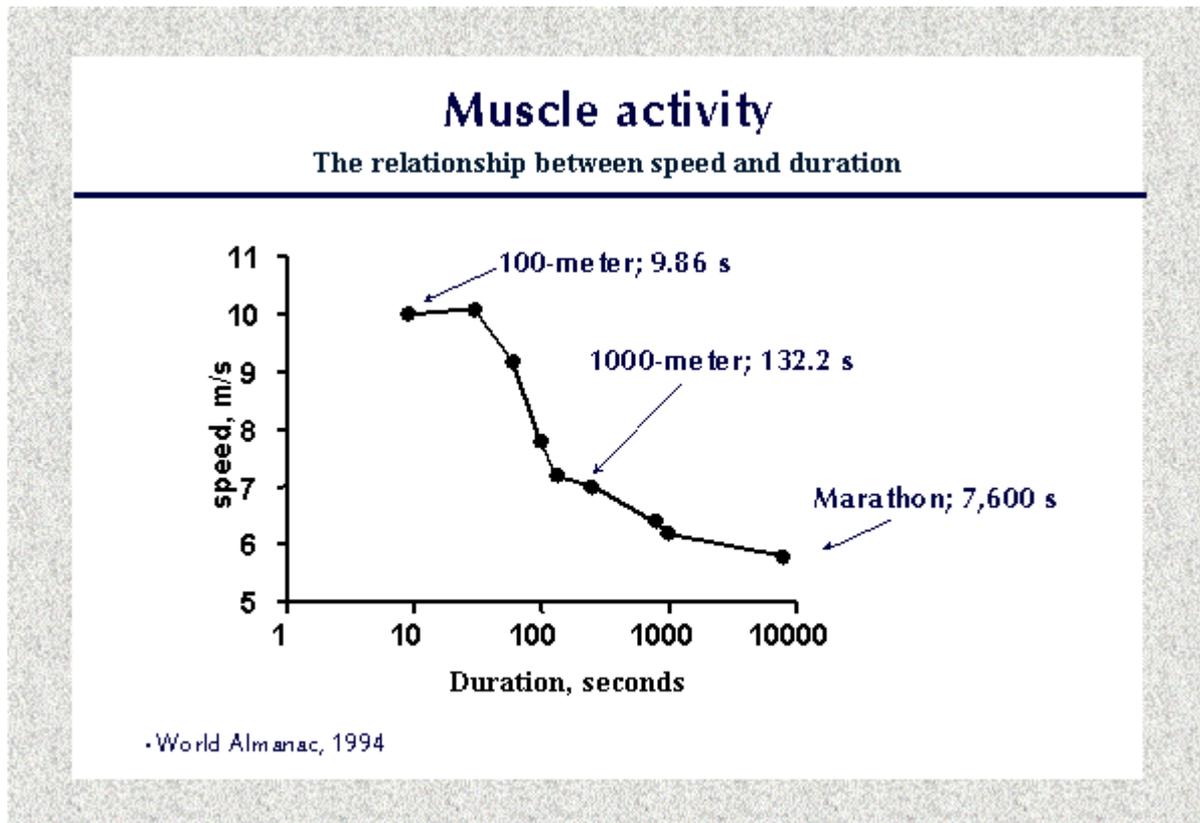


Work and Energy in Muscles

Why can't I sprint forever?

I'll start this section with that silly question. What lies behind the undisputable observation that we must reduce speed if we want to run longer and longer



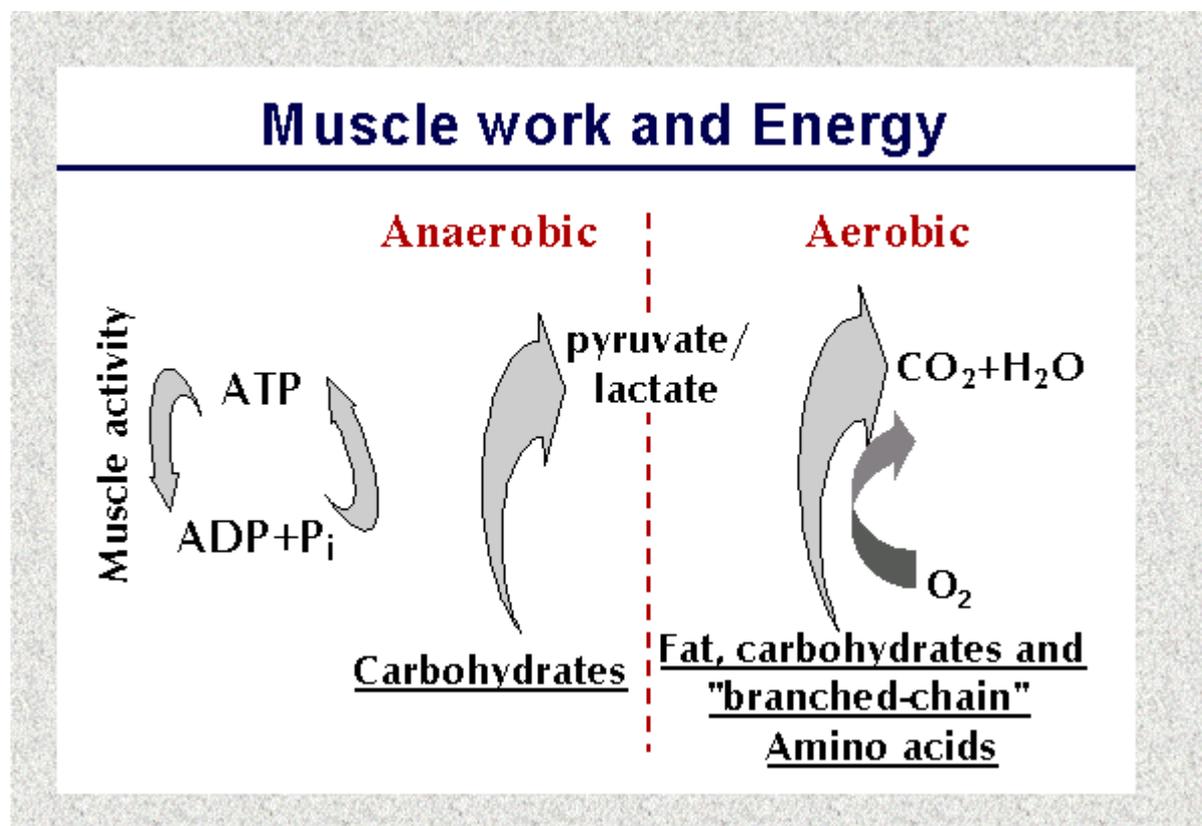
distances? Even the most motivated athletes are bound by this simple rule. We can see this in the following graph. These data are from the 1964 Olympic competitions. Running speed is plotted against the duration of the race. Competitors running more than 30-40 seconds reduced their velocity markedly and a continual and gradual decrease occurred after about 2 minutes. Marathon runners ran approximately half as fast as sprinters.

The explanation for this phenomena is that differing energy sources are used by working muscles, the choice being related to the rate of usage. Stored high-energy phosphates energy (ATP-ADP and phosphocreatine) give the most rapid regeneration of utilized ATP. A 100 meter sprint takes less than 10 seconds . During this very short period the driving force is stored high-energy phosphate. The runners can perform almost without breathing, using energy stored as ATP or creatine phosphate (~P) or glycogen in the active muscles. In contrast to long-distance runners, sprinters are often large, very muscular people. They are "specially equipped" for explosive function for very short periods.

The energy supply for those who run from about 60 seconds to three minutes is also stored energy, but in this case it is primarily glycogen stored in muscles (and blood glucose) that provides energy. Glycogen must be oxidized to pyruvate, lactate and CO_2 to provide the ATP required for muscle activity.

Metabolism of carbohydrates in muscle.

Energy production, that is ATP synthesis from ADP and P_i , can occur anaerobically (without the use of oxygen) or aerobically (using mitochondrial reactions and oxygen). These reactions, especially anaerobic metabolism, are quite rapid. Use of ATP usually does not lead to a decrease in ATP levels, due to the very rapid resynthesis. Extreme muscle activity leads to no more than a 20%



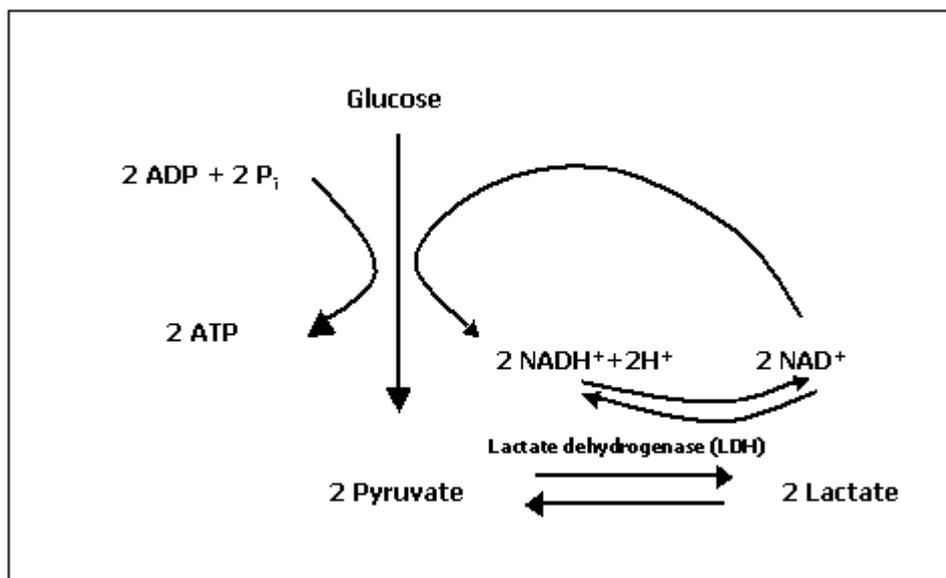
reduction in ATP concentration in muscles. Only carbohydrates (glycogen or blood sugar) can be used anaerobically. Neither amino acids nor fatty acids can be processed without use of oxygen. Muscles differ in their ability to produce ATP through anaerobic and aerobic reactions. Fast-twitch white muscles with few mitochondria are the "anaerobic" fibers. Those with many mitochondria are the aerobic, slow, red fibers.

Anaerobic ATP synthesis is coupled to formation of lactic acid from glucose. Three ATPs are produced during oxidation of each glucosyl group in glycogen and only two are produced during oxidation of glucose to lactate. This is in contrast to aerobic oxidation where between 36 and 38 ATPs are formed for every glucose molecule that is oxidized to CO_2 . Why do people burning glycogen anaerobically run faster than those who use aerobic metabolism? The answer is simply that anaerobic oxidation is exceedingly rapid. Large quantities of ATP are

synthesized during the three minutes or so that this process dominates muscle metabolism. However, glycogen reserves are rapidly exhausted and lactic acid accumulation quickly leads to muscle stiffness and pain. Continuing high-performance work after muscle glycogen is exhausted leads to massive uptake of glucose from the blood with a resulting fall in blood glucose levels. This leads to central effects, with a "black out" as the final consequence. Races between 100 and 2000 meters are a balance between too high and too little energy use; run slowly and lose, run fast and pass out!

Lactate, energy metabolism's "blind way".

Why do anaerobically active muscles spew out lactate and pyruvate?



The answer is that glycolysis is completely dependent on a stable supply of NAD⁺ to oxidize glucose and glycogen to pyruvate. Remember, conversion of 1 glucose to 2 pyruvate molecules requires 2 ADP and 2 NAD⁺ (check the figure at the left). So, in order to run anaerobic metabolism while the substrate is still there, muscles must use lactic dehydrogenase to restore NAD⁺ levels. There is no other rapid source for NAD⁺! Production of lactate is not to form an acid byproduct. If it were not for the need for oxidation of NADH we could just pump out pyruvate. We do, in fact excrete pyruvate from working muscles, but the ratio of pyruvate to lactate is determined of the ratio between NAD⁺ and NADH⁺ + H⁺. There is much more NAD⁺ than NADH⁺ in cytosol, so lactate dominates the picture.

Now, there are two forms of lactate dehydrogenase, so-called isoenzymes. Skeletal muscle has the M₄ isoenzyme while heart muscle has the H₄ isoenzyme.

Liver has a mixture of these. What is the functional difference between these? Well, both forms of LDH are inhibited by pyruvate, but the M₄ enzyme is less affected. This allows the M₄ enzyme to form lactate from pyruvate in anaerobically active muscles and keeps the NAD⁺ production going. In the heart and liver, the H₄ and H₂M₂ forms may allow more rapid uptake of lactate which then can serve as a substrate for energy production.

Whole body lactate metabolism is more complicated than that which is described above. [Click here for a more complete discussion of lactate metabolism.](#)

Aerobic Energy Metabolism

Events that persist for more than roughly three minutes are powered by aerobic metabolism. Glucose goes through anaerobic glycolysis and the pyruvate formed

Substrate	Relative Rate	
Phosphocreatine	100	Direct ~P transfer, no substrate oxidation required.
Glycogen (anaerobic glycolysis)	55	Phosphorolysis, formation of G-1-P without use of ATP, "tree-structure" gives many simultaneous reaction sites. Yields lactate and pH fall.
Glucose (aerobic glycolysis)	23	Limited by rates of membrane glucose transport, glycolysis and mitochondrial oxidation.
Fatty Acids	10	Lipolysis only at interface between oil droplet and cytosol, limited by transport and mitochondrial oxidation.

is taken up by mitochondria and oxidized to CO₂. The total ATP produced per glucose molecule is over 10 times that produced in anaerobic metabolism. However, the rate of aerobic ATP production is much lower than that of direct phosphorylation of ADP or anaerobic glycolysis. Muscle activity must therefore be adjusted to the reduced tempo of high-energy phosphate synthesis. This is summarized in the table to the left.

Activity lasting over many minutes and hours cannot be supported by the limited bodily reserves of glucose and glycogen. Fatty acids from food and adipose tissue, therefore, supply most of the substrate used by muscle tissue working over time. Branched-chain amino acids can also serve as substrates for mitochondrial ATP synthesis. It is striking that the substrates we have least of are metabolized swiftly, while those present in large amounts are slowly

metabolized. These facts are directly related to the speed at which muscles can operate. Short intervals, high speed, long intervals, low speed!

Energy substrates in the human body are either carbohydrates, fat or proteins.

	Energy/g, Dry	Water, g/g dry wt.	Energy/g, Wet	Total Stored Energy, kcal
Carbohydrates	4	2-3	1-1.5	840
Triacylglycerols	9	0	9	135000
Protein	4	2-3	1-1.5	24000

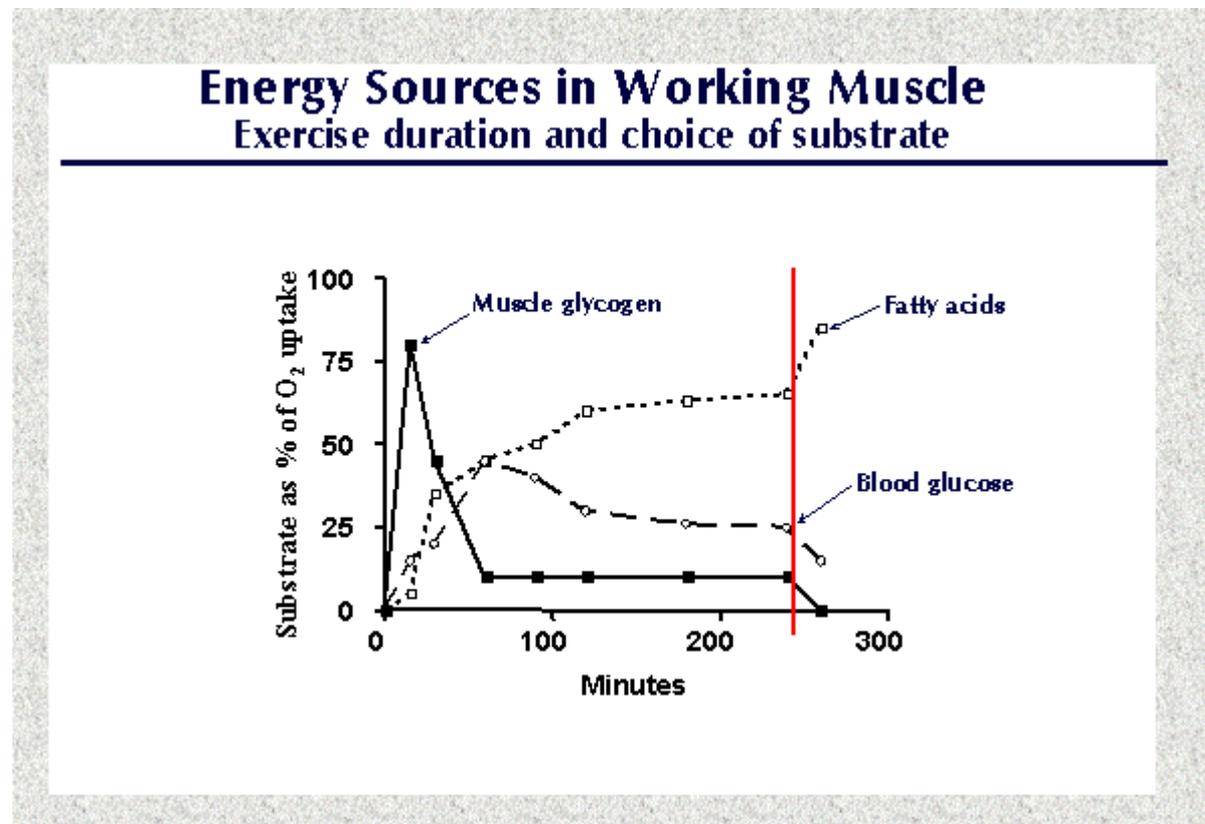
Baynes and Dominiczak, Medical Biochemistry, 1999

Protein degradation yields amino acid residues which can be converted to carbohydrates and used in energy production. Carbohydrates (sugars) and amino acids from proteins give approximately 4 kcal/gram dry weight when burned in the body. Fatty acids from adipose tissue or food give 9 kcal/gram. Fat stores are anhydrous, that is, they do not bind water. Proteins, amino acids and carbohydrates do bind water and are therefore both heavier and less energy-rich than stored fat. The storage form of fats, triacylglycerol, is approximately 9 times more energy-rich than proteins and carbohydrates. It is not so surprising that we store fat instead of the storage form of carbohydrates (glycogen). Proteins are mainly converted to carbohydrates before serving as energy substrates. The "skin-and-bone" appearance of prisoners is clear evidence of the conversion of muscle protein to blood sugar which holds life in such unfortunates.

Consciousness and muscle activity

Muscle activity and running speed is closely coupled to the rate of synthesis of ATP in muscles. Fuels giving the most rapid rates of energy production are found in limited amounts. Long-term exercise must be supported through the use of fat as an energy source. Since lipid metabolism is relatively slow, long-term activities must progress at a slower rate than high speed short-term activities.

The following figure shows the change in oxidative substrate during exercise which continues for several hours. We assume that the person described here



starts the work period eagerly, using stored glycogen at the beginning of the work session. Muscle glycogen remains is the major source of energy during the first half-hour. After this period we see that fatty acids and blood glucose takes over as important energy sources. There are approximately 20 grams of glucose in blood and extracellular fluids. Most of the glucose measured in the blood comes from breakdown of liver glycogen. Adrenalin, noradrenalin and glucagon activate liver phosphorylase and initiate this release. These same hormones activate hormone-sensitive lipase in adipose tissue, leading to a gradual increase in the fatty acid concentration in blood. In the model shown here we see that stabilizing of energy metabolism in time depends increasingly upon fatty acids as the source of fuel. Blood glucose rises and falls thereafter to a stable level which is somewhat higher than that seen at rest. Blood sugar levels remain adequate for brain metabolism so long as glycogen is available in muscle and liver. However, at some point "something happens" (the red line). We are built such that muscle activity can exhaust blood sugar. The brain is totally dependent on blood sugar for function. When blood glucose levels fall below about 2-3mmol/l we miss consciousness (comatose before being eaten?). Recovery does occur, but this takes time: amino acids must be converted to glucose to normalize blood sugar levels.

[Click here for the next sections.](#)