Muscle Metabolism and Training

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Skeletal muscle accounts for at least 50% of the normal body weight. These muscles are comprised of three main fiber types:

Type I Slowly contracting red fibers where aerobic metabolism dominates.

Type IIA Fibers of intermediate contractility where both anaerobic and aerobic processes are active.

Type IIB Rapidly contracting white fibers where anaerobic metabolism is the major energy supply.

The organization of fibers in each of us is determined genetically. People with a large proportion of type I fibers are not especially fast runners, but can continue activity longer than those with a dominance of white fibers. The latter are quicker, but drain their carbohydrate stores earlier. "Give me a muscle biopsy and I'll tell you whether you should be a sprinter or a marathon runner" is a well-known citation from sport physiologists. A picture of a muscle tissue biopsy from a champion marathon runner, Frank Shorter (Olympic Gold 1972, Olympic Silver 1976), was recently published in PLoS Biology 2, 1525-1527:2004. We see that a majority of the fibers are darkly stained slow twitch type 1 fibers. These are rich in mitochondria and have a high aerobic activity. While these fibers are "slow" in contraction rate, they can utilize both carbohydrates and lipids for energy production over long time periods. This is a "typical" muscle fiber distribution for a long-distance runner. Go to the article for a good review of fiber types and their contractile and metabolic properties (click here).

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If we look at key enzymes in these muscle types we can easily understand why these differences in function are found. In the first table we see enzyme values in "normal" muscles. Two key enzymes from anaerobic metabolism, hexokinase and phosphofructokinase and two from aerobic mitochondrial metabolism are shown here (data from Newsholme and Leech, 1992). The rate-limiting step in

Key Skeletal Muscle Enzymes

Fiber Type	Hexokinase	Phosphofructo-kinase	Citrate Synthase	Carnitine palmitoyl-Transferase
	Enzyme Activity, µmol/min/g			
I (slow)	**1.6**	**20**	**23**	**0.6**
IIB (fast)	**0.6**	**96**	**10**	**0.1**
IIA (intermediate)	**1.5**	**72**	**35**	**0.7**

glycolysis starting from glycogen is that catalyzed by phosphofructokinase (PFK). We can clearly see that type IIA and IIB fibers have a far greater PFK activity than type I fibers. This permits a rapid glycolysis with formation of ATP and lactate in these fibers until the substrate is used up. In contrast to this, type I fibers have higher levels of citrate synthase (the beginning of aerobic handling of pyruvate) and of carnitine-palmitoyl transferase, the enzyme which is the starting point for aerobic metabolism of fatty acids. Note that all of these fiber types have hexokinase activity and that this is highest in the slow and intermediate fibers. All types of human skeletal muscle can utilize blood glucose under stress.

Now, perhaps the most interesting part of this story is the effect of training on

Key Skeletal Muscle Enzymes After Training

Fiber Type	Hexokinase	Phosphofructo-kinase	Citrate Synthase	Carnitine palmitoyl-Transferase
	Enzyme Activity, µmol/min/g			
I (slow)	2.4	24	41	1.2
IIB (fast)	0.7	88	18	0.2
IIA (intermediate)	4.1	58	70	1.2

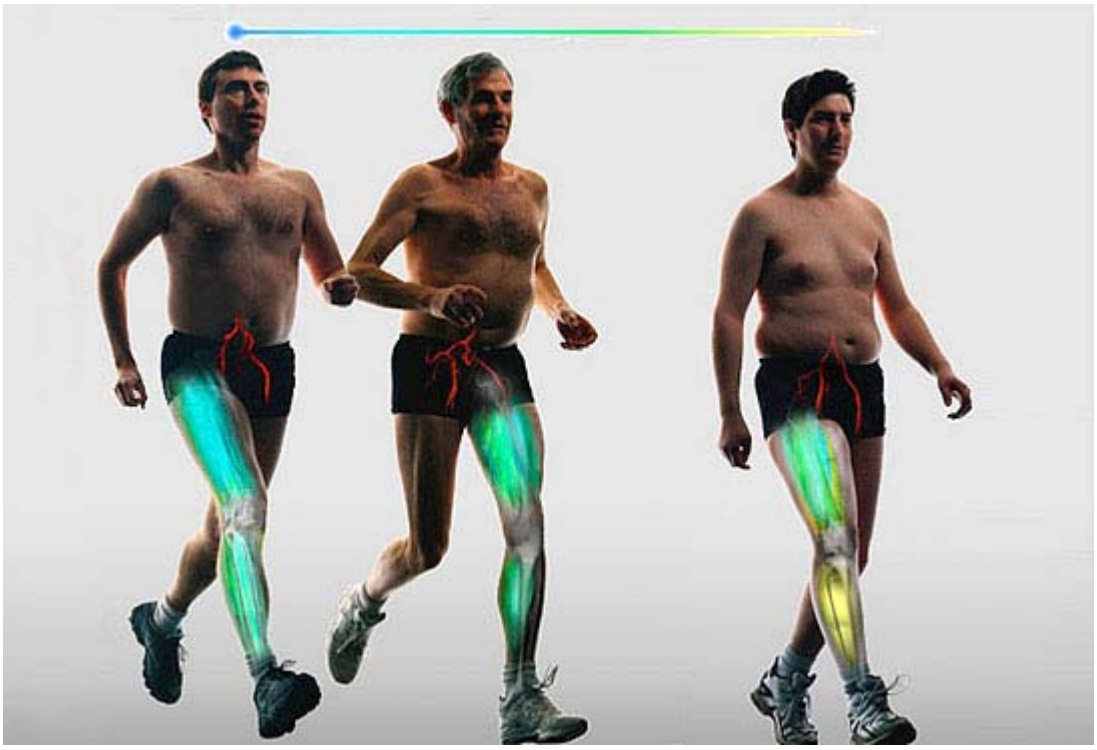
the levels of these enzymes. Newsholme led subjects through a vigorous conditioning period and then took muscle biopsies. The most striking finding here was that one trained up the aerobic system; phosphofructokinase activity was relatively unaffected following the training period. Citrate synthase and carnitine-palmitoyl transferase activities were approximately doubled in all fiber types. Hexokinase, which is essential for use of blood sugar, was also markedly increased in both type I and type IIA fibers.

This coordinates well with previous work showing that training boosts muscle mass and the capillary bed surrounding the conditioned muscles. This increases gas exchange and supports the rise in mitochondrial and oxidative capacity.

"On the move for the sake of science"

The most striking picture of the effects of training on muscle metabolism that I am aware of can be found in National Geographic, September 2000 in an article entitled "The Unbeatable Body: Pushing the Limit". A simplified picture and explanation follow.

"On the move for the sake of science, subjects in a Yale University fitness study are measured against



seven-year-old Rich (left) and 60-year-old Larry (center), both of whom exercise regularly, are neck and neck in cardiovascular fitness. By comparison, 35-year-old Salvatore (right) leads a sedentary life that negatively affects his cardiovascular and respiratory fitness. His heart and major arteries are visibly smaller, and his VO2max—the amount of oxygen his body is able to use—is lower. The brighter colors in his leg show that his muscles had to work harder to complete an hour on the treadmill *. The point? Our bodies are programmed to exercise.

Exercise study conducted at Yale University School of Medicine. Study team: Thomas B. Price, Raynald Bergeron, Jim Rambo, Terry Hickey, Thomas R. McCauley, Adam Anderson, John C. Gore, and Douglas L. Rothman. Study subjects shown: Salvatore Iorio, Richard Kennan, and Lawrence W. Rosen".

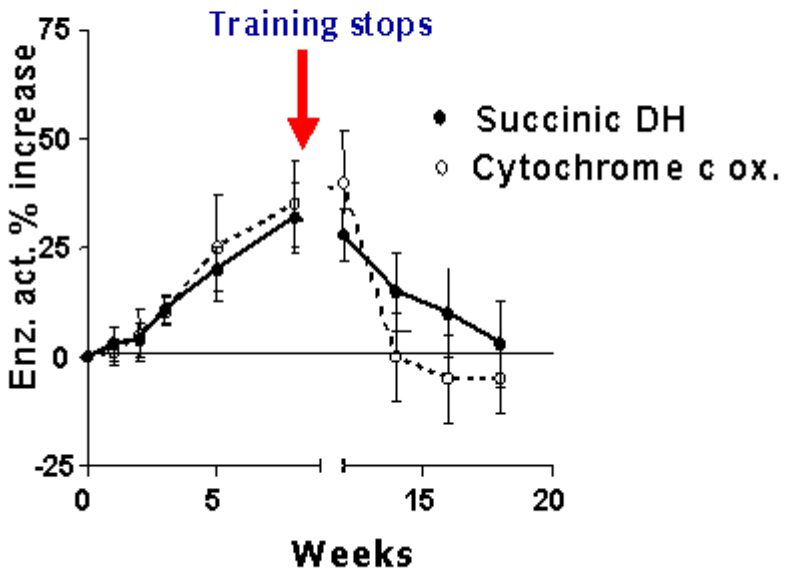
* The color scale also shows the relative use of aerobic (blue) and anaerobic metabolism (yellow). Interested readers are urged to go to the original article for insight in muscle metabolism, blood flow and condition. You can download a more informative version of this figure from National Geographic by clicking on the thumbnail. Be patient, the file is large and downloading takes time. Important physiological data are included in this figure. The men to the left are 37 and 60 years old respectively. Both train daily and completed the one hour running period on a treadmill. The younger man ran faster and longer. If you examine the date you will see that the older man had a reduced vital capacity and iliac artery diameter. These are natural effects of the aging process. Salvatore, at the right, was only 35 years old. He was a sedentary worker and followed no training program. His vital capacity and iliac artery diameter (and presumably blood flow to his legs) were the lowest of these three men. He walked through the exercise period. We need to be physically active to maintain good health, strength and the ability to work!

"Our bodies are programmed to exercise"

This quote from the article above underlines a major point that has been all to often forgotten in modern times. Physical condition is dependent upon daily exercise.

Figures from two studies that have emphasized this follow. In the first of these

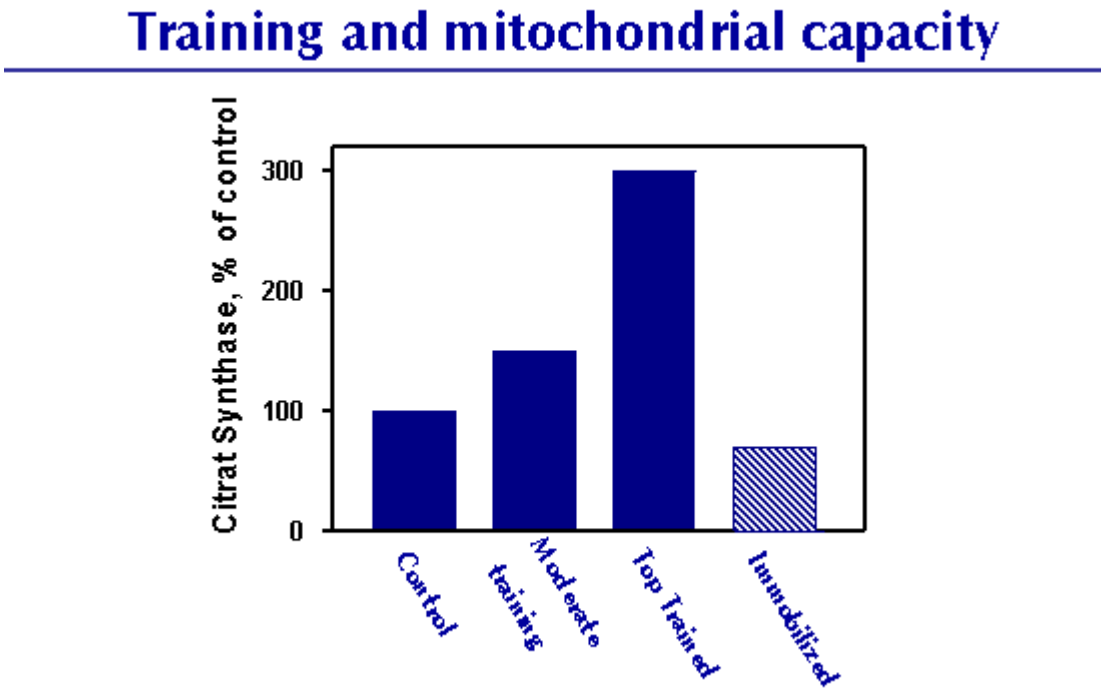
Effect of Training and Inactivity on mitocondrial Enzyme Activity



we can see increasing succinic dehydrogenase and cytochrome c oxidase activity found in biopsies taken during a 5-week training period. These are key enzymes in the mitochondrial production of ATP from carbohydrates and lipids. The volunteer's conditioned limbs were then held more or less inactive during the following 5-week period. The trained muscles soon lost the conditioning effect of training. Cytochrome c oxidase levels fell below normal! This emphasizes the fact that daily activity is the best way to keep fit.

Most experts suggest that walking between 30 minutes to a hour daily is necessary for good fitness and health. Gym visits are fine, but daily activity seems to be even more important.

Another study showing the effects of training on citrate synthase is shown in the next figure. This is the "entrance" enzyme to aerobic metabolism for both lipids

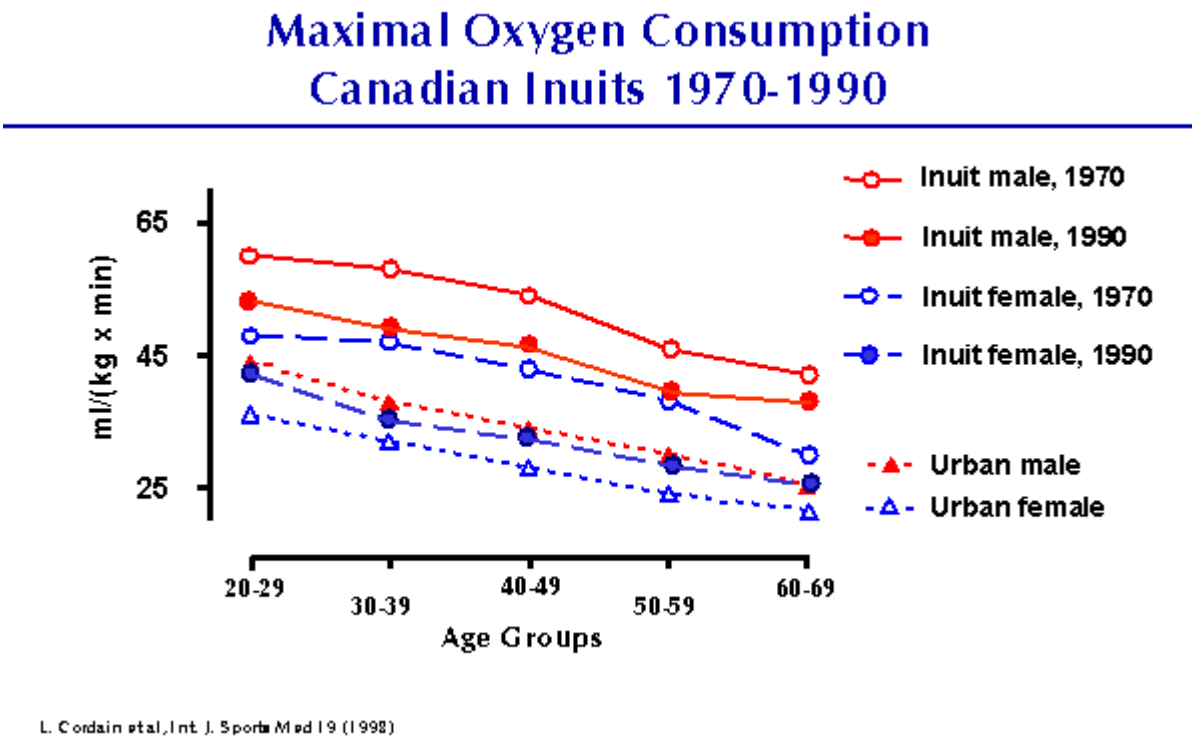


and carbohydrates. Once again, we can see that training increases enzyme activity and mitochondrial oxidative capacity. The striking point here is that immobilization reduced enzyme activity markedly. All of us that have gone with a cast for weeks have experienced loss of muscle mass and the pronounced weakness that follows and that this figure indicates.

I may perhaps be accused of overdriving, but once more will I emphasize that the global surge of overweight with the illnesses that this brings with it is the result of reduced exercise and training. The urban life style that is being adopted by ever-increasing numbers is cause of world-wide poor health. Lack of motion leads to muscle weakness which leads to even less motion...

Canadian Indians exercise less too

We can see another example of the effects of modern life on Canadian Indians. These people live in the Hudson Bay area. There is a film about their modern life

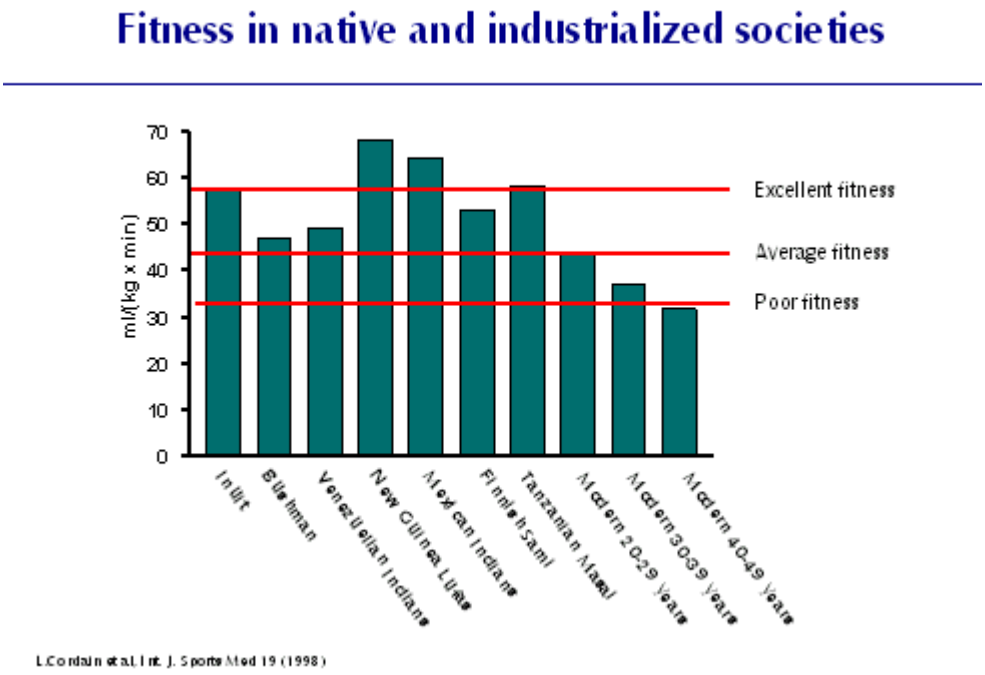


L. Cordain et al, Int. J. Sports Med 19 (1998)

made in the late 1920s entitled Nanuk of the North. Even at that time, they were much less active than previously. The data I have is from 1970-1990. One measured maximal oxygen uptake in women and men of differing age-groups. As would be expected, capacity decreased with age, and was larger in men than women. The striking here is that even among these people who live in a simple but demanding milieu, we find a decrease in physical condition.

The triangles give values for urban men and women. The men have a vital capacity approximately identical to that of the 1990 Indian women while the vital capacities of urban females were significantly lower.

There are, in fact, many studies that take up the differing fitness of native and urban people. Another that I value is shown in the next figure. Here, the authors have looked at oxygen uptake in native people around the world and compared these values with city people in differing age groups. The vital capacity of modern urban men was defined as "average fitness". Clearly, vital capacity declined among urban people with increasing age, with "poor fitness "being characteristic for older city people. None of the native groups fell under "average fitness". Go to the original article for details.



What are the sources of energy in working muscles?

Muscle has several possible energy substrates and these are listed in the next table. (The data in the following three tables are from R.W. McGilvery, Biochemistry, a Functional Approach, W. B. Saunders, Philadelphia 1970).

ATP IS the "currency" of energy metabolism. Muscle contraction, that is coupling between actin and myosin is powered by ATP (and ONLY ATP). There is only a

Energy Sources in Working Muscle

	ATP	Creatine Phosphate	Anaerobic Glycolysis	Aerobic Glycolysis	Fatty acid Oxidation
Amount	5 mmoles/kg	17 mmoles/kg	350 g Muscle Glycogen	440 g Glycogen Muscle/Liver	9000-15000 g
Total ~P available (mmoles)	220	660	6700	84000/19000	>4,000,000
Maximum Rate of ATP synthesis	-	73 mmoles/sec	40 mmoles/sec	17/6 mmoles/sec	7 mmoles/sec
Duration		4 seconds	2-3 minutes	1-2 hours	Many hours
Comments		Most rapid ATP source	Rapid, limited by H^+ formation and substrate amount	Rate limited by O_2 and pyruvate transport to mitochondria	Slow, ATP/O_2 ratio lower than carbohydrates. Slow FFA transport

small lager of this material in muscle cells but this is backed up by several buffer systems. The most rapid of these is the creatine phosphate/creatine phosphokinase system. This is also the smallest reserve and at maximum utilization it is exhausted in about 4 seconds. This is a major source of high-energy phosphate for sprinters. The next largest energy source is anaerobic glycolysis. Only glycogen stored in muscles and blood glucose can serve as substrates for anaerobic glycolysis. In quantity, aerobic glycolysis follows, being able to supply enough energy for muscle activity over several hours (dependent upon intensity). Fatty acid oxidation has the largest ATP-producing capacity. This is relatively slow but can produce energy over many hours if work intensity corresponds to the rate of ATP production. It is fascinating to note that the most rapid sources of energy are also the most limited. This simple fact underlies the

common observation that running speed falls off with the duration of a race. We can step up the running rate, exceeding the ATP delivery rate from aerobic metabolism even when glycogen reserves are used up. Muscle then takes glucose from the blood. The problem with this is that blood sugar levels then fall and we lose consciousness. To work at a maximum exertion over time, the load must be in step with aerobic energy production.

Energy Source, 100 Meter Sprint

ATP utilization ca. 60 mmol/kg			
	At start	After race	Net ATP used
	mmoles/kg		
ATP	5	4	1
Creatine Phosphate	25	7	18
Glycogen*	56	42	42

* As glucose

We can look at two examples of this, where the work intensity has been adjusted according to the estimated duration of a race.

A 100 meter sprint is the first case. Here, speed is maximal and the runner has drawn on his ATP pool, creatine phosphate and glycogen to replenish the high-energy phosphate used in muscle contraction. This is an extreme example and a decrease in ATP is seen. A prominent observation is that ATP decreased only 20% in spite of the physical effort. Most of the energy used came from the ATP-buffer systems creatine phosphate/creatine kinase and anaerobic glycolysis. Around 14 mmoles of glycogen (as glucose) times 3 (3 ATPs from each 6-carbon fragment from glycogen) gave 42 ATP from glycolysis. Eighteen ATPs came from creatine phosphate.

The next example is from an experimental situation which resembled a

Energy Sources in Working Muscle

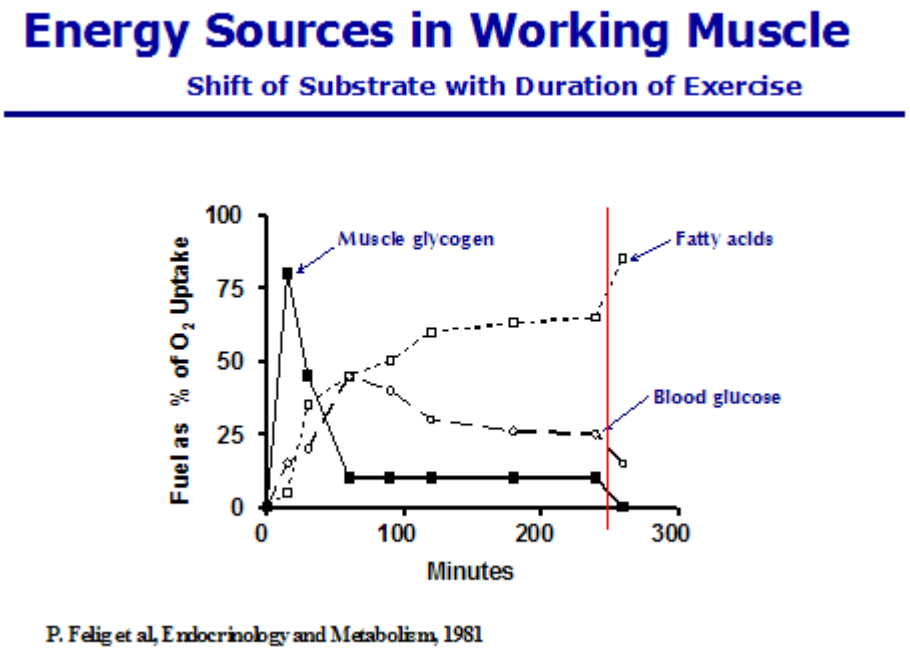
"Maraton"

Running time, minutes	% Contribution to O_2 Uptake		
	Glucose	Fatty acids	Muscle glycogen
40	27	37	36
90	41	37	22
180	36	50	14
240	30	62	8

From Felig and Wahren, 1975

marathon. Here, the runner had to keep going for about three hours. The speed in this kind of a race is quite a bit lower than in a sprint. It is based on aerobic metabolism which gives us a "slow" but constant flow of ATP production coupled to O_2 reduction. During the first two hours carbohydrates (blood glucose and glycogen). With time there was a switch in the substrate utilized. A gradual stimulation of lipolysis led to increases in circulating fatty acid levels and a concurrent increased use of fatty acids as the substrate for aerobic metabolism.

These changes are more apparent in the figure below, originally published by P. Felig in 1981. Here you can see the clear progression from a carbohydrate-based energy metabolism to a state in which lipids provide more and more energy. Liver glycogen levels are used to support blood glucose levels. Falling blood glucose lead to exhaustion and eventually loss of consciousness, indicated by the red line. This is due to the brain's dependency on glucose as its sole energy substrate.



P. Felig et al, Endocrinology and Metabolism, 1981

To summarize, creatine phosphate and anaerobic glycolysis supply energy for intense, short work sessions while aerobic metabolism of both carbohydrates and fat supply energy for longer work sessions. So, if we could just build up creatine phosphate reserves we really could run fast and forever? No, in spite of many many advertisements this does not work. Click here if you want to know more about creatine supplements.

The teenage weakling; glycogen storage disease

Clearly, the oxidation of sugar and glycogen in anaerobic metabolism is a very important contributor to the energy supply of skeletal muscle. Mutations of the enzymes in glycolysis can inhibit this system. In the following case we will see that reduction in the level of phosphofructokinase, the pace-setting enzyme in glycolysis, leads to muscle weakness.

"The Teenage Weakling"

	Glycogen mg/g	G-6-P µmol/g	F-6-P µmol/g	F-1,6 Bis fosfat, µmol/g
Peter	43.8	9.2	1.6	0.02
Control	10	0.5	0.1	0.6

· Biochemistry for the Medical Sciences, Higgins, Turner and Wood, 1994

"Peter" had a long history of muscle weakness. He was more or less normal while resting, but experienced severe muscle pain under hard work. The figure shows serum lactate accumulation during exercise in a control group and in Peter's case. While there was an abrupt production of lactate in the control group, this was absent in Peter's instance.

Analysis of a muscle biopsy clearly demonstrated that Peter had much higher glycogen, G-6-P and F-6-P levels than control persons. Furthermore, he had very low levels of fructose 1,6 bis phosphate. This metabolic "crossover" is indicative of a lack of phosphofructokinase, the enzyme which catalyses conversion of fructose-6-phosphate to fructose 1.6 bis phosphate. This enzyme is essential and rate-limiting for ATP production in anaerobic glycolysis. Peter's case demonstrates the important role of anaerobic glycolysis. He was unable to utilize muscle glycogen or blood glucose as an energy source. Here, aerobic oxidation of fatty acids (an almost unlimited but slow process) had to drive production of skeletal muscle ATP.

The present case presents one of several forms of glycogen storage disease, mainly affecting skeletal muscle. Other forms affect both liver and/or muscle and can be fatal.