with more than 50,000 men and women runners completing such races in 1979. The high intensity and prolonged duration of these grueling 42 km (26.2 mile) road races clearly illustrate the role of body fuels in sustained exercise. Furthermore, a study of high-intensity prolonged aerobic exercise can shed light on many facets of intermediary metabolism that are broadly applicable to other hypercatabolic states, such as occur in trauma, starvation or during surgical procedures. Recent data increasingly suggest several metabolic benefits of long-distance running.[1,2] The following review was undertaken to provide background for these emerging concepts, as well as to assist runners preparing for such an event.

The energy expenditure of a marathon is roughly 60 kcal per km (96 kcal per mile). Pace has little effect on the caloric cost per mile.[3,4] The intensity of a competitive marathon is between 70 percent and 80 percent of the maximal oxygen uptake (Vo_2 max). Vo_2 max defines the point at which oxygen consumption and combustion can no longer keep up with the breakdown of adenosine triphosphate (ATP) by contracting muscles; that is, when oxidative (or aerobic) exercise can no longer continue. Thus, a marathon is an aerobic event. This contrasts to the sprint events, in which ATP is supplied principally by anaerobic glycolysis and consumption of the stored phosphagens ATP and creatine phosphate.

The fuel stores in an average man in the resting postabsorptive state are given in Table 1. At the pace of a competitive marathon, if only carbohydrate stores (glucose and glycogen) were used, the blood glucose would be consumed in less than half a mile, the hepatic glycogen by two miles, and the entire muscle glycogen supply in an

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ABBREVIATIONS USED IN TEXT

acetyl-CoA = acetylcoenzyme A
ADP = adenosine diphosphate
ATP = adenosine triphosphate
FFA = free fatty acids
Vo_2 max = maximal oxygen uptake

TABLE 1.—*Fuel Reserves in an Average Man**

Fuel	*Tissue*	*Fuel Reserves in an Average Man*	
		Kcal	*Grams*
Triglyceride ..	Adipose tissue	100,000	15,000
Glycogen	Liver	200	70
	Muscle	400	120
Glucose	Body fluids	40	20
Protein	Muscle	25,000	6,000

*Reprinted by permission from Newsholme,[34] p 88.

additional four miles. Obviously the large adipose reserve must be mobilized for fuel. Protein is largely, although not entirely,[5] inaccessible as fuel.

Muscle fuels are either endogenous (glycogen and triglyceride) or exogenous (free fatty acids [FFA] and glucose).[6] Endogenous fuels are handled more efficiently because they do not require mobilization or uptake, and are instantly available for energy when the contractile apparatus activates.

The reservoir for blood glucose is hepatic glycogen, which is converted through a series of enzymatic steps to glucose-6-phosphate. This in turn is converted to glucose by the enzyme glucose-6-phosphatase, and delivered into the blood for use by body tissues. Muscle lacks glucose-6-phosphatase. Hence, muscle glycogen can *only* by utilized by the individual muscle fiber in which

TABLE 2.—*Characteristics of Type I and Type II Fibers in Human Skeletal Muscle Studied in Needle-Biopsy Specimens of Quadriceps**

Characteristic	*Type II Fibers*	*Type I Fibers*
Reaction to myosin ATPase stain	Pale staining, low activity	Dark staining, high activity
Morphology and histochemistry		
Fiber size, μ (untrained men)	68.9	69.2
Relative fiber frequency, % (untrained men)	58	42
Capillary, no. of capillary contacts per unit cross-section ($\mu^{-2}10^{-3}$)	1.03	0.85
α-Glycerophosphate dehydrogenase, microphotometry	Lower activity	Higher activity
NADH tetrazolium reductase, microphotometry	Higher activity	Lower activity
Contractility		
Relaxation rate (% force loss per 10 milliseconds)	7.6	15.7
Contraction time (milliseconds to peak twitch)†	102,60,105,102 (4 motor units)	44,62 (2 motor units)
Fatigability†		
Repetitive stimulation	Resistant	Fatigable
Repetitive voluntary contractions	Resistant	Fatigable
Metabolic heat production (cal • $min^{-1}g^{-1}$)	0.35	2.15
Enzyme activity (pooled or individual fibers, freeze dried)		
Mg^{++}ATPase		
mol • 10^{-4}g • protein^{-1}min^{-1} (24°C)	0.3	0.85
Creatinine phosphokinase		
mol • 10^{-4}g • protein^{-1}min^{-1} (24°C)	13.1	16.6
Myokinase		
mol 10^{-4}g • protein^{-1}min^{-1} (24°C)	6.6	12.1
Lactate dehydrogenase (lactate→pyruvate)		
mol • 10^{-4}g protein^{-1}min^{-1} (24°C)	1.45	3.66
Phosphofructokinase		
mmol • kg^{-1}min^{-1} (25°C)	25.8	49.4
Succinate dehydrogenase		
mmol • kg^{-1}min^{-1} (25°C)	29.6	19.3
Energy stores (pooled or individual fibers, freeze dried)		
Glycogen, mmol • kg^{-1}	355	359
Triglyceride, mmol • kg^{-1}	207	74

NADH = nicotinamide adenine dinucleotide

*Source: Edwards R, Young A, Wiles M: Needle biopsy of skeletal muscle in the diagnosis of myopathy and the clinical study of muscle function and repair. N Engl J Med 302:261-271, Jan 31, 1980

†Determined in medial gastrocnemius, peroneus longus.

the glycogen is stored. The glucose-6-phosphate units enter the Embden-Meyerhof pathway for cellular combustion. Similarly, the reservoir for the plasma free fatty acids is the body adipose tissue. Hormonal stimulation of adipose lipase cleaves stored triglyceride into glycerol and three FFA, which are released into the blood. As is the case for muscle glycogen, muscle triglyceride is not exportable, as shown by the inability to show glycerol efflux from working muscle.[7]

Fiber Types

Human skeletal muscle is a mosaic of two fiber types, designated type I and type II on the basis of myofibrillar ATPase activity measured at alkaline pH.[8] Type II fibers (high ATPase activity) are further subdivided into types IIa and IIb (Table 2). The proportion of fiber types is genetically inherited and independent of sex, although variability is greater in males.[9] The average composition of the human quadriceps muscle is 52 percent type I, 33 percent type IIa and 14 percent type IIb.

As shown in Table 2, type I, or slow twitch fibers, are characterized by higher oxidative enzyme activities, greater vascularization, higher myoglobin content and higher lipid stores.[10] These fibers are ideally suited for activity of myofibrillar ATPase and glycolytic enzymes. Type II fibers develop peak tension more rapidly than type I fibers, but fatigue more rapidly, because of their lesser oxidative capabilities. Type IIa fibers have greater oxidative capacity than type IIb fibers.[10]

Glycogen content is the same in both types of muscle fiber. By doing biopsies on muscle after different types of exercise, the degree of glycogen depletion in each of the fiber types gives an indication of which type is used preferentially.[11,12] As expected, type I fibers are utilized for prolonged, aerobic work. Type II fibers are used for high intensity work of short duration. In exercise at marathon intensity (70 percent to 80 percent Vo_2 max) type I fibers are used primarily. Type II fibers are utilized at the initiation of exercise, before vasodilatation and substrate delivery to type I fibers are maximal, and are recruited as exercise is prolonged and type I fibers fatigue. Thus, recruitment of type II fibers is dependent on the intensity and duration of exercise.

As might be expected, an increased proportion of type I fibers would confer a metabolic advantage in an event like the marathon, because of the increased aerobic capacity of the muscle. Several studies have documented positive correlations between Vo_2 max and percent of type I fibers, and between time to fatigue and percent of type II fibers.[13,14] That elite athletes gravitate to events at which they have genetic favorability is substantiated by biopsy data showing a high proportion of type I fibers (up to and over 90 percent) in successful long-distance runners versus the predominance of type II fibers in sprinters.[15]

Training does not change the inherited proportion of fiber types,[16] although there are data that show conversion of type IIb fibers to their more oxidative type IIa profile with endurance training.[17] Training, however, is much more important than genetics in predicting success. Endurance training further increases oxidative capacity by inducing mitochondrial proliferation in the type I fibers,[18] changing type II fibers to a more oxidative profile,[17] enhancing the activity of enzymes which mobilize and transport fatty acids to the muscle,[19-24] and increasing sensitivity to the various hormones which orchestrate the metabolic response.[25] This increased oxidative capacity is reflected by the increased Vo_2 max in elite distance runners. However, fuel utilization characteristics are applicable to all runners of all abilities, and the following comments apply to all runners.

Endogenous Fuels

Triglyceride

Although muscle triglyceride can contribute up to between 50 percent and 70 percent of the total fatty substrate with exercise,[6] the endogenous triglyceride levels in muscle seem not to affect performance. Depletion rates are related to the amount stored, and not to intensity or duration of exercise.[26] In fact, elite runners have lower endogenous muscle lipid levels. The lesser importance of endogenous lipid supply to total fat metabolism may be related to the fact that FFA uptake is not rate-limiting in muscle.[27]

Glycogen

Repeat muscle biopsy specimens obtained during the course of running at a steady intensity to exhaustion show a curvilinear decline in muscle glycogen as exercise is continued. The amount of muscle glycogen decreases from a normal level of 9 to 20 grams per kg of muscle to 0.6 to 1.0 gram per kg (wet weight).[28] With muscle glycogen depletion, exhaustion occurs and the running pace can no longer be sustained. Regardless

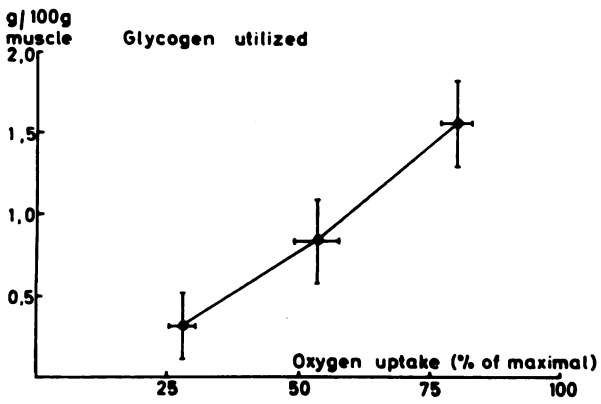

Figure 1.—Decrease of muscle glycogen after one hour of exercise at three different work levels (mean ±SD, n=8). (Reprinted by permission from Hermansen et al,[28] p 129.)

of the pre-exercise glycogen level, fatigue occurs with glycogen depletion.[29] At intensities of 70 percent Vo_2 max, pace cannot be sustained when muscle glycogen content falls below 3 to 5 grams per kg of muscle.[30] No other variable, including blood glucose, lactate, pyruvate, change in heart rate or oxygen consumption, or fall in body weight (with fluid depletion), correlates so consistently with fatigue during sustained aerobic exercise. Glycogen depletion occurs in a characteristic pattern during aerobic exercise of this intensity, first from the aerobic type I fibers and only later from type II fibers as they become recruited.[11]

Two important points about the glycogen depletion pattern deserve emphasis. First, at a given exercise intensity (70 percent to 80 percent Vo_2 max for the marathon), the *pre-exercise glycogen content* of the muscle will determine the *duration* of sustained optimal pace. Second, the shape of the curve shows a disproportionate depletion occurring at the initiation of exercise. Much of this, up to 20 percent of the total glycogen utilized, is consumed in the first five minutes of exercise.[6] This "glycogen burst," perceived by the runner as discomfort before the "second wind" begins, is due to the recruitment of type II glycolytic fibers for anaerobic glycolysis at the beginning of running, before blood flow is redistributed to the working muscles bringing oxygen and substrates for oxidative metabolism. Whether true local hypoxemia or high catecholamine levels (principally epinephrine) at the beginning of the race mediate the glycogen burst is unclear. The glycogen burst is reflected by the rising levels of lactate in blood and muscle at the onset of exercise, which gradually clear as exercise continues.[6,31]

The other critical point about glycogen depletion is that the *rate* of utilization is directly proportional to exercise intensity (percent Vo_2 max), or pace (Figure 1).[28] Whereas fats alone can supply most of the needs for resting muscle, exercising muscle has an *obligate* requirement for carbohydrate substrate, which is met primarily by glycogen, and this obligate requirement increases with intensity of effort.

The reason for this obligate use of glycogen is not entirely clear, but may be related to the following: increasing recruitment of glycolytic type II fibers as pace quickens[11,12]; the greater high-energy phosphate yield per mole of oxygen consumed for carbohydrates (P:O=3.0) in comparison to fats (P:O=2.8 for palmitic acid, the most abundant saturated fatty acid)[32]; the increasing hormonal stimulus to glycogenolysis as intensity increases, principally mediated by increasing catecholamine levels,[33] and the increasing cellular adenosine diphosphate (ADP) to adenosine triphosphate ratio, which favors glycolysis over fatty acid oxidation.[34]

The performance corollary is that increasing intensity (pace) will shift the glycogen depletion curve to the left, and for a given exercise intensity, shorten the duration of sustained effort. The rate of muscle glycogen depletion in the marathon effort (70 percent to 80 percent Vo_2 max) is approximately 0.5 gram per kg of muscle per km.[30]

Realizing that glycogen depletion determines duration of exercise, a simple calculation underscores the marathon runner's dilemma. Assuming a working muscle mass of 20 to 25 kg, and a normal glycogen content of about 18 grams per kg of muscle, the available muscle glycogen will be approximately 400 grams. At the known glycogen depletion rate for marathon pace, 10 to 12.5 grams of glycogen will be used per km as obligate substrate. Therefore, total glycogen depletion will occur between 32 and 40 km (19.8 and 24.8 miles) of a 42 km (26.2 mile) race.

What happens then is known in runner's parlance as "hitting the wall." Although other factors contribute to the "wall" in the marathon, including dehydration and mental fatigue, glycogen stores are the final determinant of exercise duration at this intensity.

It follows from the shape of the glycogen depletion curve that attempts to either shift the curve upwards and to the right, or change the rate of depletion, would enhance endurance.

The influence of diet on exercise performance

was described by Christensen and Hansen in 1939.[35] They showed that subjects ingesting a carbohydrate-rich diet could work substantially longer than those ingesting a protein-fat diet (210 minutes to exhaustion versus 80). More recently, Bergstrom and Hultman explored this relationship using muscle biopsy specimens.[28,36] These investigators exercised subjects to glycogen depletion at 75 percent Vo_2 max, and then fed them either a carbohydrate-poor or a carbohydrate-rich diet for three days. They then re-exercised their subjects.

As seen in Figure 2, duration of work correlated well with the initial glycogen level, as predicted. Surprisingly, a pronounced effect of diet on glycogen storage was documented, with individual subjects storing up to 45 grams per kg of muscle, more than double the normal upper limit. This allowed a doubling of work duration at an intensity of 75 percent Vo_2 max. Note that these data predict that a marathon run in less than 2 hours 30 minutes would be nearly impossible without elevated glycogen stores.

Four important observations have been made regarding this supercompensation in glycogen storage.

- Supercompensation occurs only following exercise-induced glycogen depletion. Carbohydrate-rich diets following a fast or low-carbohydrate diet only replenish muscle stores to normal levels, and over several days.[36]
- If depletion is followed by two to three days of low-carbohydrate diet, and then by a high-carbohydrate diet, glycogen storage is significantly higher.[29]
- Glycogen storage occurs only in those muscles which have been depleted by previous exercise, and only in those fibers which have been depleted. Thus, in experiments studying one-legged exercise to exhaustion, only the depleted (exercised) leg supercompensated after high-carbohydrate feeding.[37] For a depleting run to be effective, it must tax the same muscles and fiber types to be used in the race.
- Finally, fully 60 percent of the total storage occurs in the first 10 hours following high-carbohydrate intake.[38] Normal levels can be reached by 24 hours. Nearly all of the ingested carbohydrate over the first 24 hours is stored in muscle. Hepatic glycogen is also rapidly restored. Muscle loading will continue for three to four days, but increasingly, excess caloric intake will be stored as adipose rather than in carbohydrate deposits.

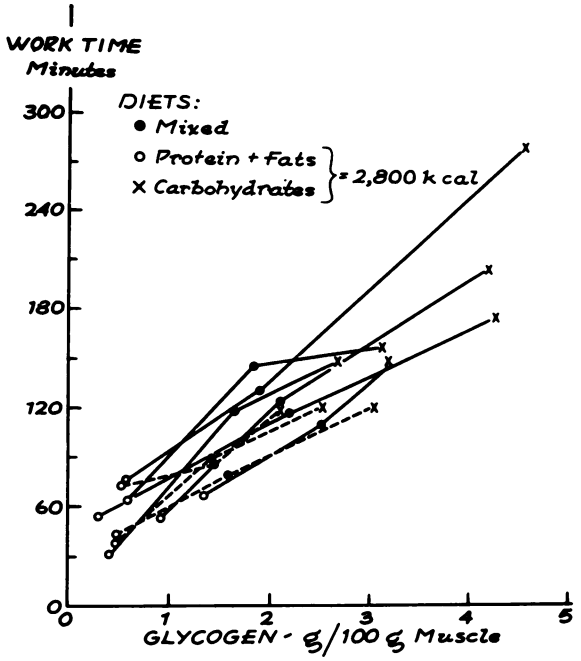

Figure 2.—Relationship between diet, initial glycogen content in quadriceps femoris and work time in nine subjects exercised at the same intensity. (Reprinted permission from Bergstrom & Hultman: JAMA 221:999, 1972[36]; copyright 1978, American Medical Association.)

Frequency of meals may also enhance carbohydrate loading, with improved storage observed with two meals per day versus multiple smaller feedings with the same total caloric value.[39]

The performance aspects of glycogen loading have been documented. Before competing in a 30 km (18.6 mile) race, runners ate either a mixed diet or followed the three-phase glycogen loading protocol, that is, a depleting run, followed by a low-carbohydrate intake for two days and a carbohydrate-rich intake for three days. Three weeks later, the same race was repeated under the same conditions, but all diets were switched. In every case, the glycogen-loaded runner had a faster time. Fatigue and inability to maintain the initial pace occurred near the time that muscle glycogen content fell below 3 to 5 grams per kg of muscle.[30] Of note, glycogen loading did not increase the initial pace for any of the runners, but only the duration for which optimal pace could be sustained.

The reasons for supercompensated storage after exercise are unknown, but may be related to observed affinity changes in the insulin receptor with exercise,[40] starvation[41] and high-carbohydrate feeding.[42] An additional benefit of glycogen loading is the 2.7 grams of water stored intracellularly with each gram of glycogen, and the 0.6 gram of

water formed by the metabolism of 1 gram of glycogen. Thus, each gram of glycogen stored in muscle yields just over 3 grams of water for repleting evaporative losses incurred with exercise.[36]

Exogenous Fuels

Glucose

The blood glucose represents a relatively small caloric source (20 grams) which must be preserved for utilization by the brain, blood cells and anaerobic tissues of the body. With exercise, peripheral uptake of glucose is greatly enhanced, despite the falling insulin levels,[43] a feature appreciated by diabetes specialists years ago. The exercise-induced glucose uptake does require small amounts of insulin, probably less than 10 to 12 mU per ml.[44] As exercise is continued, glucose turnover can increase 10-fold to 15-fold, and by three hours at moderate intensity can account for about a third of the total oxidative metabolism of the leg in human subjects.[45] In trained runners, who display improved FFA mobilization and utilization, less glucose is used, but it may still account for 10 percent to 20 percent of total metabolic needs.

Hepatic glucose output increases progressively up to fivefold as exercise continues, first through glycogenolysis, and later through enhanced gluconeogenesis, as three-carbon substrates (principally alanine, lactate, glycerol and pyruvate) become available.[43,46]

All the major hormonal changes of exercise serve to preserve the blood glucose, and to mobilize stored complex fuels to simpler forms that can be utilized by working muscle. Of major importance are the rise in catecholamines and fall in insulin levels. Thus, epinephrine stimulates glycogenolysis, inhibits insulin release and interferes with insulin action peripherally[47-50] norepinephrine mobilizes FFA from adipose tissue; falling insulin levels minimize peripheral glucose uptake while allowing lipolysis and glycogenolysis, and glucagon levels rise to stimulate splanchnic glucose output in concert with increased epinephrine and falling insulin levels.[51,52]

If liver glycogen is depleted, either through starvation or prolonged exercise, and the intensity of effort is such that the obligate carbohydrate requirement for the working muscle exceeds the glycogen content, blood glucose will be utilized. Gluconeogenesis alone cannot maintain the blood glucose at high work intensities, and hypoglycemia occurs, stopping exercise.[53]

At moderate work levels ingested glucose can be utilized by working muscle, thus sparing muscle glycogen.[54] But at marathon race pace, ingested glucose has little sparing effect on glycogen.[55] This may be due to the increased epinephrine levels at high work loads. In fact, large doses of glucose preceding exercise will raise portal vein insulin levels and substantially lower blood sugar by impairing hepatic glucose output.[56]

Free Fatty Acids

Free fatty acids are the major exogenous substrate for working muscle. They are taken up and oxidized almost to completion in direct relationship to arterial concentration.[7,57] The rate-limiting step in muscle FFA use is in mobilization from adipose stores. The latter occurs principally through norepinephrine stimulation of adipose lipase,[58] which cleaves triglyceride, yielding glycerol and three FFA molecules, which are transported in blood bound to albumin.

At initiation of running, FFA levels decline owing to uptake by working muscle.[59] Subsequent FFA mobilization is rapid, mediated by sympathetic outflow and falling insulin levels. After the initial lag, mobilization outstrips uptake as documented by rising levels of plasma FFA and glycerol. After 40 to 60 minutes of running, FFA levels have risen to six times basal levels. Turnover of FFA rises as well, reflecting increased muscle utilization of fatty substrate as exercise continues, shown by the falling respiratory quotient in exercising subjects. Except for the initial lag period, mobilization continues to supply FFA faster than demand, and fractional extraction of FFA actually decreases as exercise is continued.[60] When exercise stops, mobilizing forces are unmasked as an overshoot in the FFA level, which is responsible for the ketosis after exercise.

The relationship of FFA utilization to exercise intensity (percent Vo_2 max) is the reverse of that for glycogen.[61] Therefore, at rest and with prolonged light exercise, fats can supply over 90 percent of the oxidative needs of the muscle. At moderate work intensities, free fatty acids become the major blood-borne fuel, supplying up to 50 percent of the needs of the muscle.[60] However, as intensity increases above 55 percent to 60 percent Vo_2 max, the amount of fat put to use declines in direct proportion to the amount of obligate carbohydrate substrate required for reasons previously discussed. This reciprocal relationship creates a continuum of fuel utilization from fats (principally

as exogenous FFA) for low-intensity prolonged energy use, to carbohydrate (principally as endogenous glycogen) for high-intensity short-duration use.

At marathon pace (70 percent to 80 percent Vo_2 max), the utilization of carbohydrate relative to fat is approximately 70:30, although it may be closer to 55:45 in trained long-distance runners. Improved fat metabolism in trained runners is due to enhancement of enzymatic and hormonal activities controlling mobilization and metabolism of FFA.[20,21,62]

The relative importance of endogenous glycogen and exogenous FFA in the fuel spectrum has been investigated.[63] At the intensity of the marathon, blocking-FFA mobilization with nicotinic acid does not impair the ability to maintain pace. However, muscle glycogen utilization increases significantly to cover that portion of oxidative metabolism previously supported by beta-oxidation of fatty acids.[64] This allows two conclusions: first, if free fatty acids are unavailable as substrate, glycogen metabolism will accelerate to cover energy needs at no cost to pace; and second, because glycogen is metabolized more quickly, the total *duration* of sustained effort will be less.

However, we have already seen that at this pace glycogen is an obligate substrate, and FFA alone cannot be used to sustain pace because of its less favorable high-energy phosphate to oxygen ratio. If the legs are first glycogen depleted by a 90 percent Vo_2 max effort, subsequent FFA-supported effort can only achieve 60 percent Vo_2 max, and then with a 45 percent reduction in time to exhaustion. If nicotinic acid is now given, so that both glycogen and FFA utilization are blocked, the blood glucose is utilized until hypoglycemia results, and exercise stops in only half the time as compared with the FFA-supported effort.[63]

At the time of glycogen depletion then, pace must slow down to that effort which can be supported by FFA metabolism. Protein is also used increasingly as substrate when glycogen stores are depleted.[65] As previously noted, the decrement in pace occurs when glycogen content drops below 3 to 5 grams per kg of muscle.[30]

The Fat-Carbohydrate Connection

It is evident that FFA spare glycogen as shown by increased glycogen depletion when FFA mobilization is blocked with nicotinic acid. How does FFA spare glycogen metabolism? Understanding this requires a brief look at biochemistry.[34,66,67]

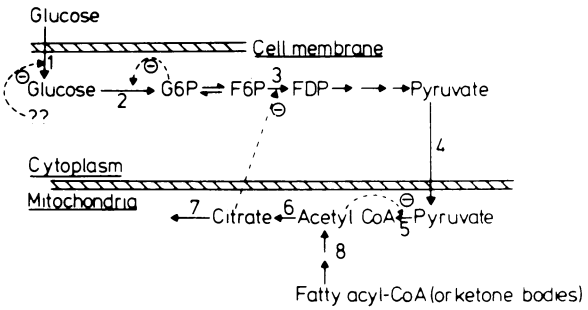

Figure 3.—Mechanism of control of glycolysis by fatty acid oxidation in muscle. The reactions are as follows: (1) membrane transport of glucose; (2) hexokinase; (3) phosphofructokinase; (4) pyruvate transport into the mitochondrion; (5) pyruvate dehydrogenase; (6) citrate synthase; (7) further reactions of the citric acid cycle; and (8) beta-oxidation system (or pathway of ketone body utilization). The dotted lines indicate allosteric regulatory mechanism by which some nonequilibrium reactions of glycolysis are controlled via the rate of fatty acid (and/or ketone body) oxidation in muscle. The allosteric factor regulating glucose transport is unknown. (FDP = fructose-1,6-diphosphate; F6P = fructose-6-phosphate; G6P = glucose-6-phosphate.) (Reprinted by permission from Newsholme,[34] p 81.)

Figure 3 illustrates cellular metabolism, including the glycolytic pathway by which glucose in the cytoplasm is metabolized to pyruvate, which then crosses into the mitochondria to enter the citric acid cycle. Fatty acid uptake and transport in muscle cells are not rate-limiting, as we have seen. Fatty acids are always available in excess with exercise, and they will be metabolized to introduce acetyl-CoA (acetylcoenzyme A) to the cycle. The increase in the acetyl-CoA to CoA ratio inhibits pyruvate dehydrogenase by converting it to its inactive form. Furthermore, rising citrate levels inhibit phosphofructokinase (PFKase). Fructose-6-phosphate levels build up in the cell causing glucose-6-phosphate levels to rise, and inhibit hexokinase. Thus, the glycolytic pathway is slowed at several steps when fatty substrates are available. Furthermore, FFA have a direct depressant action on membrane glucose transport through unknown mechanisms.

As previously described, however, increasing intensity of exercise obligates glycogen breakdown regardless of FFA levels. As pace increases, the ATP to ADP ratio in the cell falls, as ATP is degraded more rapidly by the contractile proteins (Figure 4). Creatine phosphate levels fall as high-energy phosphate is transferred to ADP. A small decrease in the ATP to ADP ratio causes large increases in several metabolites, including adenosine monophosphate (AMP), inorganic phosphate and

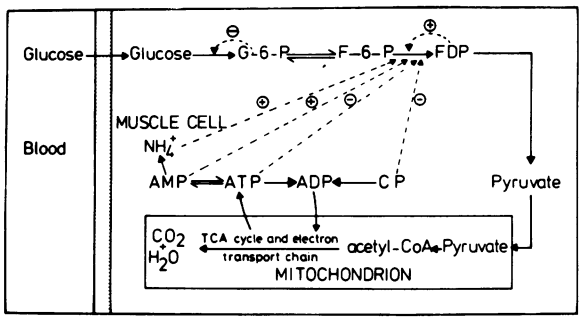

Figure 4.—Regulation of glycolysis in muscle at the glucose transport, hexokinase and phosphofructokinase reactions. (ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; CP = creatine phosphate; FDP = fructose-1,6-diphosphate; F6P = fructose-6-phosphate; G6P = glucose-6-phosphate; TCA = tricarboxylic acid.) (Reprinted by permission from Newsholme,[34] p 81.)

ammonium ion. These regulator molecules all feedback on PFKase to relieve the citrate block and accelerate glycolysis. Furthermore, pyruvate will be preferentially utilized over fatty acetyl-CoA at entry into the electron transport chain as the ADP concentration rises. Therefore, the ratio of ATP to ADP, which reflects the *intensity* of effort, or pace, precisely determines the ratio of carbohydrate to fat metabolism. At lower intensities, fat metabolism spares glycogen, but as intensity increases, more efficient high-energy phosphate generation is required, and fat metabolism is replaced by glycogen.

Thus, we have seen that (1) free fatty acids are mobilized more rapidly than they are metabolized by the working muscle—this accounts for the rising FFA levels as exercise continues; (2) FFA uptake and utilization are not rate-limiting, and (3) the pace, by determining the cellular ATP to ADP ratio, will determine to what extent FFA can be used to spare glycogen. Therefore, with exercise, FFA are always available in excess of the needs of the working muscle, and raising levels further would not be expected to enhance performance.

There is only one point during exercise when FFA availability to muscle may not be optimal. This occurs at the beginning of exercise, when FFA levels fall slightly while mobilizing mechanisms lag behind muscle uptake. This occurs at the same time as the glycogen burst, and because FFA spares glycogen breakdown, it follows that raising the FFA levels at the onset of exercise may spare glycogen for later use. Because the glycogen burst can consume up to 20 percent of the total glycogen stored, this may make a significant contribution to performance.

In rats given a fatty meal and heparin to maximize FFA levels, and then run on a treadmill for 30 minutes, glycogen depletion was substantially less than in control animals. Both skeletal muscle (type I fibers) and hepatic glycogen were spared, with total glycogen depletion decreased by 40 percent. Increased citrate levels were observed in both muscle and liver, consistent with increased FAA metabolism.[68] As predicted, time to exhaustion was consistently prolonged in the animals with initially elevated FFA.[69]

Results were similar in human subjects given a fatty meal five hours before exercise and heparin intravenously just before a 70 percent Vo_2 max, 30-minute treadmill run.[70] Muscle biopsy specimens showed a 40 percent decrease in glycogen consumption. Total carbohydrate consumption decreased 17 percent and fat consumption rose 32 percent more than in controls. Blood glucose levels were higher also, presumably reflecting FFA inhibition of glucose uptake by muscle.

Caffeine will also raise FFA levels through its phosphodiesterase and catecholamine-releasing activity.[71] Runners were given 330 mg of caffeine or placebo orally in a single-blind study, 60 minutes before an 80 percent Vo_2 max run to exhaustion. In all runners, caffeine increased time to exhaustion by an average of 19.5 percent, from 75 to 90 minutes.[72] The total carbohydrate consumed (240 grams) was identical with and without caffeine as expected, but fat metabolism rose from 57 to 118 grams after caffeine. This permits glycogen spared from the original glycogen burst to be utilized later, thereby increasing duration of exercise.

Summary and Conclusions

The following data summarize studies of fuel metabolism as applied to the marathon.

- The pre-exercise muscle glycogen content determines the duration of performance.
- There is obligate glycogen utilization at the pace of a competitive marathon, approaching 0.5 gram per kg of muscle per km.
- When muscle glycogen falls below 3 to 5 grams per kg of muscle, pace must decrease, as effort is sustained by fat metabolism.
- The glycogen burst at the initiation of exer-

cise contributes a significant portion (approximately 20 percent) of total glycogen utilization.

- Dietary manipulation can double muscle glycogen levels.
- Free fatty acids spare glycogen to that required for the obligate carbohydrate substrate as determined by the ATP to ADP ratio (pace).
- The rate-limiting step in FFA metabolism is mobilization from adipose tissue.
- Mobilization lags behind utilization only at the onset of exercise, coincident with the glycogen burst. Otherwise, FFA are available in excess of need.
- Raising levels of FFA at the onset of exercise can substantially spare glycogen that would otherwise be consumed in the glycogen burst and, hence, enhance performance.

In practical terms, the following guidelines should be useful to marathon athletes.

- Optimal glycogen loading involves the three phases of depletion (exercise), a carbohydrate-poor diet followed by a carbohydrate-rich diet. Depletion exercise must use the same muscles as will be used in the race. A carbohydrate-poor diet for two days will optimize subsequent glycogen storage. A carbohydrate-rich (greater than 70 percent carbohydrate) diet should be consumed for three days before competition, with only light training, to preserve muscle glycogen stores. The runner should maximize caloric intake (as carbohydrates) for the first 10 to 24 hours of carbohydrate loading, and then eat only isocaloric, high-carbohydrate diet for the remaining 2 to 2½ days before competition. This takes advantage of the high specific storage immediately after depletion, and minimizes storage in adipose tissue, with its potentially disadvantageous weight gain.[73] Two meals per day may achieve higher glycogen levels than many small feedings.
- The last sugar intake should be four to six hours before competition to assure high hepatic glycogen stores while allowing insulin levels to decrease to postabsorptive levels; 100 grams of carbohydrate (two candy bars) is adequate.
- Caffeine (5 mg per kg of body weight; one NoDoz tablet contains 100 mg of caffeine) taken orally an hour before competition will raise FFA levels and spare glycogen that would otherwise be consumed in the glycogen burst at the beginning of the race.

Although these metabolic considerations can benefit runners at any level of ability, it is important to realize that metabolic manipulations can in no way approach the beneficial effects of consistent training on performance.

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