A Primer for the Exercise and Nutrition Sciences

Thermodynamics, Bioenergetics, Metabolism

Edited by
Christopher B. Scott

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Preface

What a journey writing this text has been. The lengthy voyage started well before the idea hatched of authoring a text that contained the word "thermodynamics"! I was informed by my good friend and sometimes colleague Dr. Jose Antonio that by including that word in the title, nutritionists and exercise physiologists might avoid the subject. But almost every step of my expedition was taken on a rather solid foundation of thermodynamics and as such the topic could not possibly be omitted from the title or the text of a book about bioenergetics and energy expenditure.

I am not a physicist. In fact I first went to college to become a football coach. That vocational choice began to deteriorate when taking the mandatory anatomy and physiology courses required of all physical education majors. This information was exciting; my interest in physical education began to wane. During sophomore year, I answered an advertisement in the school newspaper requesting research subjects. The request was made by a master's student who was correlating the presence of the anaerobic threshold with the rating of perceived exertion (RPE) during treadmill running to exhaustion (it happens at the point when the subject perceived that the work being performed was "somewhat hard" to "hard"). This was a cool endeavor! So cool that I asked the study's author if it were possible to hang out and help. Soon, I was calibrating the equipment in addition to helping with subject testing. It was this experience more than anything else that defined my chosen career path.

During my senior year internship, I met Dr. La Von Johnson, who offered a full scholarship to obtain a master's degree in sports medicine. Dr. Johnson remains the most influential of all my academic acquaintances; a true teacher, professor, mentor, and friend. Our mutual academic interest in strength, speed, and power planted a seed that still grows today (thank you, Dr. Johnson!).

With graduate school supposedly complete, I entered the workforce; a manager or exercise programmer for a fitness center. It soon became clear that this was not going to be a career. Later, at yet another fitness facility, more and more time was spent in academic libraries doing "armchair research." A short year-long stint with an author who was writing fitness and nutrition-related material soon followed. As a research editor, I found myself spending even more time in armchair research-related endeavors. My future was seemingly in view: Do not just read about research, do

it. The next step, it seemed, was to become something of a respected authority in the exercise sciences. Becoming a Ph.D. scientist should have something to do with that! A doctoral degree was needed to help accomplish this. Surprisingly, every school I applied to rejected my admission requests. Although painful at the moment, these academic institutions were correct in doing so. The educational background I had chosen emphasized exercise as a human behavior, motivating or instructing others on how to properly train. I was attempting to get into Ph.D. programs that were built on the more basic sciences, where exercise was used as a model or tool to study human physiology. Simply put, I was not adequately trained to become an authority in exercise science.

I was not alone on the preliminary path I had chosen. Now as a college professor, students routinely enter my office with an agenda of avoiding academic challenge, choosing classes that ignore a second semester of chemistry, a full year of organic chemistry and not even considering biochemistry, molecular biology, and cell physiology. A desperation phone call to a world-renowned exercise physiologist, whom I had never met, helped me through my "why didn't I apply myself" crisis. As an armchair researcher, I had read many of his professional publications and was quite shocked that he took my phone call. Dr. Phil Gollnick (1935–1991) convinced me to go back to school to get *another* master's degree, this time with an emphasis on science and research. And so at the age of 27 I did.

Dr. Fred Roby served as my next graduate school mentor and with his guidance my thesis was completed and published ("The maximally accumulated oxygen deficit as an indicator of anaerobic capacity"). In the academic arena, while most graduate students are doing work dictated by laboratory heads and mentors, Dr. Roby allowed me to pursue a project of my own interest. His encouragement is appreciated (and I will never forget his ever-present smile).

My next career move seemed somewhat of a miracle. Years earlier, an internship was completed at the Cooper Institute for Aerobics Research in Dallas, TX, under the supervision of Dr. Jill Upton (among others). Dr. Upton recognized my passion for exercise science and provided my superiors with glowing reviews. Though the internship itself was brief ($\sim$6 weeks), friends and colleagues were made, and I took it upon myself to visit the Aerobics Institute whenever traveling through Dallas. How shocked I was to receive a phone call that informed me of a position opening up at the Cooper's Aerobics Institute. I applied, was accepted, and immediately took the job as a research associate in charge of the exercise physiology laboratory. This was an incredible experience. My colleagues at the Cooper Institute for Aerobics Research are too numerous to name, but working with the likes of Dr. Neil Gordon, Dr. John Duncan, Kia Vaandrager, Dr. Steve Blair, and Dr. Bill Kohl was a dream come true. I thank them for providing me not only with access to their expertise, but allowing me to collect data, be a part of research design and in the process become an author and colleague on well over a dozen scientific manuscripts. Moreover, this exercise physiology laboratory was and is world renowned to the higher echelon of accomplished athletes. The list of elite world-class amateurs and professionals that came to the lab for testing was nothing less than astounding, and I was the guy who tested them. Every exercise stress test I had performed at the Aerobic

Institute included the measurement of gas exchange (along with an ECG). Even so, my passion for anaerobic energy expenditure, which fueled strength, speed, and power, never faltered (a colleague once informed me, "This is the Cooper Institute for Aerobic Research, not Anaerobic Research").

A physician at the Cooper Institute had left to join a private cardiology practice, I was asked to come along. During the ensuing interview I was questioned, "How would you fit into our facility? Your background is in the testing of athletes not diseased patients." My reply was immediate and straight forward, "been there done that, it's now time to apply my exercise stress testing skills to cardiac and pulmonary patients". And so I did, for another 5 years (in two cardiology practices). This experience too was rewarding. Patients who could not walk for 2 min on the treadmill were tested (this was a far cry from athletes who could run for almost 30 min). But the times were soon to be changing. Business-related cuts being made in "our" practice were harsh and I felt that, void of an MD degree, my head was on the employee termination chopping block. It was time to leave medicine, "call my own shots," and to focus exclusively on anaerobic and aerobic metabolism in the pursuit of a doctoral degree. During the ensuing good-bye handshakes, I inquired about how many exercise stress tests I had performed. The answer was, "somewhere between 5,000 and 10,000 tests;" again, all of them completed with full gas exchange measurements and ECG interpretation.

In hindsight I had to this point undergone an extensive 10-year apprenticeship. Academic texts were not being memorized; exercise physiology was actively being practiced. Taking objective notice of my interests, it became clear that I was spending more time reading comparative physiology studies, where animals were being used as exercise models, not athletes or patients. This was a new frontier for me and I pursued it. But before moving on, notes were beginning to be collected that eventually became part of the text you are now reading. Such note taking was encouraged by several encounters I had with Dr. Roland Coulson (1915–2004). Since graduate school, my interest has never waned in the measurement of anaerobic metabolism and it was Dr. Coulson's metabolic studies using alligators that drew me toward him (reptile muscles are fueled in large degree by anaerobic metabolism during exercise). The elderly but very active Dr. Coulson was no longer accepting Ph.D. students when I first contacted him, but he was always willing and able to talk about metabolism. It was he who informed me, "if you want to really learn something, write a book about it" (he also was the first authority figure with whom I had a scholarly discussion on the metabolism of dinosaurs; I was in heaven that night). Dr. Coulson's statement represents the very start of my foray into thermodynamic studies. Visits to Roland Coulson were an experience where as a guest at his New Orlean's residence I was awoken at around 3:00 in the morning, accompanied by him on bicycle to his laboratory, and then promptly helped clean alligator poop from his numerous cages (he was conducting feeding and growth studies)!

Toward the end of my clinical career I had begun researching Ph.D. programs that focused on both zoology and physiology and found one that accepted me. I was now 37-years old. Obtaining this degree involved difficulties, as most change does. I put my house on the market (in Savannah, Georgia) and moved West (to

Wyoming). My salary fell from $45,000/yearly to an $8,500/yearly stipend. At first I worked with an animal model that underwent seasonal hibernation (better referred to as metabolic torpor). My friends questioned the move ("What does this have to do with exercise physiology?"), but I had a rationale. Metabolic torpor is the exact opposite of VO2 max; it represents the lowest possible limits of aerobic metabolic energy expenditure, not the highest. I wanted to understand both ends of the metabolic spectrum. Sadly, this experience did not last, after a year and a half my doctoral advisor canned our project and just as I was planning to abandon the program I was approached (and "saved") by Dr. Paul Thomas and Dr. Richard McCormick who needed assistance with a cardiology-related project. I accepted. The experience was again rewarding, spending several years at the cellular and molecular level, examining a rat heart's re-modeling of connective tissue after a myocardial infarction. The assistance of Drs. Scott Boitano, Robert George, and Paul Wade will not be forgotten (they recognized my deficiency in cellular course work and designed a program to eliminate this flaw; I now present aspects of cellular physiology as part of most every undergraduate course I teach).

During my doctoral studies notes for this text continued to be collected, ending at something around 400 pages. The experience was a resounding success. But even so, while I had much material, the project was nothing more than an amateurish collection of scribblings. It took another several years to focus these pages toward the subject of whole-body energy exchange. The first accomplishment was to write the thermodynamics section. Thanks go to Dr. Jerry Bell (of the American Chemical Society), who faithfully and promptly answered my many thermodynamic queries. Gratitude also is given to Dr. Zoran M. Djurisic, a combustion scientist at U California, Berkeley, who worked with me in detailing the molecular differences in glucose and fat combustion. (Apologies to Dr. Bell and Dr. Djurisic if I take too much liberty with thermodynamic interpretation.)

As I explored potential publishers for this text I was somewhat taken back by the reply of some editor's, "We already have an extensive collection of biochemistry texts, none more are needed." I had not explained myself well. It was not a biochemistry textbook I was thinking about, though it certainly did employ some biochemistry. Moreover, this text was not an attempt to re-name exercise biochemistry or bioenergetics as other have. Bioenergetics is presented here not as a series of independent biochemical reactions that supply ATP to working muscle, but as a mechanical energy-exchange device of sorts with moving parts and all; as much engineering as biochemistry. The last section takes thermodynamic and bioenergetic principles and applies them toward the estimation of metabolic energy expenditure. Many of these applications are new. In fact, I have been told more than once that some of the ideas presented represent little more than "excrement" on paper. Even so, no critic has ever satisfactorily answered fundamental questions I have had for decades and attempt to answer here (a typical response to my queries was, "you need to read more"). Some examples include: How and why does a measurement of oxygen uptake represent the energy expenditure of a metabolism that does not utilize oxygen? Incorrect answer: because it does. Correct Answer: it does not. Why is the energy associated with the oxidation of glucose greater than that of fat per volume

of oxygen consumed? Incorrect answer: glucose is a more efficient fuel than fat. Correct answer: because glucose metabolism contains an anaerobic component, fat does not. Why is metabolic biochemistry based on a diffusion-oriented system when evidence indicates it cannot possibly be? Incorrect answer: because that is the way it has been. Correct answer: it should not be.

My passion for the measurement and estimation of both aerobic and anaerobic energy expenditure during strength, speed, and power has never diminished and it is in this area that I continue much of my research. I also am very much interested in markers of aerobic and anaerobic energy exchange in the diagnosis and prognosis of heart vs. lung vs. skeletal muscle limitations to exhaustive exercise.

Wrapping this preface up in full circle, in a long-ago conversation with Dr. Jose Antonio (about 15 years prior), I emotionally laid out a case as to why the oxygen consumed in the recovery from exercise could not represent anaerobic energy expenditure during the exercise. Joey informed me, “there are more people than you think Chris, who will not disagree with you.” I hope my case, more thoroughly displayed in these pages, provides some meaningful answers.

Gorham, ME Christopher B. Scott

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Part III Metabolism

Chapter 1
Introduction: Thermodynamics, Bioenergetics, Metabolism

Some things feel hot, some cold. This sense has meaning. Heat comes and goes, appearing and seemingly disappearing; thermodynamics studies thermal activity. The measurement of heat helps portray fundamental aspects of matter and energy. Originally devoted to uncovering the hows and whys of a steam engine's ability to convert heat into mechanical work, thermodynamics quickly expanded into the field of chemistry . . . and more. We have known for many thousands of years, perhaps far longer, that life and heat are related (1). Because of your association with thermal energy, a proper examination of nutrition and exercise cannot be initiated without addressing thermodynamics to some extent.

Matter and energy are distributed about the Universe and the Earth, and in similar fashion throughout you and all your cells. These distributions are dynamic; energy undergoes transfer, so too does matter, from one place to another. The transfer of matter and energy can be spontaneous, or not. A gradient – a difference over a distance (2) – can both promote and prevent the "flow" of energy and materials. Gradients empower dynamics. Perhaps the most obvious example of a gradient is founded in our planet's topography where gravity is the driving force and the spontaneous direction of change is downhill; uphill gradients are said to be nonspontaneous (Fig. 1.1).

Up and down gradients can also be expressed in left and right formats. Chemistry for example uses a left-to-right and right-to-left format to respectively describe the direction of spontaneous and nonspontaneous chemical reactions:

$$\text{High} \rightarrow \text{Low}$$

A left-to-right arrow signifies a downhill or spontaneous gradient.

$$\text{High} \leftarrow \text{Low}$$

A right-to-left arrow signifies an uphill or nonspontaneous gradient.

The secret to life is a gradient. Life uses a variety of gradients to facilitate matter and energy exchanges. The cardiovascular system for example operates off a pressure gradient measured in millimeters of mercury (mm Hg). Upon contraction the

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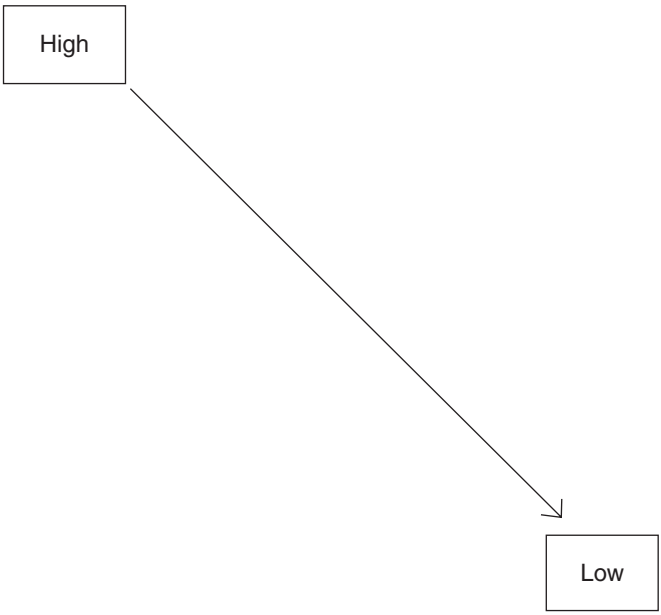

Fig. 1.1 A gradient is shown in the format of a ramp. If placed on this gradient, matter, in the form of a rubber ball, would be transferred in the downhill direction, from uphill to downhill. Energy too flows naturally in the downhill direction. Uphill transfer is nonspontaneous (in fact, energy is required to "push" matter uphill)

heart creates high pressure within the arteries; within veins the pressure is much lower. The result is blood flow, from high pressure to low, arteries to veins. Gases too flow from areas of high-to-low pressure, the result of a partial pressure gradient (also measured as mm Hg).

In addition to transfer from one place to another, matter and energy also undergo conversion from one form to another. Survival is dependent on devices that favorably enable matter and energy conversions. We understand steam engines, automobiles, refrigerators, light bulbs, and the like, as devices or machines that convert matter and energy from one form to another. An active metabolism – the biochemistry contained within all your bodies cells – has been identified as the place(s) where life's energy and matter conversions take place. Energy transfer and energy conversion are both collectively described in the context of energy exchange. Bioenergetics is a continuing scientific narrative, a human attempt to identify the source of all energy and material exchanges (i.e., transfer and conversion) within and without life. Biology, nutrition, physiology, chemistry, physics, engineering – bioenergetics is all these and more.

The costs of living are defined by studying the conversion and transfer of matter and energy (exchanges) within and without the boundaries that separate life from its immediate surroundings. Energy and matter exchanges within cells are the result of a working metabolism, often considered the biochemistry of life. All life forms share something in common: continuous matter and energy intake from, and

matter and energy expenditure to, the environment. By measuring energy intake in the form of food and drink, for example, a nutritionist may gain an understanding of the energy and material needs of survival, or in the case of an athlete, the needs of training and competing. A measurement or estimate of energy expenditure can likewise be used in an attempt to identify and account for the costs of living and working. Sometimes the two reciprocal movements – intake and expenditure – through a boundary need to be considered for a more complete analysis of the exchanges made between a living organism and its surroundings. One example of this is the quantification of oxygen uptake taken from and carbon dioxide given-off to the environment. Indeed, the measurement of metabolic gas exchange continues to be a powerful tool in providing an estimate of the costs of living, training, and competing.

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Part I
Thermodynamics

Chapter 2
Within and Without: Systems and Surroundings

A specified region or space that is surrounded by a boundary is called a system. The surroundings reside outside of the system. Sometimes the boundary in mind between system and surroundings is not explicit, but, real or imagined, it must be carefully defined. Take, for example, our solar system. That is a big system to be sure, whose boundaries appear more subjective than objective. Yet our solar system is soundly understood in the context of what it contains: the sun, eight planets, along with Pluto, various other moons, comets, asteroids, etc. On other scales, a single atom, a protein molecule, a chemical reaction, a linked-together series of biochemical reactions (a metabolic pathway), a living cell, also each represent unique systems located within a specified surrounding.

Life too shares a boundary with its surroundings. The human system resides within the boundary of its skin; many types of exchanges take place with our environment: the consumption of food, the excretion of waste, oxygen uptake, carbon dioxide, and heat production are but a few examples. Nature often complicates matter and energy exchanges. A hot muggy day for example may create a life-threatening reversal of heat exchange for an exercising athlete, from rather than to the environment.

How many cells are you made of? Each represents an independent system with its external membrane allowing for a selective exchange of matter and energy with the surroundings (Fig. 2.1). Cells are also highly compartmentalized within creating further internal boundaries that contribute to the unequal distribution of interior matter and energy. Systems and surroundings interact or do not interact depending on the type of border involved. External and internal cell borders create and exploit energy and matter gradients by separating a system from the immediate surroundings. Boundaries enable gradients, gradients empower life.

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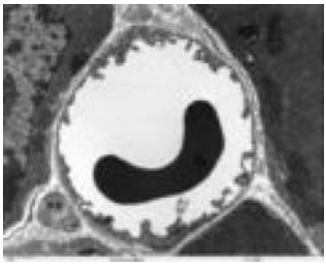

Fig. 2.1 The *dark u-shaped object* is a red blood cell within the confines of its immediate environment, a blood vessel (in this case a capillary). Louisa Howard grants anyone the right to use this work for any purpose, without any conditions, unless such conditions are required by law (commons.wikimedia.org)

2.1 Isolated Systems

Isolation precludes the exchange of matter and energy; the boundary is impermeable. Matter and energy held within an isolated system do not leave that system. An insulated bottle that contains hot soup represents an attempt to isolate a system: the bottle withholds soup (matter), the insulation attempts to withhold heat (energy), no exchanges take place. Suffice to say, few systems on earth are isolated systems. Life cannot thrive in isolation.

2.2 Closed Systems

A closed system's boundaries do not allow the exchange of matter to take place with the surrounding environment. Energy, however, in the form of heat or work, can be exchanged with the surroundings. Engineering and chemistry texts champion closed systems, both immerse themselves fully in the topic of thermodynamics, the very study of heat exchange.

Imagine a house in the format of a closed system, where once inside, the premises was in fact completely shut-down; materials from the environment stay out: no open doors, no open windows, no piped liquids in or out, no leakage of solid materials (matter) anywhere. But heat (a form of energy) can appear or disappear both within and without the system dependent on the surrounding conditions. Once upon a time, the fire-pit of a house-hold was considered the "soul" of the premises. On warm days, the fire was used to cook meals. On cold days, the fire pit was used to both cook food and warm the house-hold. In a closed system, the boundaries (including the chimney) are sealed, preventing the loss or gain of materials that include wood, oxygen (O_2), and carbon dioxide (CO_2). A fire within a closed system eventually consumes all available oxygen, and as smoke accumulates throughout, the fire eventually extinguishes itself. On a cold day, heat (energy) from within the enclosed house would eventually and entirely leak to the surroundings (Fig. 2.2). During the warmest of days (when no internal fire is lit) a reversal of heat movement occurs, the house-hold may take-in heat from the surroundings and become uncomfortably hot.

Test-tube chemical reactions represent closed systems; the reactants and products do not leave but heat (energy) is exchanged through the glass boundary.

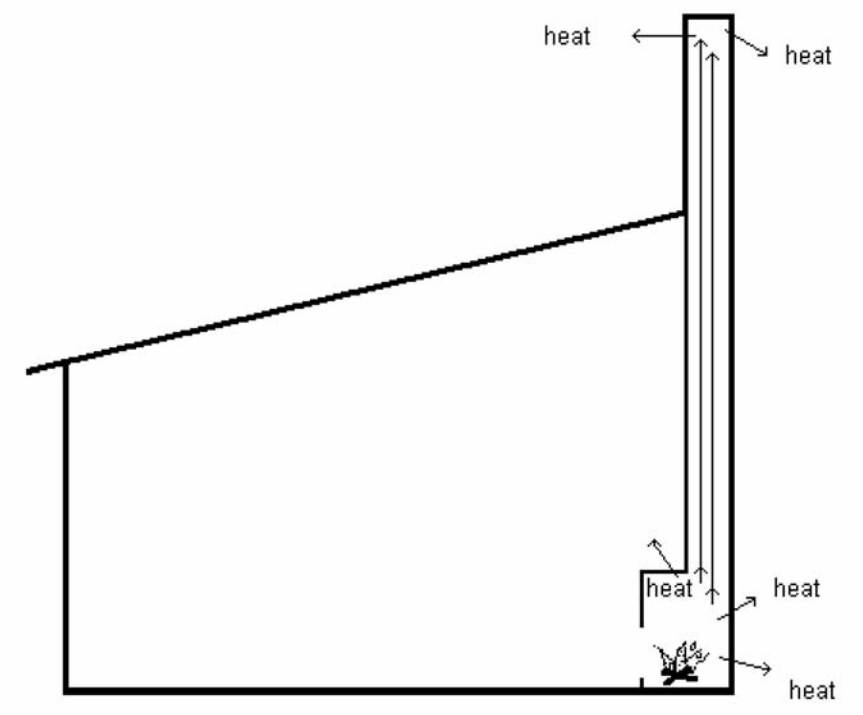

Fig. 2.2 A house is portrayed falsely as a closed system. In colder climates, many houses retain a source of thermal energy; in this example, it is a fire-pit. In a closed system, no exchange of matter (the chemical elements) occurs with the environment. In this example, all material matter (oxygen, wood, smoke particles, etc.) remains inside this closed system, but energy in the form of heat can leak in or out

Chemical test-tube reactions represent well-documented closed system scenarios. Indeed, from the incubus of test-tube chemistry, biochemistry evolved. The nutritional and exercise sciences followed. In reality however the description of a closed system provides rather narrow guidelines to a living system that involves material exchanges in addition to energy exchanges.

2.3 Open Systems

An open system is just that, open to the surroundings. In the presence of gradients, exchanges of matter and energy are made between the system and the immediate surroundings, import and export continuously takes place. If the aforementioned house-hold were to be described in the context of an open system, the scenario changes rather drastically. On a cold day, the house fire-pit would be used to cook food and warm the premises. Matter (materials) in the form of groceries would have

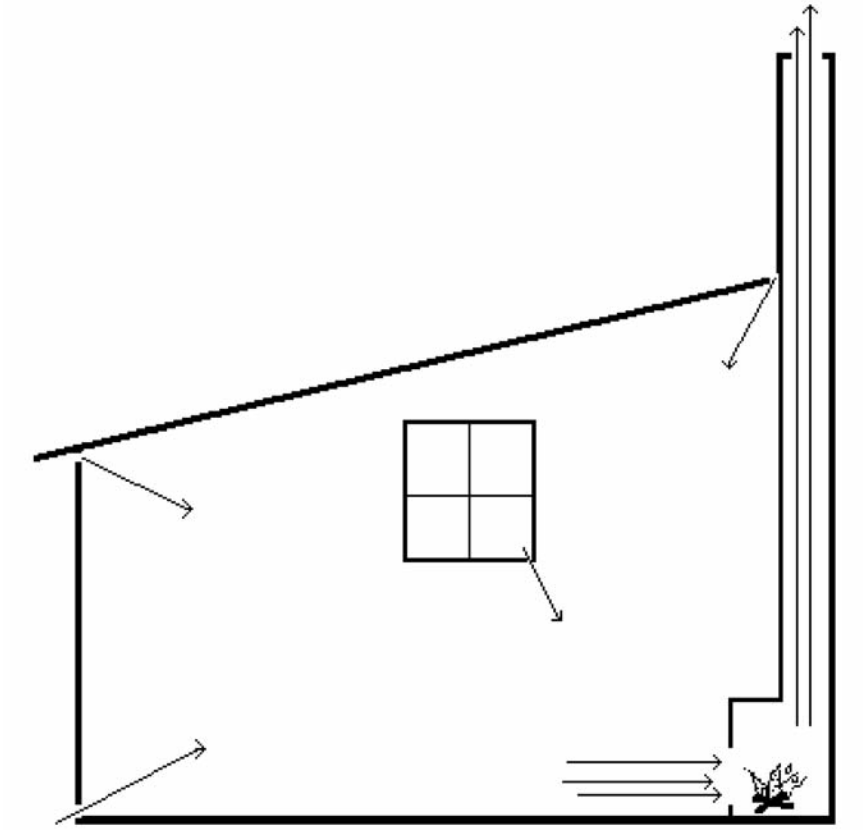

Fig. 2.3 Your house in reality is an open system that requires the continuous exchange of energy and materials with the surroundings. In this figure, hot air, smoke, and moisture from the fire rise up and leave the chimney, causing the room's pressure to decrease slightly; a pressure gradient is subsequently created (high → low empowerment). As a result outside cooler air is drawn through the cracks and leaks of doors, windows, and walls into the house. An uninterrupted supply of wood and fresh air from the environment continuously fuels the fire

had to come into the house, trash and garbage must leave; closed systems do not allow this. Continuation of a fire also requires the constant influx of materials, wood, and oxygen (O_2), and efflux of materials, ash, soot, carbon dioxide (CO_2), and water (H_2O). Heat (energy) is rising from the fire-pit, up the chimney and displaced to the surroundings.

Using the example of a house, care must be taken in the recognition of how all thermal energy is being distributed because air is continuously both entering and leaving the dwelling (Fig. 2.3). On a cold day of course, the heat from a fire should be directed toward warming the house. But with a poorly designed chimney flume, much of that heat may get dispensed upward and outward, to the surroundings. The influx of cold oxygenated air from the outside environment must also be considered.

This cold air "feeds" oxygen to the fire-pit. It is possible that together with the heat going up the chimney, the net flux of thermal energy could allow the house-hold to become slightly cooler, not warmer.

In the presence of gradients, open systems are dynamic; movements not only take place, they are expected. Organized movement within and without an open system has a degree of empowerment. Notice how the open house system of Fig. 2.3 reveals an organized dynamic: influx of "cool" dry air (through leaks in the house) and the efflux of "warm" wet air (up the chimney). This well-organized pattern of continuous movement, from one specific place and to another, has been described as a chimney effect (also known as a stack effect). As a result of differences in outdoor and indoor air density (i.e., buoyancy), cooler outside air coming from the leaks in windows, doors, and wall frames is actively drawn-inward as a result of hot moist air traveling up the chimney and being dispensed to the surroundings. The available thermal energy within this house certainly is used to cook food and provide warmth, but in this example, the chimney can be described as an energy-exchange device that further promotes or empowers the continuous flow or streaming of air across a gradient: from the outside, through leaks in the house, to the fire, and up the chimney. Organized movement comes at a cost. In this example of "empowered" air movement throughout a house, some of the chemical energy contained within the wood and oxygen that fuels the fire is used to cook food and warm the premises; it is also used to promote the chimney effect.

2.4 Life is an Open System

Life has an absolute requirement for gradients that allow for organized exchanges to take place with the surrounding environment; open conditions are a prerequisite of survival. Within every cell of all living organisms, energy and materials undergo constant and continuous exchanges comprised of conversion (from one form to another) and transfer (from one place to another). In brief:

$$\begin{aligned}\text{matter \& energy exchange} = {} & \text{matter \& energy conversion} \\ & + \text{matter \& energy transfer}\end{aligned}$$

At rest, a living organism appears to be in a steady nonchanging state. Such an appearance is deceiving. In fact, the exploitation and maintenance of energy- and matter-exchange gradients comes at a cost whether the organism resides in an apparent steady or nonsteady state. Moreover, the devices life uses to convert and transfer matter and energy from one form to another also operate at an expense. These costs are paid for by taking in matter (food and oxygen) from the environment, exploiting the energy within that matter, and then dispensing a lower energy version of these materials to the environment; every step along the way employs some type of gradient. In fact, survival of a cell further entails the exploitation of one type of gradient toward maintenance of another type of gradient (Fig. 2.4). Were life's exchanges with the surroundings prevented for a long enough period of time, death would be

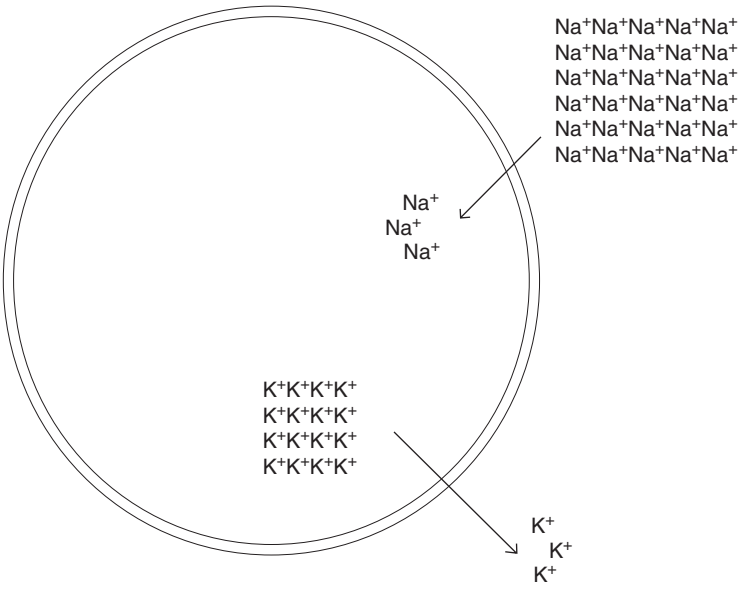

Fig. 2.4 The cartoon depiction of a typical cell with a bilipid external membrane is shown. In animal cells this membrane is dedicated toward the encouragement of an ionic gradient where sodium ion concentrations [Na^+] are greater external to the membrane, and potassium ion concentrations [K^+] are greater internal to the membrane. Cell membranes are not perfect barriers (perhaps by design); ions are constantly leaking through the membrane in the "downhill" direction: Na^+ leak inside; K^+ leak outside. Cell survival is dependent on the maintenance of ionic gradients, the energy to do so comes from the food and drink we consume

the certain result. Another way to describe death is by the disappearance of those gradients that allow exchanges to take place.

The surroundings change as a direct result of life's taking (consuming) and giving (excreting). These changes – internal and external to the system – can be studied to determine what the costs of living are. System intake and expenditure, whether for a single cell or an exercising athlete, are explored in some detail by the nutritional and exercise sciences (e.g., food and nutrient consumption, energy conversion and transfer, oxygen uptake, carbon dioxide and work output, and aerobic and anaerobic metabolism). However, it was the science of physics and later chemistry that defined the hows and whys of energy-exchange gradients within and without a given type of system.

Chapter 3
Conservation

Being curious creatures, humans ask questions. Scientist's efforts at answering questions are called hypotheses. A hypothesis is not immediately accepted as factual. Indeed, because human beings are error prone, so too are most hypotheses. Scientists devise experiments that test hypotheses over-and-over in an attempt to disprove them. If, over time, disproof of the hypothesis is not found, then the hypothesis may be regarded as theory. It is the rare hypothesis that leads to a full-blown theory.

Over still more time a theory may become a natural law, leading one and all to think in an explicit direction and with specific focus. One such example is the conservation of matter and energy. Matter and energy cannot be spontaneously created from nothing nor can they be destroyed leaving no perceptible trace. This observation has never been disproven. No one has yet come forth with an experiment that clearly refutes the concept of matter and energy conservation (and such an idea did not take hold overnight).

It was the seventeenth-century physicist Isaac Newton (1642–1727) who first informed us of the concept of conservation when he noted that momentum is conserved. Newton stated (in 1687) that an object at rest tends to stay at rest and an object in motion tends to stay in motion unless acted upon by an outside force. In other words, motion (as a whole) was the sum of its parts, no more no less; period. Newton's concept of conservation slowly became incorporated into everyday thinking. In the eighteenth century, Mikhail Lomonosov was the first to apply the concept of conservation to matter (1711–1765). He understood Newton's law of momentum well when he stated, "All changes that we encounter in nature proceed so that . . . however much matter is added to any body, as much is taken away from another . . . this . . . general law of nature . . . is also found in the rules of motion." It took another 100 years for energy to follow matter in regards to conservation.

About a half-dozen nineteenth-century scholars, working independently, and all seemingly within the same time frame (∼1850), came to a collective moment of truth concerning the concept of energy conservation. Like matter they found that energy too cannot be created or destroyed but it can and does change form. In application this always means that the total amount of energy involved in any type of exchange – conversion or transfer – remains equal when all is accounted for.

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Energy conservation defines the first law of thermodynamics. Being a fundamental starting point, the first law must be acknowledged by bioenergetics and applied to the measurement of energy expenditure.

In the twentieth century, Albert Einstein (1879–1955) recognized the interconvertibility of matter and energy:

$$E = MC^2$$

where E = energy, M = mass, and C = celestias (the speed of light).

The speed of light is a large number (299,792,458 m s^{-1}), and when it is squared, it becomes a downright enormous number. Putting this into limited perspective, an infinitesimal portion of matter, something as small as an atom, contains a rather stupendous amount of energy. Conversely, a somewhat absurdly large amount of energy is required to create a smidgeon of matter. Such exchanges take place routinely as part of thermonuclear reactions, within stars like our sun for example. Obviously enough, living cells do not exchange matter and energy in a thermonuclear format. Life's gradients are much more subtle. Instead, life exploits the respective conversion of matter and energy from one form to another as:

$$\text{matter} \leftrightarrow \text{matter}$$
$$\text{energy} \leftrightarrow \text{energy}$$
$$(\text{but not, matter} \leftrightarrow \text{energy})$$

The utilization of fire, a form of oxidation known as combustion, has been rather favorable to humanity. We recognize wood and coal as useful oxidative fuels. On the other hand carbon dioxide (CO_2) is viewed as a waste molecule that we have little use for. But according to Einstein a single molecule of CO_2 contains a vast reservoir of energy. Perhaps some day the full energetic potential of a fuel-tank full of CO_2 will provide more than enough energy to power a rocket's trip from the Earth to the Moon.

It is recognized that the molecular rearrangements that take place during combustive or metabolic oxidation, each forming CO_2 in the process, has only a finite amount of energy to offer. Of course our metabolic systems cannot oxidize wood, but we can and do oxidize glucose and fat. Regarding matter, a molecule of glucose ($C_6H_{12}O_6$) undergoing either metabolic or combustive oxidation leads to water (H_2O) and CO_2 formation as shown here:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2$$

Note that the above reaction is balanced *stoichiometrically* so that an identical number and kind of matter in the form of atoms are found on each side of the reaction (6 carbons, 12 hydrogens, 18 oxygens). Stoichiometry is built on conservation principles.

In regard to energy conservation, the above equation must be rewritten as:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2 + \text{heat (energy)}$$

Not all of the atomic energy contained within a molecule of glucose and six molecules of oxygen is available to a living cell because some of that energy is dispensed as heat to the environment as part of the molecular exchange. But even so, some energy, albeit a lesser amount of energy (originally available within glucose and oxygen), is still contained within the molecules of water and carbon dioxide that are dispersed to the environment.

Chapter 4
Matter and Energy

4.1 Matter

Matter is regarded as any substance that occupies space; it exists in three states: solid, liquid, and gas (these states can undergo physical change as a result of heating or cooling where for example ice, water, and water vapor describe the different states of H_2O). Matter has properties by which it is recognized. We can identify some of these properties with the use of our senses: sight, touch, smell, taste. Other properties are described in the context of melting, boiling, and freezing points, density, electrical properties; the list goes on.

An element cannot be broken down into any other substance so that each element represents an original type of matter. Ninety-nine percent of the human body is made up of only six elements, oxygen (O), carbon (C), hydrogen (H), nitrogen (N), calcium (Ca), and phosphorous (P). Earth's matter is presently known to consist of 85 natural elements, all of which are displayed in the periodic table (Fig. 4.1).

Each element is made of the same kind of atom. Atoms consist of a densely packed nucleus containing positively charged protons (+) and neutrons that carry no charge. Negatively charged electrons (−) orbit the nucleus. Orbitals are said to inhabit discreet areas of space about the nucleus. Orbitals have distinct shapes and are located at specific distances from the nucleus. Atoms therefore consist of electrical charges and moving parts.

Electrons (e^-) that orbit closest to the nucleus are strongly attracted to the protons (+) within the nucleus (opposite charges attract); these are the core electrons – they do not react with other atoms. An atom also has valence electrons, with orbitals further from the nucleus than the core electrons. Valence electrons interact with other atoms (hydrogen, the first element on the periodic table, has one electron that is considered a valence electron; it does not have a core electron). The atoms of each element have specific properties of electronegativity (i.e., electron affinity or the ability to attract electrons) and electron arrangement (e.g., number of electron orbitals).

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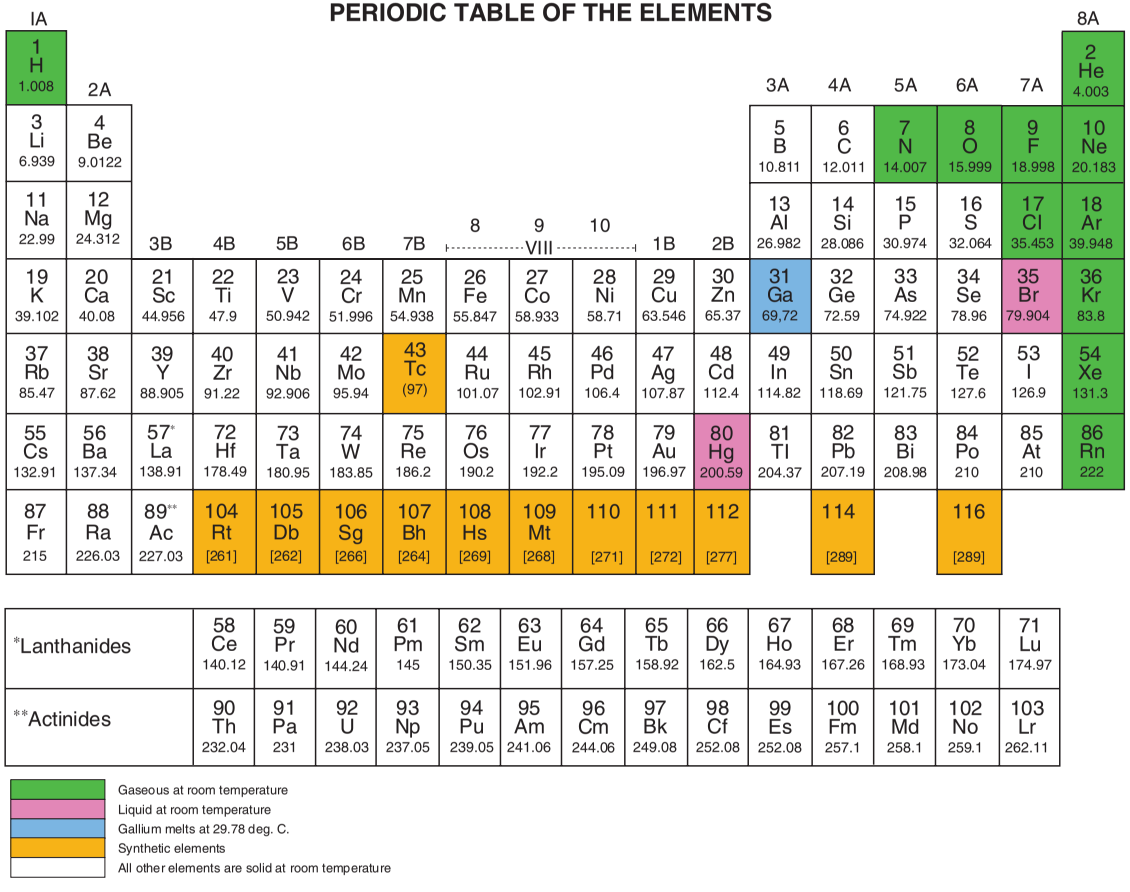

Fig. 4.1 Hundred and ten total elements are known (25 elements are man made). This periodic table of the elements is in the public domain and may be downloaded and printed without restriction (http://www.csudh.edu/oliver/chemdata/periodic/periodic-1.htm)

Molecules are combinations of atoms, as few as two atoms or perhaps as many as millions of atoms (e.g., a polymer). Much of what is known about molecules was derived from observations of collections of molecules called compounds. As an example, water is a compound of two hydrogen atoms and one oxygen atom – H_2O – whose molecular properties were largely derived from observations of many water molecules ($[H_2O]_n$) within a fixed container.

In addition to understanding molecules from observations of compounds, modern research and development has allowed us to better understand the interaction of chemical compounds by acknowledging the arrangement of the atoms within. Atomic and molecular arrangements dictate the energetic properties of matter.

4.2 Energy

Energy can be more difficult to conceptualize as compared with matter perhaps because of the limits of our senses; it is not always possible to quantify the energy held within a substance by holding, looking at, tasting or smelling it. Energy exists in several forms that include (but are not limited to) chemical, mechanical, electromagnetic, nuclear, light, and heat (thermal). Nutritionists and exercise physiologists often focus on chemical, mechanical, and heat exchanges that take place as the internal mechanisms within muscle cells perform work. Work entails a force, acting on an object, causing the object to be displaced:

$$W = fd$$

where $W =$ work, $f =$ force, $d =$ displacement (or distance).

Energy can be defined as an ability to perform work or an ability to cause change so that lower energy states have less ability while high energy states have a greater ability to perform work or cause change. So how does energy content differ among atoms and molecules?

The most stable energy state for an atom occurs in its lowest energy state, when the valence electron shell is either completely filled or completely empty. Only a few elements are stable enough to exist as single atoms in their natural state: these are the noble or inert gases. Other atoms are more stable in molecular form; it takes two atoms of hydrogen (H), oxygen (O), and nitrogen (N) to form their respective and more stable molecules, H_2, O_2, and N_2.

An atomic or molecular system that has or has had force acting on it acquires energy. A system is in possession of mechanical energy if it is held in position or if it has motion.

Potential energy (PE) is stored energy; specifically, whenever an object that has mass holds a position within a field. A typical example of this is a weight held at a distance from the ground where:

$$\mathrm{PE} = mgh$$

where PE = potential energy, m = mass, g = earth's gravitation, and h = height. (The gravitational constant is $6.6742 \times 10^{-11}\,\mathrm{m^3\,kg^{-1}\,s^{-2}}$.) The earth's gravitational field is relatively constant but potential energy can change by either altering the mass, the distance of the weight from the ground, or both.

Kinetic energy (KE) is found whenever an object with mass has velocity. Everything moving has kinetic energy:

$$\mathrm{KE} = \frac{1}{2}mv^2$$

where m = mass, v = velocity. Kinetic energy is changed by altering the mass of the object in motion, by varying that object's velocity, or both.

As mentioned previously, electrons "orbit" the nucleus in discreet areas of space. Energy is associated with the distance of the electron from the atomic nucleus. On such a small scale it might appear that atoms and molecules would hold little energy, but keep in mind, as Einstein informed us, this assumption would be false.

From an atomic perspective, kinetic energy can be envisioned as a rapidly orbiting electron around the nucleus of an atom. In actuality the electron does not travel along a fixed orbital path in a specific direction and so its exact movement cannot be traced. Conceptualizing the probable region where an electron might be is a more realistic endeavor as compared with calculating an electron's exact position so that electrons are better portrayed as regions of waves that surround the nucleus (rather than as orbitals). The kinetic energy of an atom is positive (+) and increases as the radius of the orbit decreases. The closer the wave is to the nucleus, the greater is the positive (+) kinetic energy (imagine swinging a ball around your head that is tethered by a string, the shorter the string, the faster the "orbit," and the greater the kinetic energy).

The potential energy of an atom is found as the attraction between the positively charged proton$^+$ in the nucleus and the negatively charged electron (e^-) "orbiting" the nucleus. The potential energy of an atom is negative (−):

$$\mathrm{PE} = (+1)(-1)/R = -1/R$$

In an atom with +1 proton and −1 electron, the product is −1. R = the distance between nucleus and electron.

Because opposite charges attract, the greater the distance between electron and nucleus the lower the negative (−) potential energy; the smaller the distance, the greater the negative (−) potential energy.

The total energy of an atom consists of the sum of its kinetic and potential energies:

$$\mathrm{TE} = \mathrm{KE} + \mathrm{PE}$$

where TE = total energy, KE = kinetic energy, PE = potential energy. Allowing for the attraction between electron and proton increases an atom's potential energy but as the electron's "orbital" radius decreases, kinetic energy increases. Atoms tend to exist in the lowest most stable energy state or ground state, where a balance

is found between the (−) potential energy (proton and electron distance) and the (+) kinetic energy (the size of the electron "orbit" or wave). Because of this balance the astute student may recognize that an increase in kinetic energy, caused by a diminishing proton (+) and electron (−) distance, keeps the potential energy "in-check," preventing the nucleus and electron from collapsing into each other.

4.3 Internal Energy

Molecules are made of individual atoms so that interactions exist among multiple atomic nuclei and electron waves. The physicist, Richard Feynman (1918–1988) succinctly described molecular potential energy when he remarked that, "... all things are made up of atoms – little particles that move around in perpetual motion, attracting each other when they are a little distance apart, but repelling upon being squeezed into one another. In that one sentence, you will see, there is an enormous amount of information about the world, if just a little imagination and thinking are applied."

Feynman's elegant description reveals that part of the energy inherent to a molecule is a function of the distance between atomic nuclei and the molecular bond length. To illustrate bond length, remember that the closer an electron wave is to an atomic nucleus (or nuclei) the greater is the (−) potential energy. Also recall, that the smaller an electron "orbital" the greater is the (+) kinetic energy. However, within a molecule, as the positively charged nuclei of two or more atoms become closer, a repulsive force is found (like charges repel; opposite charges attract). To the contrary, incomplete valences invoke an attractive force between atoms. Taking these additional energies of repulsion and attraction into account, molecular bond formation takes place at a bond length where the total energy of the molecule is held at a minimum. Similar to atoms, molecules also tend to exist in the most stable energy state. Yet energy *is* there. Dependent on atomic make-up and molecular configurations then, matter contains various amounts of energy.

Heat is a form of energy, and so its impact on molecules must also be considered. Temperature is perhaps best known as a measurement of the hotness or coldness of an object. The kinetic energy of molecules governs the behavior of a gas. The average kinetic energy of a gas is proportional to its absolute temperature; the higher the temperature the greater the kinetic energy. Gas pressure and volume are related to the average molecular kinetic energy as represented by the ideal gas law:

$$PV = nRT$$

where P = pressure, V = volume, n = moles of gas, R = universal gas constant, T = temperature. (R is a constant of proportionality at $8.314\,\mathrm{J\ K^{-1}}(1.985\,\mathrm{cal\,^{\circ}C^{-1}})$.

A sealed container (a closed system) full of a known gas contains atoms (or paired atoms) that are moving about in random motion. These atoms are not bonding

with each other and so the intermolecular forces described earlier are not present. Solids and liquids on the other hand are held together by chemical bonds and so they possess additional intermolecular forces.

Chemical energy is held within the intermolecular bonds that hold atoms together. There are several types of molecular bonds but it is the covalent bond that is of special interest from an available energy perspective. Covalent bonds exist as the sharing of valence electrons between two atoms (i.e., electrons that are both shared by and attracted to the nucleus of both atoms). The chemical energy of any given molecule is determined by the position of the atomic nuclei in respect to one another and subsequent electron density in accordance with bond types, bond lengths and bond angles.

Specific heat is the amount of heat required to raise the temperature of a unit mass one degree Celsius. It takes much more heat energy to raise the temperature of one gram of water as compared with say one gram of bone. Why is this? Molecular kinetic translational energy is the energy of linear motion; collisions between atoms and molecules that invoke linear changes in direction are measured as temperature. There are also molecular rotational and vibrational kinetic energies that contribute to a molecule's internal energy but these energies are not measured as temperature. Water has a higher specific heat as compared with many solids because when heat is added to water some of this energy goes toward increasing the molecular rotational and vibrational kinetic energy of the water molecules, energies that are not measured via temperature. The addition of heat to a solid acts to primarily increase the kinetic translational energy and is measured as temperature.

It is of interest that many animals, whether "cold-blooded" or "warm-blooded," tend to maintain body temperature at $\sim$36–40°C perhaps to influence or be influenced by the physical properties of the water they carry around (1). For example, the lowest amount of thermal energy required to raise the temperature of water one degree Celsius is near 36°C. Moreover, half of the influence that temperature has on the thermodynamic properties of water (as a solid, liquid, and gas) is found at 40°C.

It is common knowledge that temperature is measured by a device called a thermometer in units of degrees. But heat and temperature while related are not identical and so a different device is needed with units that are distinctly associated with heat energy. Heat is measured with a device called a calorimeter (see Chap. 14). Tradition has it that heat (energy) units were measured as calories but the more contemporary scientific international system (SI) quantifies heat as Joules. (Joules are discussed in more detail in the next section.) A calorie is defined as the amount of energy required to raise the temperature of one gram of water one degree Celsius, from 14.5°C to 15.5°C. A kilocalorie (kcal) refers to one liter of water and in lay terminology is interchangeable with the term calorie (cal). If one liter of water at 1,000 g (1 kg) were to be heated from 0°C to 10°C then:

$$10^{\circ}\mathrm{C} \times 1{,}000\,\mathrm{g} = 10{,}000\ \mathrm{cal}\ \mathrm{or}\ 10\ \mathrm{kcal}$$

Because heat was *added* to the water we can go one step further and notate this heat increase with a positive sign as:

$$+10 \text{ kcal}$$

If 1 L (1,000 g or 1.0 kg) of water was cooled from 30°C to 20° then a 10° *loss* of heat from the water to the surroundings has taken place and is noted with a negative sign as:

$$-10^{\circ}\text{C} \times 1{,}000\,\text{g} = -10 \text{ kcal}$$

Put succinctly, systems may be comprised of atomic and molecular, kinetic, potential, work, and heat energies. Collectively these energies are known as the internal energy, symbolized as U, where $U =$ internal energy.

4.4 Internal Energy (U) Exchanges

It is unfortunate that a simple and direct means of quantifying all of the individual energies that comprise the internal energy within a specific system is not yet available. For many students of chemistry this marks a point of retreat. But all is not lost. Energy always reveals itself when it undergoes change. And these changes are readily quantified in the form of heat and work. In fact, the study of thermodynamics evolved from the recognition that work and heat were related aspects of energy (*thermo* signifies heat energy; *dynamics* signifies change).

The fundamental relationship between heat and work was elegantly revealed by James Joules' (1818–1889) prolific experimentation with energy-exchange devices. One famous experiment was constructed as a paddle wheel in water that operated by a falling weight, an insulated water bath surrounded the apparatus and careful recordings of the water temperature took place. After a multitude of experiments, Joule revealed that 772 ft lb of falling weight caused the paddle wheels to agitate the water enough to produce a rise in temperature of one degree Fahrenheit (per pound of water). Joule's conclusion was a bold one: work and heat are interchangeable; energy *was* conserved!

Joule defined energy as matter in transition. Notice how the definition contains elements of both potential and kinetic energies: the word *transition* incites the term *kinetic energy*; the latent notion of potential energy arises from the implication of a starting position and the ending point of a transition. Joule described the presence of heat as energy in transition. This description too provides insight; when energy undergoes exchange, heat is lost to the environment. The heat exchanges between a system and its surroundings are used to describe energy exchange. Some examples of energy exchange and the devices that enable this to occur are provided in Table 4.1 (2).

Being interchangeable, work and thermal energy share the same unit, the Joule. Work is the amount of energy required to exert a force of one newton over a distance

Table 4.1 Energy exchange and the devices that enable the conversion

Energy exchange	Conversion device
Thermal to mechanical	Steam engine
Chemical to thermal	Burning coal
Chemical to electrical	Battery
Electromagnetic to thermal	Electric stove
Chemical to mechanical	Muscle

of one meter (one newton is the force that imparts a mass of one kilogram to an acceleration of one meter/second/second):

$$1\,\mathrm{J} = 1\,\mathrm{N\,m}$$

(This represents the energy required to lift 1 kg to a height of 10 cm)

Some other conversions:

$$1\,\mathrm{J} = 0.737562\,\mathrm{ft\ lb}$$
$$3,600\,\mathrm{J} = 1\,\mathrm{W\ h}$$
$$1\,\mathrm{J} = 0.239\,\mathrm{cal}$$
$$1\,\mathrm{cal} = 4.184\,\mathrm{J}$$

Heat (energy) can be lost from a system to its surroundings, decreasing the internal energy of the system. The opposite also is true. Thus, the addition or subtraction of heat to or from a system changes the internal energy:

$$\Delta U = \pm Q$$

where Δ = change, U = internal energy, $\pm Q$ = addition or loss of heat. Heat is not the only means of increasing internal energy. When work is added to a system in terms of a physical force, then similar to the addition of thermal energy, this too will increase the internal energy of the system. As an example, if a force were applied to a system from the surroundings or from a system to the surroundings, internal energy changes.

$$\Delta U = \pm W$$

where ΔU = change in internal energy, $\pm W$ = addition or loss of work.

It is understood that energy cannot be created or destroyed, that is the first law of thermodynamics. This means that if heat or work or both are added to a system, then the internal energy of that system must increase. If work or energy are taken away or subtracted from the system, then the internal energy of that system decreases. The following equation provides a mathematical description of energy exchange derived from the conservation of energy:

$$\Delta U = \pm Q + \pm W$$

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Chapter 5
Energy Accountability: Enthalpy (H)

The internal energy (U) of a given system can be difficult to quantify directly. However, changes (Δ) in the internal energy of a system are accounted for by the measurement of heat or work. The horse power produced by a steam engine for example is initiated by system changes (gas expansion) within an enclosed cylinder, subsequently influencing volume (V) and performing work on a moveable piston. Yet for chemical reactions in biological systems (within a cell), volume is not taken into account. Gas-related pressure–volume work has limited use to the exercise physiologist and sports nutritionist who are more concerned with the internal energy of those solids and liquids that make-up and fuel life. Dismissing volume-related work in the description of energy exchange allows for the introduction of a new thermodynamic property (or quantity), enthalpy. Enthalpy approximates the internal potential energy of a chemical system:

$$\mathrm{H} \approx U$$

where H = enthalpy and U = internal energy.

5.1 The Chemical Reaction System

Chemical reactions invoke the breaking and formation of chemical bonds. The bonds of chemical reactants are broken; the bonds of chemical products are formed. Energy often needs to be added or taken in by a chemical system to break a molecular bond so that bond cleavage is endothermic. To the contrary the formation of a chemical bond releases energy where bond formation is exothermic. If weak chemical bonds within reactants are replaced by stronger chemical bonds within products, then the overall chemical reaction is exothermic. A stronger bond is a more stable bond and has less potential energy as compared with weak chemical bonds that by their very nature are unstable. Weak bonds are less stable and therefore have greater potential energy. If strong chemical bonds within reactants are replaced by weaker chemical bonds within products, then the reaction is endothermic (energy is required to make a strong bond weak).

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As with internal energy it is difficult to quantify the enthalpy content of an element (an atom) in its standard state. Scientists have consequently found an ingenious solution; they often do not bother to perform such a measurement! Instead, elements in their standard state are regarded as a reference point whose enthalpy values are defined as zero [0]. With zero as a starting point, enthalpy can be accounted for only when a change takes place:

$$\Delta \mathrm{H} = \text{change in enthalpy}$$

Whenever matter undergoes conversion from one form to another an exchange of energy occurs. Changes in enthalpy can be determined by measuring heat exchanges using a precise scientific instrument known as a direct calorimeter (see Chap. 14). Chemists use calorimeters to measure the enthalpy changes of chemical reactions. Food scientists use calorimeters to measure the energy content of food. Calorimeters also have been designed to measure the energy exchanges of living cells. Large room-sized calorimeters have been constructed to house whole animals, where again enthalpy exchanges are quantified. Direct calorimetry provided conclusive evidence of the first law of thermodynamics within both nonliving and living systems.

Exothermic reactions indicate that thermal energy has been removed (subtracted) from a system. The energy gradient is from the reactant–product chemical system to the surrounding environment, and the enthalpy change is given a negative sign:

$$\text{System} \rightarrow \text{Surroundings}(-\Delta \mathrm{H})$$

Endothermic reactions indicate that thermal energy was added to the reactant–product chemical system from the environment, the enthalpy change is given a positive sign:

$$\text{Surroundings} \rightarrow \text{System}(+\Delta \mathrm{H})$$

It cannot be assumed that all exothermic reactions $(-\Delta \mathrm{H})$ proceed spontaneously or, that all endothermic reactions $(+\Delta \mathrm{H})$ are nonspontaneous. Thus, the sign given to enthalpy suggests the direction of the thermal energy gradient but it does *not* indicate the spontaneity or nonspontaneity of a chemical reaction. Notice that the arrows above between system and surroundings or surroundings and system both point to the right; in reality however, the energy flow across a boundary involves two vantage points (the surroundings and the system) that offer four different perspectives:

The surroundings	**The system**
From $(-)$ the surroundings	To (+) the system
To (+) the surroundings	From $(-)$ the system

5.2 Chemical (Standard) Enthalpy Exchanges

Enthalpy changes are founded when elements combine to form the covalent bonds of molecular compounds; this is regarded as the enthalpy of bond formation. When

molecular covalent bonds are broken the enthalpy of bond cleavage is measured. For any given chemical bond the enthalpy of bond formation is equal and opposite to the enthalpy of bond cleavage.

Let us explore enthalpy changes (ΔH) in more detail by examining the enthalpy of formation of a molecule of carbon dioxide (CO_2) derived from its elements in their standard form [where $H = 0$]. Because the enthalpy change in the formation of molecular bonds is dependent on temperature, environmental conditions must be standardized. Standard temperature is considered to be "room temperature" (25°C; 72°F; 298 K). Standard pressure is 1.00 atm: sea level (760 mmHg). Standard conditions are noted by the superscript, °. For the formation of CO_2, carbon in its standard atomic form is a solid [C; $H^\circ = 0$] and oxygen in standard molecular format is a gas [O_2; $H^\circ = 0$]. When combined as an oxidation reaction heat is released to the surroundings as an exothermic reaction (note the negative sign to the enthalpy change, thermal energy has left the system). Two very stable and very strong carbon–oxygen bonds are formed (CO_2 or O=C=O, where = represents a double bond):

$$\begin{aligned} &C + O_2 \rightarrow CO_2 \\ &\Delta H^\circ = -393.5 \text{ kJ mol}^{-1} \end{aligned}$$

Energy is required to break the covalent bonds within CO_2 to re-form atomic carbon and molecular oxygen. The breaking of two carbon–oxygen bonds is thus endothermic, the thermal gradient is from the surroundings to the system (note the positive sign to the enthalpy change):

$$\begin{aligned} &CO_2 \rightarrow C + O_2 \\ &\Delta H^\circ = +393.5 \text{ kJ mol}^{-1} \end{aligned}$$

The overall enthalpy change of a chemical reaction is determined by knowing what bonds are broken as reactants and what bonds are formed as products. As an example, four atoms each of the elements hydrogen (H) and oxygen (O) have the potential to form two molecular products: hydrogen peroxide or water and oxygen:

two molecules of hydrogen peroxide ($2H_2O_2$ or 2H−O−O−H, where − represents a single bond):

$$4H + 4O \rightarrow 2H_2O_2$$

or

two molecules of water ($2H_2O$ or 2H−O−H) and one molecule of oxygen (O_2 or O=O):

$$4H + 4O \rightarrow 2H_2O + O_2$$

Let us determine the enthalpy change (ΔH°) when hydrogen peroxide decomposes to water and oxygen:

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

The overall enthalpy change can be determined by summing the enthalpies of molecular bond breakage within the reactants and bond formation within the products.

To begin, we need to determine the sum of the enthalpy change of the reactants ($\sum H_{(\text{reactants})}$) as they are broken down into their respective elements (remember, energy is required to break molecular bonds):

$$2H_2O_2 \rightarrow 4H + 4O$$

The two molecules of the reactant hydrogen peroxide (2H−O−O−H) are broken down into their respective elements, four atoms of hydrogen and four atoms of oxygen, by breaking two oxygen−oxygen single bonds:

$$2O-O \text{ bonds at } 142\,\text{kJ mol}^{-1} \text{ per bond} = +284\,\text{kJ mol}^{-1}$$

and four hydrogen−oxygen bonds:

$$4H-O \text{ bonds at } 460\,\text{kJ mol}^{-1} \text{ per bond} = +1{,}840\,\text{kJ mol}^{-1}$$

As measured by direct calorimetry, the complete reaction is endothermic:

$$\begin{aligned} 2H_2O_2 &\rightarrow 4H + 4O \\ \sum H^{\circ}_{(\text{reactants})} &= 284\,\text{kJ mol}^{-1} + 1{,}840\,\text{kJ mol}^{-1} \\ \sum H^{\circ}_{(\text{reactants})} &= 2{,}124\,\text{kJmol}^{-1} \end{aligned}$$

Next we need to determine the sum of the enthalpy of formation of the products ($\sum H_{(\text{products})}$). The enthalpy of formation of two molecules of water and one molecule of oxygen from the four hydrogen and oxygen atoms requires forming one oxygen−oxygen double bond:

$$1O = O \text{ bond at } -499\,\text{kJ mol}^{-1} \text{per bond} = -499\,\text{kJ mol}^{-1}$$

and four hydrogen−oxygen bonds:

$$2H-O-H \text{ bonds at} -460\,\text{kJ mol}^{-1} \text{ per bond} = -1{,}840\,\text{kJ mol}^{-1}$$

As measured by direct calorimetry, the reaction is exothermic (energy is given off during bond formation):

$$\begin{aligned} &4H + 4O \rightarrow 2H_2O + O_2 \\ &\sum H^{\circ}_{(\text{products})} = -1{,}840\,\text{kJ mol}^{-1} + -499\,\text{kJ mol}^{-1} \\ &\sum H^{\circ}_{(\text{products})} = -2{,}339\,\text{kJ mol}^{-1} \end{aligned}$$

The overall enthalpy change of the reaction can be derived by summing the enthalpy changes for the two reactions:

$$\Delta H^{\circ}_{(\text{overall reaction})} = \sum H^{\circ}_{(\text{reactants})} + \sum H^{\circ}_{(\text{products})}$$

As measured by direct calorimetry, the overall (exothermic) enthalpy change is:

$$2H_2O_{2(\text{reactants})} \rightarrow 2H_2O + O_{2(\text{products})}$$
$$\Delta H^{\circ}_{(\text{overall reaction})} = \sum H^{\circ}_{(\text{reactants})} + \sum H^{\circ}_{(\text{products})}$$
$$\Delta H^{\circ}_{(\text{overall})} = 2,124\,\text{kJ mol}^{-1}_{(\text{reactants})} + -2,339\,\text{kJ mol}^{-1}_{(\text{products})}$$
$$\Delta H^{\circ}_{(\text{overall reaction})} = -215\,\text{kJ mol}^{-1}$$

A glucose molecule is more complex containing several covalent bonds among different elements (Fig. 5.1).

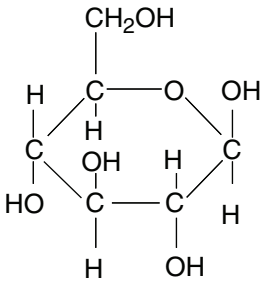

Fig. 5.1 Glucose ($C_6H_{12}O_6$) contains 5C—O bonds, 5O—H bonds, 7C—H bonds, and 5C—C bonds

The enthalpy of formation of glucose from atoms and molecules in their standard state requires six carbon atoms (found in solid form as graphite), six molecules of hydrogen (found in gaseous form), and six molecules of oxygen (found in gaseous form); the reaction is exothermic:

$$6C + 6H_2 + 3O_2 \rightarrow C_6H_{12}O_6$$
$$\Delta H^{\circ} = -1,274.4\,\text{kJ mol}^{1}$$

The degradation of a glucose molecule back to its constituents in their standard state is an equal but opposite endothermic process:

$$C_6H_{12}O_6 \rightarrow 6C + 6H_2 + 3O_2$$
$$\Delta H^{\circ} = +1,274.4\,\text{kJ mol}^{-1}$$

5.3 Chemical (Nonstandard) Enthalpy Exchange

In the preceding examples the enthalpy of bond formation and bond cleavage was examined using the elements in their standard state. However, biochemical reactions consist of materials (reactants and products) whose molecules were *not* derived from elements in their standard state. The glucose molecules we eat come from CO_2 and H_2O not C (graphite), O_2 (gas), and H_2 (gas). Fortunately, the energy changes of

Table 5.1 The enthalpy of bond formation for some typical chemical bonds

Bond	ΔH°(kJ mol^{-1})
C—O	−351
O—H	−460
C—H	−414
C—C	−347
O—O	−142
O=O	−499

C carbon; *H* hydrogen; *O* oxygen; —, single bond; = double bond.

almost any conceivable chemical or biochemical reaction in gaseous, liquid or solid form can be calculated because the enthalpy of bond formation has been measured for thousands of different bonds (these values are available in most chemistry textbooks). Some examples are provided in Table 5.1.

Using only the enthalpy of bond formation (not bond breakage) for both reactants and products, the change in enthalpy can readily be determined as the enthalpy difference between the end (final) and the start (initial) of a reaction:

$$\Delta H^{\circ} = H_{\text{final}} - H_{\text{initial}}$$

ΔH° = change in enthalpy; H_{final} = final enthalpy; H_{initial} = initial enthalpy

(this equation strictly utilizes the data of bond formation, not bond cleavage).

The enthalpy change of glucose formation is different when the starting or ending points are different. Glucose formation begins with carbon dioxide and water as part of photosynthesis (the reaction, below, is endothermic; energy must be put into the system to make glucose):

$$6H_2O + 6CO_2 \rightarrow C_6H_{12}O_6 + 6O_2$$
$$\Delta H^{\circ} = +2,801.64\,\text{kJ mol}^{-1}$$

Glucose oxidation is the reverse of photosynthesis so that the enthalpy change is equal and opposite that of photosynthesis; as can be identified below, the products formed are not 6C, $6H_2$, and $9O_2$ but are instead $6H_2O$ and $6CO_2$. Calculated in detail the overall enthalpy change for glucose oxidation is obtained by subtracting the enthalpy of formation of the reactants from that of products:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2$$

ΔH° **reactants**	ΔH° **products**
Glucose at $-1,274.4\,\text{kJ mol}^{-1}$	Water at $-285.83\,\text{kJ mol}^{-1}$
Oxygen at $0\,\text{kJ mol}^{-1}$	Carbon dioxide at $-393.51\,\text{kJ mol}^{-1}$

Molecule	$\Delta H^{\circ}_{(\textbf{reactants})} \rightarrow$	**Molecule**	$\Delta H^{\circ}_{(\textbf{products})}$
$C_6H_{12}O_6$	$-1,274.4\,\text{kJ mol}^{-1}$	$H_2O \times 6$	$-1{,}714.98\,\text{kJ mol}^{-1}$
$O_2 \times 6$	0	$CO_2 \times 6$	$-2{,}361.06\,\text{kJ mol}^{-1}$

$$\Delta H^{\circ}_{(\text{overall})} = -4,076.04\,\text{kJ mol}^{-1}_{(\text{products})} - 1,274.4\,\text{kJ mol}^{-1}_{(\text{reactants})}$$
$$\Delta H^{\circ} = -2,801.64\,\text{kJmol}^{-1}$$

In the chemical oxidation of glucose, the system is defined as the glucose and oxygen molecules that undergo reaction and the water and carbon dioxide products that undergo formation. As is typical of any chemical reaction, thermal energy is exchanged with the surroundings. In the case of glucose oxidation the reaction is exothermic. If glucose combusts within a closed system (such as a calorimeter) and no work was performed as a result of that combustion, then a measurement of the thermal energy exchanged between system and surroundings represents the enthalpy (ΔH) of the reaction.

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Chapter 6
Energy Has Bias: Entropy (*S*)

In the presence of a gradient, energy undergoes exchange from one form to another (conversion) and/or from one place to another (transfer). Observations of energy exchange reveal undisputable characteristics that have never been disproven. Chief among these observations is that any concentration of energy has the natural tendency to spontaneously spread out or disperse over time. The term *concentrated energy* usually (but not always) implies both a system and its surroundings, where energy may be localized within and generalized without, respectively. When existent, the energy gradient is meaningful; the spontaneous direction is "downhill." The words "over time" offer no indication of the speed or the rate of energy dispersal. Be it nanoseconds or eons, if an energy gradient exists, it will eventually and spontaneously "flatten-out." It has been said that nature abhors a vacuum; another interpretation is that nature abhors a gradient (1).

6.1 Second Laws of Thermodynamics

Energy is distributed unequally throughout the Universe and the Earth, ourselves and our cells. Some areas contain high amounts of energy while other areas contain lower amounts. Unequal distributions of energy expose the potential for change, the presence of a gradient. When a gradient no longer exists, equilibrium is found (equilibrium can be defined as the absence of a gradient). Energy cannot spontaneously undergo further exchange at equilibrium. Unequal distributions of energy – the opposite of equilibrium – are described by the scenarios of nonequilibrium and far-from-equilibrium.

One of the second laws of thermodyamics (there are two) reveals that energy undergoes spontaneous exchange only in the "downhill" direction. This is an observation that has never been disproven. No one has yet witnessed the spontaneous "uphill" exchange of energy. Steam engines first typified this principle when it was recognized that they operated off or exploited a thermal gradient or temperature differential; heat dependently and spontaneously flows toward cold, never

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the opposite:

$$\text{hot} \rightarrow \text{cold}$$

In actuality heat is not a substance that "flows." Instead, an exchange of thermal energy is found, from heat source to heat sink: "When two objects are in thermal contact, the one that tends to spontaneously lose energy is at the higher temperature (2)". If you were sitting in a warm room with a hot cup of coffee, the warmth of the room would never serve to further increase the temperature of the coffee. A hot cup of coffee will always lose heat to a cooler room, until the coffee was room temperature (in fact, the temperature of a well-insulated room would ever-so-slightly increase as the coffee's heat dissipates to the room).

The engineer Sadi Carnot (1796–1832) was the first to recognize the potential and direction of heat exchange in terms of the performance of work by a heat engine. His analogy was to a waterfall in the turning of a mill wheel; "... we can compare with sufficient accuracy the motive power of heat to that of a fall of water ... the motive power of a fall of water depends on its height and on the quantity of liquid; the motive power of heat depends also on ... the difference of temperature of the bodies between which the exchange of [heat] is made." The physicist Rudolph Clausius (1822–1888) later understood that thermal energy exchanges were not at all consistent, depending heavily on the conditions at hand. It was Clausius who recognized heat in terms of a *temperature-dependent* rationale and a *configurational-dependent* rationale; the former is unavailable to perform work, the latter is useful and capable of undergoing conversion into work. Moreover, dispersed energy is unavailable energy. Below configurational energy is portrayed in the spontaneous context of concentration to dispersal:

$$\text{concentrated energy} \rightarrow \text{dispersed energy}$$

The concept of energy availability (i.e., concentrated energy) and unavailability (i.e., dispersed energy) allows us to begin to understand the second of the second laws of thermodynamics. In Table 6.1 the temperature differentials of three hypothetical heat engines are shown to be equivalent ($\Delta 475\,\text{K}$). Notice however that different heat source and heat sink temperatures result in three different so-called operational "efficiencies". The loss of heat (energy) also is a part of energy exchange.

Energy exchange is imperfect. When energy is spontaneously converted from one form to another the "value" or the usefulness of that energy is degraded because the

Table 6.1 The operational parameters of three hypothetical heat engines

Heat engine	Heat source (K)	Heat sink (K)	Difference (ΔK)	Efficiency (%)
1	773	298	475	61
2	843	368	475	56
3	2,773	2,298	475	17

Temperatures are in Kelvin (K = 273 + °C). Efficiency is rationalized as the difference in temperature between the heat source and heat sink divided by the heat source temperature. The apparent gradient, $\Delta 475\,\text{K}$, appears similar among engines, but the exchange of useful energy (i.e., efficiency) differs tremendously.

gradient has been permanently eroded. Moreover, when energy is transferred from one place to another, the move has a "cost." Clausius recognized that *all* energy exchanges are inefficient because not all heat (energy) undergoing conversion or transfer is available to perform useful work. In simple terms this is known as efficiency where input and output are different. In the world we live in, no exchange of energy is 100% efficient. The concept of less-than-perfect efficiency pretty much sums up the second of the two laws of thermodynamics:

$$\text{energy out/energy in} < 100\%$$

6.2 Energy Distribution

Efficiency is a *qualitative* concept, but more to the point, energy gradients conceal different *quantitative* capacities for the exchange of available energy. Note that engine no. 3 (Table 6.1) has the lowest capacity or ability to convert heat to work; it has the poorest efficiency as compared with engine nos. 1 and 2 even though the thermal gradient is identical for all three engines. Whenever energy undergoes exchange the capacity to do work also changes as dictated by the conditions at hand (e.g., heat source and heat sink temperatures). Clausius quantified the "lost" energy that was unavailable to perform work as the entropy:

$$S = \Delta \mathrm{H}/T$$

where S = entropy, $\Delta \mathrm{H}$ = heat source and heat sink differential, and T = heat source temperature.

While temperature differentials are of the utmost importance to mechanical engineers, thermal flow does not explain chemistry in its entirety. As has been previously mentioned, whether or not a chemical reaction is spontaneous cannot be determined by heat gained or lost by the system. Yet, whether discussing heat engines or chemical reactions, one thing is certain: when energy is found concentrated in a particular location there is a tendency for that concentrated energy to disperse or to spread itself out over time until equilibrium is reached, that is the bias of energy. Chemistry uses a different means of measuring the probability of energy distribution before and after a chemical reaction.

Every compound – reactant and product – has both a specific molecular distribution and a specific distribution of the quantity of energy within any given molecule. Molecular distribution describes positional entropy. The distribution of energy quanta among molecules is known as thermal entropy. As an example of each recall the open system house presented in Chap. 2 (Fig. 2.3), where the oxygen entering the warm house from the cold outside has different positional (inside it is part of an organized flow) and thermal (its temperature has increased) entropy. Other examples are evident. As will be demonstrated the carbon dioxide within your cells contains no more energy then it does when located within the bloodstream (each being 37°C). However, the positional energy of that carbon dioxide is different in

Table 6.2 The absolute entropy (S°) of some standard biological materials

Substance	S° ($J\,K^{-1}\,mol^{-1}$)
C	5.7
$C_6H_{12}O_6$	212.1
O_2	205.1
H_2	130.7
H_2O	69.9
CO_2	213.7

Simply put, entropy describes the number of ways that energy is distributed. The greater the entropy, the greater energy is dispersed or spread out throughout the compound, system, or surroundings (note that units are in Joules, not kilojoules).

terms of the partial pressure gradient between inside and out:

$$\text{high intracellular } PCO_2 \rightarrow \text{low extracellular } PCO_2$$

(Positional entropy also explains why air rushes out of a punctured bicycle tire.)

The absolute entropy for any given compound can be described in relative terms as the number of ways energy may be distributed within that compound (or system). The absolute entropy (S°) of some well-known biological compounds (molecules) at standard temperature is shown in Table 6.2.

The absolute entropy content of any given element or compound is of interest because it helps describe the *change in entropy* of a chemical reaction:

$$\Delta S = \text{entropy change}$$

The entropy is so essential to understanding energy exchange that the probability of spontaneous energy conversion and transfer is defined by entropy change. Indeed, some interpretations of the second law state explicitly that a positive change in entropy ($+\Delta S$) signifies spontaneity. If a spontaneous energy exchange takes place *within* a closed system, the entropy of that system always increases.

A simplistic way of acknowledging an increase in entropy for a chemical reaction is to look at the number of molecules in the reactants and products. More molecular products as compared with reactants indicate the potential for an increase in the number of ways molecular energy has been distributed; that is, as an increase in the entropy. Let us look at the formation of glucose from its elements. Is the formation of glucose from the elements in their standard state spontaneous?

$$6C + 6H_2 + 3O_2 \rightarrow C_6H_{12}O_6$$
$$15\,\text{reactant molecules} \rightarrow 1\,\text{product molecule}$$

By counting the reactant and product molecules it appears that the direction of the above reaction does not invoke a greater distribution or spreading out of molecular

energy. In fact, quite the opposite occurs. The reaction reveals a concentration of molecules from 15 molecular reactants into a one-molecule product. The reaction is not spontaneous.

Entropy change can be calculated from a more rigorous standpoint under standard conditions of temperature and pressure as:

$$\Delta S^{\circ}_{\text{reaction}} = S^{\circ}_{\text{products}} - S^{\circ}_{\text{reactants}}$$

Starting with the reactants C, H_2, and O_2 in their standard state, six atoms of carbon ($C; S^{\circ} = 34.44\,\text{J K mol}^{-1}$), six molecules of hydrogen ($H_2; S^{\circ} = 784.08\,\text{J K mol}^{-1}$), and three molecules of oxygen ($O_2; S^{\circ} = 615.3\,\text{J K mol}^{-1}$) have a sum entropy of $1,433.82\,\text{J K mol}^{-1}$. The entropy content of the product glucose is $212.1\,\text{J K mol}^{-1}$. These numbers can be substituted into the entropy equation and as predicted from counting the number of reactant and product molecules, the reaction is not spontaneous ($-\Delta S$):

$$\begin{aligned}
\Delta S^{\circ}_{\text{reaction}} &= S^{\circ}_{\text{products}} - S^{\circ}_{\text{reactants}} \\
\Delta S^{\circ}_{\text{reaction}} &= S^{\circ}_{\text{glucose}} - S^{\circ}_{\text{6C,6H2,3O2}} \\
\Delta S^{\circ}_{\text{reaction}} &= 212.1\,\text{J K mol}^{-1} - 1{,}433.82\,\text{J K mol}^{-1} \\
\Delta S^{\circ}_{\text{reaction}} &= -1{,}221.72\,\text{J K mol}^{-1}
\end{aligned}$$

It should not be a surprise that the above reaction is nonspontaneous. If you were to put carbon, hydrogen, and oxygen into a container, they do not spontaneously combine to form glucose ($C_6H_{12}O_6$). It takes energy to promote a nonspontaneous reaction.

The oxidation of one molecule of glucose and six molecules of oxygen (seven reactant molecules in total) to produce six molecules of carbon dioxide and six molecules of water (12 product molecules in total) suggests an increase in the number of molecular arrangements of products as compared with reactants. An increase in molecular distribution indicates entropy has increased. From a more rigorous perspective it is apparent that the entropy change for glucose oxidation is positive and therefore spontaneous ($+\Delta S$):

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2$$

Reactants	$S^{\circ}(\text{J K mol}^{-1})$	**Products**	$S^{\circ}(\text{J K mol}^{-1})$
$C_6H_{12}O_6$	212.1	$H_2O \times 6$	419.46
$O_2 \times 6$	1,230.6	$CO_2 \times 6$	1,282.2

$$\begin{aligned}
\Delta S^{\circ}_{\text{reaction}} &= 1{,}701.66\,\text{J K mol}^{-1} - 1{,}442.7\,\text{J K mol}^{-1} \\
\Delta S^{\circ}_{\text{reaction}} &= +258.96\,\text{J K mol}^{-1}
\end{aligned}$$

A positive entropy change within a system indicates a spontaneous process because energy has been dispersed over the course of the reaction (the bias of energy).

There are however plenty of examples where the entropy of a system can in fact decrease, indicating that energy concentration has taken place. As an aforementioned example, the opposite of glucose oxidation is photosynthesis where six molecules of carbon dioxide and six molecules of water (12 molecules in total) are concentrated into one molecule of glucose and six molecules of oxygen (seven molecules in total). The entropy change for photosynthesis is negative indicating a nonspontaneous process ($-\Delta S$):

$$6H_2O + 6CO_2 \rightarrow C_6H_{12}O_6 + 6O_2$$

Reactants	$S^\circ(\mathbf{J\,K\,mol^{-1}})$	**Products**	$S^\circ(\mathbf{J\,K\,mol^{-1}})$
$H_2O \times 6$	419.46	$C_6H_{12}O_6$	212.1
$CO_2 \times 6$	1282.2	$O_2 \times 6$	1,230.6

$$\Delta S^\circ_{\text{reaction}} = 1{,}442.7\,\text{J K mol}^{-1} - 1{,}701.66\,\text{J K mol}^{-1}$$
$$\Delta S^\circ_{\text{reaction}} = -258.96\,\text{J K mol}^{-1}$$

How is photosynthesis possible when the natural bias of energy is to undergo dispersal and not concentration? The answer is that photosynthesis requires energy to proceed, solar energy to be specific. And the extreme thermonuclear reactions that generate solar energy are associated with profound increases in entropy! Recall that for open and closed systems, exchanges of energy are taking place between the system and the immediate surroundings (the environment). If entropy is found to be reduced within a system – a nonspontaneous process – then the entropy of the surroundings must have necessarily increased to allow this to happen. Life changes its surroundings. Moreover, harnessing and exploiting energy exchange from the environment is "expensive." The concepts here are important ones. Concentrating energy in a specific location within a system takes place at the expense of increasing the distribution of energy somewhere else; the entropy of the surroundings necessarily increases, the energy of the universe disperses:

$$\Delta S_{\text{universe}} = \Delta S_{\text{system}} + \Delta S_{\text{surroundings}}$$

Entropy change can be negative or positive within a system. If entropy does decrease within a system, however, then the entropy of the surroundings must have increased to an extent larger than the reduction within the system. For *any* act of energy exchange within a system, the overall entropy of the universe *always* increases.

Two important concepts require emphasis: (1) heat is a product of energy exchange and (2) positive entropy changes ($+\Delta S$; energy dispersal) also result from energy exchange, with entropy being distinct from heat (Fig. 6.1). But make no mistake, heat and entropy are related. Indeed, entropy changes are typicall portrayed in association with temperature (T) as:

$$T\Delta S$$

Based within these two concepts, a more complete knowledge of life's matter and energy exchanges requires more than the measurement of heat exchanged, entropy

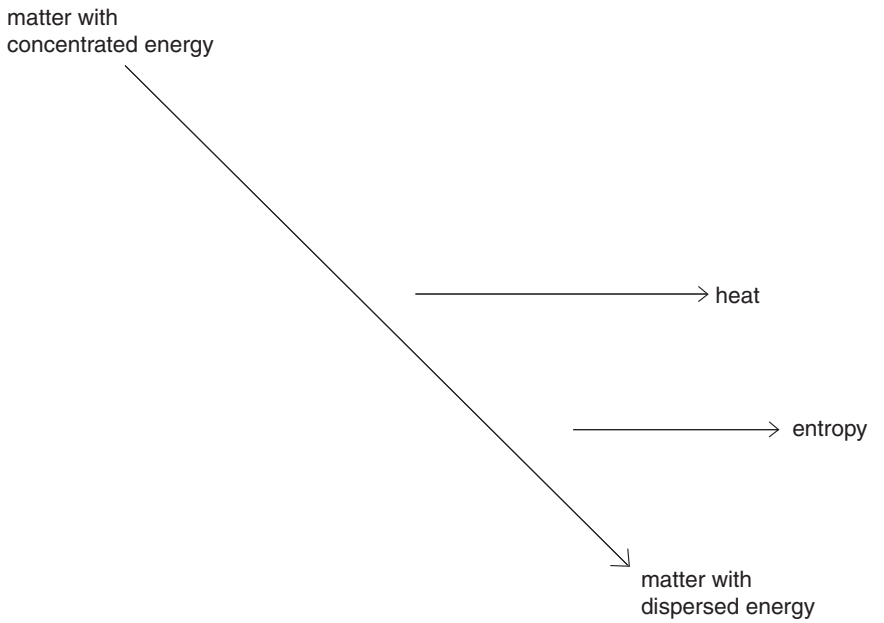

Fig. 6.1 A spontaneous gradient is shown between concentrated energy and dispersed energy. As energy undergoes spontaneous exchange within a system (conversion and transfer) increases in both heat and entropy are founded. In this example it is the heat and the entropy of the surroundings that increases

too must be accounted for. "The heat exchange between the system and its surroundings is identical with the change in entropy only under the special conditions of complete reversibility . . . and in this instance the organism would exhibit a net absorption of heat instead of heat loss (3)." As is demonstrated throughout this text the biochemical reactions of life are thought to be irreversible as part of an open system where, ". . . not all the heat produced inside the system will leave, but a part of it may be used for some irreversible processes (4)." Thus, the costs of living are best quantified when both heat and entropy are accounted for (to the contrary entropy has been recognized in other texts, "as the everyday concept of heat (5)").

Enthalpy changes (ΔH) between system and surroundings are accounted for as the difference in thermal energy between the two. Yet *calculating* entropy changes for both a system and its surroundings is a difficult endeavor because entropy cannot be directly measured. Because of this difficulty another thermodynamic variable will be introduced to succinctly describe whether or not a chemical reaction can take place spontaneously within a system without direct knowledge of entropy changes in the surroundings. Before this new variable is explained it must be reemphasized that entropy provides a description of energy distribution but it is not a representation of energy that is available for useful purposes. Any machine, whether mechanical or biological, cannot operate off of an entropy gradient.

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Chapter 7
The Energy Exchange Gradient: Gibbs Energy (*G*)

Perplexed about entropy? You are not alone. Josiah Willard Gibbs (1839–1903) understood this confusion all too well, almost 150 years ago, "...a method involving the notion of entropy, the very existence of which depends upon the second law of thermodynamics, will doubtless seem to many far-fetched, and may repel beginners as obscure and difficult of comprehension. This inconvenience is perhaps more than counter-balanced by the advantages of a method which makes the second law of thermodynamics so prominent, and gives it so clear and elementary an expression.... (1)." Gibbs profoundly altered our understanding of chemistry with his insights. At a time when it was mostly a philosophical concept, Gibbs went straight for application and made entropy relevant. Rapid advancements and heralded achievements in the chemical sciences ensued.

Enthalpy (H) is a measure of the internal energy of a system, but this energy has an availability issue; some of that energy is useful, some is not. Enthalpy also provides no information about the spontaneity of energy exchange. Entropy (S) does indicate the probability of energy exchange (i.e., spontaneous, $-\Delta S$, or nonspontaneous, $+\Delta S$), but it is not useful energy and so it provides little information on the quantity of energy that is available to perform work. Energy that is available to perform useful work is known as Gibbs energy, symbolized as G. Gibbs energy has also been termed *free energy.* Yet energy is anything but "free" and so that term will not be used here.

7.1 ΔG°

Like enthalpy (ΔH) and entropy (ΔS), the Gibbs energy (ΔG) of formation for many chemical compounds is available in most chemistry texts. The information in Table 7.1 is provided using standard conditions of temperature and pressure (298 K, 1 atm).

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Table 7.1 Standard Gibbs energy of formation (ΔG°) for some well-known biological materials

Substance	ΔG° (kJ mol^{-1})
C	0
$C_6H_{12}O_6$	−910.52
O_2	0
H_2	0
H_2O	−237.13
CO_2	−394.36

Similar to the [products–reactants] methodology seen previously with ΔH and ΔS, the change in Gibbs energy of a given chemical reaction is defined as:

$$\Delta G^\circ_{\text{reaction}} = \Delta G^\circ_{\text{products}} - \Delta G^\circ_{\text{reactants}}$$

Unlike enthalpy and entropy it is the change in Gibbs energy (ΔG) that clearly describes energy exchange in terms of both *spontaneity and amount* of available energy. Indeed, this information is often the focus of most biochemistry texts. A spontaneous reaction is defined as having a negative Gibbs energy; in other words, useful energy has been taken out of or subtracted from the system.

$$\text{System} \rightarrow \text{Surroundings}(-\Delta G)$$

As with enthalpy and entropy the symbol Δ represents a difference between the beginning and end to chemical energy exchange, but nothing else. Within a closed system what takes place in-between the start of a reaction until final product formation at equilibrium is irrelevant; ΔG is not dependent on time and provides no information of reaction rate. What ΔG does provide is essential information about the direction and the amount of useful energy exchanged during a chemical reaction; that is, ΔG describes the chemical gradient found between reactants and products (Figs. 7.1–7.4). ΔG can also be represented as a force that many years ago was portrayed as a *chemical affinity* that caused chemicals to react.

As a generality, spontaneity describes molecular breakdown where products outnumber reactants. For glucose oxidation then, 7 reactants → 12 products. Let us look at the Gibbs energy change for the spontaneous oxidation of glucose with a more rigorous examination (from Table 7.1):

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2$$

The ΔG° of reactants involves one molecule of glucose (−910.52 kJ mol^{-1}) and six molecules of oxygen (6×0 kJ mol^{-1} = 0 kJ mol^{-1}). The ΔG° of products involves six molecules of water (6×-237.13 kJ mol^{-1} = −1,422.78 kJ mol^{-1}) and six molecules of carbon dioxide (6×-394.36 kJ mol^{-1} = −2,366 kJ mol^{-1}).

$$\begin{aligned}
\Delta G^\circ_{\text{reaction}} &= \Delta G^\circ_{\text{products}} - \Delta G^\circ_{\text{reactants}} \\
\Delta G^\circ_{\text{reaction}} &= (-1{,}422.78\,\text{kJ mol}^{-1} + -2{,}366\,\text{kJ mol}^{-1}) \\
&\quad -(-910.52\,\text{kJ mol}^{-1} + 0\,\text{kJ mol}^{-1}) \\
\Delta G^\circ_{\text{reaction}} &= -2{,}878.4\,\text{kJ}
\end{aligned}$$

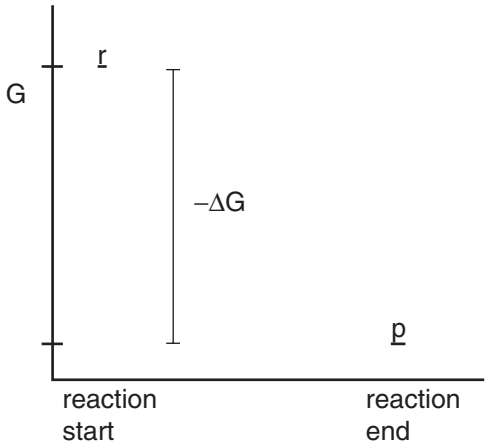
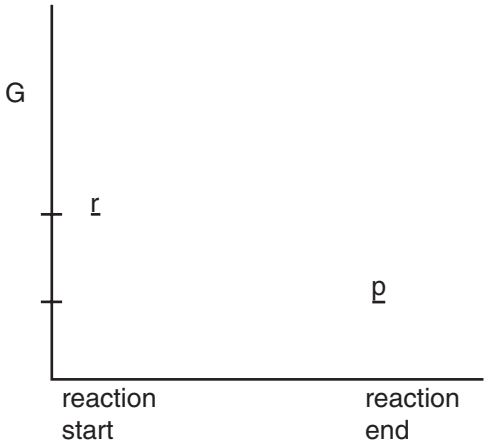


Fig. 7.1 Notice there is no visible pathway connecting reactants (r) to products (p), the exact path taken from reactants to products is irrelevant. The available information does however indicate that the Gibbs energy of products at the end of the reaction is much less than that of reactants at the start of the reaction. Thus, the driving force for the above reaction between reactants and products is spontaneous or downhill ($-\Delta$G) and rather large (i.e., a steep high → low gradient)

Fig. 7.2 Another spontaneous reaction ($-\Delta$G) is shown. In this example, the difference in Gibbs energy, the driving force, the gradient between reactants (r) and products (p) is less then that of Fig. 7.1



7.2 Energy Unification

Up till now the first and second laws of thermodynamics have been treated separately. Once Gibbs energy is considered, the first and second laws can be united providing the proof for energy conservation. For any chemical reaction, the enthalpy change (ΔH), the change in the arrangement of energy (ΔS) and the available energy to perform work (ΔG) can be succinctly unified in the following equation (Note: Gibbs energy changes are dictated by enthalpy and entropy):

$$\Delta \mathrm{G} = \Delta \mathrm{H} - T\Delta S$$

where ΔG = Gibbs energy change, ΔH = enthalpy change, T = temperature, and ΔS = the entropy change.

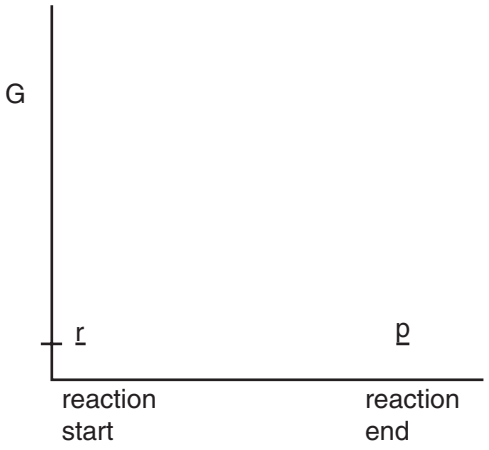


Fig. 7.3 In this figure, equilibrium is shown, where the Gibbs energy is the same for both reactants (r) and products (p). The ΔG for the reaction is zero [0]; there is no gradient

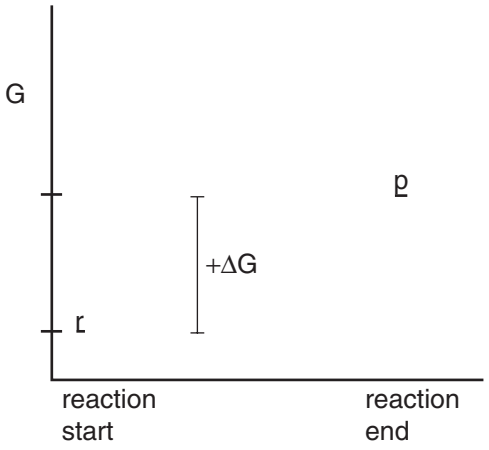


Fig. 7.4 A reaction is shown where the Gibbs energy of products (p) is larger than that of reactants (r) + ΔG. The gradient reveals a non-spontaneous or uphill reaction (the driving force is high ← low). In this example it would *require* energy to convert reactants into products

Based upon earlier calculations of ΔG, ΔH, and ΔS, here is the mathematical proof of energy conservation for the oxidation of glucose:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2$$

where ΔG = energy that is available to do work ($-2{,}878.4\,\text{kJ mol}^{-1}$), ΔS = energy that is unavailable to do work ($0.258\,\text{kJ K mol}^{-1}$), ΔH = available energy + unavailable energy ($-2{,}801.6\,\text{kJ mol}^{-1}$), and $\Delta G = \Delta H - T\Delta S$.

$$-2{,}878.4\,\text{kJ mol}^{-1} = -2{,}801.6\,\text{kJ mol}^{-1} - (298\,\text{K})(0.258\,\text{kJ K mol}^{-1})$$
$$-2{,}878.4\,\text{kJ mol}^{-1} = -2{,}878.4\,\text{kJ mol}^{-1}$$

(Note: slight discrepancies can occur because of the number and rounding of decimal places.)

7.3 $\Delta G^{\circ\prime}$: Closed Systems Under Standard Conditions

Entropy – spontaneous energy distribution – is thought to overwhelmingly dictate the change in Gibbs energy during energy exchange (1–3). Yet enthalpy also plays a role. Changes in enthalpy (ΔH) can be measured. Changes in entropy (ΔS) however cannot. Thankfully, when entropy dictates energy exchange, product and reactant concentrations can be measured before and after a chemical reaction, and Gibbs energy availability is associated with the ratio of product-to-reactant concentrations. Spontaneous closed system reactions reveal a negative Gibbs energy change ($\Delta G < 0$) and a positive entropy change ($\Delta S > 0$); products outnumber reactants so that the ratio of products to reactants is greater than 1.0 (>1.0). Note that measurement of the Gibbs energy change takes place under strict conditions of temperature, pH, ionic strength and molar concentrations of product and reactant:

$$\Delta G^{\circ\prime} = -RT \ln \text{products/reactants}$$

where $\Delta G^{\circ\prime}$ = Gibbs energy change at molar starting concentrations,$^{\circ}$ = standard temperature (298 K) and pressure (1 atm), prime = pH of 7.00, R = gas constant at 0.008289 kJ $mol^{-1}\,{}^{\circ}C^{-1}$, T = temperature, ln = natural logarithm, and products/reactants = ratio of products to reactants.

Another expression of this equation is in $\log_{10}$ form:

$$\Delta G^{\circ\prime} = -2.303RT \log_{10} \text{products/reactants}$$

Up to this point chemical reactions have been displayed as occurring in one direction only, from left to right as reactants → products:

$$A + B \rightarrow C + D$$

In reality many reactions are reversible so that a reaction can proceed in both directions:

$$A + B \rightleftharpoons C + D$$

But regardless of the starting direction, reactions rarely proceed naturally to a point where either the reactant or product is eliminated, some amount of reactant and product almost always remains (Fig. 7.5). The end point of a given reaction is known as equilibrium (recall this point as an absence of the gradient). At equilibrium the reaction is not completed in the true sense of the word *stop*. At equilibrium both the forward and reverse *rates* of the chemical reaction are equivalent and the final concentrations of product and reactant do not change over time.

The ratio of product to reactant concentration at equilibrium is known as the equilibrium constant or K'_{eq}:

$$K'_{eq} = [C][D]/[A][B]$$

where K'_{eq} = equilibrium constant (under standard conditions), [ ] = concentration, C and D = products, and A and B = reactants.

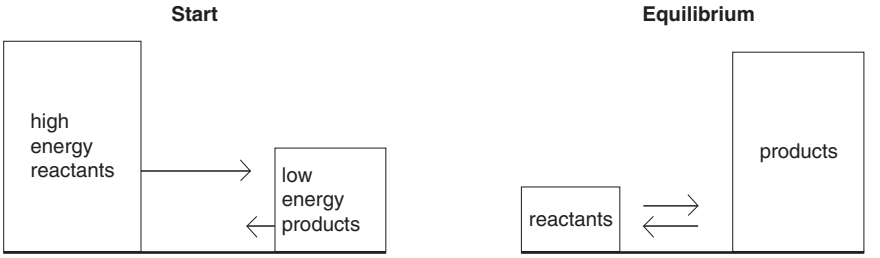


Fig. 7.5 At the start of a reaction (*left*) reactants outnumber products; the length of the horizontal arrows indicate that the reaction is poised to go to the right ($-\Delta G$). At equilibrium (*right*) the horizontal arrows denote that both the forward and reverse reaction rates are equal, where final product concentrations outnumber reactants and $\Delta G = [0]$

What dictates end-point concentrations of products and reactants (i.e., K'_{eq})? The answer is entropy, where the greatest distribution of energy is found among the remaining concentrations of products and reactants (2, 3). Gibbs energy and the equilibrium constant are related. Table 7.2 denotes the relationship between Gibbs energy change ($\Delta G^{\circ\prime}$) and the equilibrium constant (K'_{eq}) for a closed system.

The equilibrium constant is related to the change in Gibbs energy as:

$$K'_{eq} = 10^{\Delta G^{\circ\prime}/2.303RT}$$

and as:

$$K'_{eq} = e^{-\Delta G^{\circ\prime}/RT}$$

Table 7.2 The relationship between the equilibrium constant (K'_{eq}) and Gibbs energy availability ($\Delta G^{\circ\prime}$)

K'_{eq}	$\Delta G^{\circ\prime}$ (kJ mol^{-1})
10^{-5}	28.53
10^{-4}	22.84
10^{-3}	17.11
10^{-2}	11.42
10^{-1}	5.69
1.0	0 (equilibrium)
10^{1}	−5.69
10^{2}	−11.42
10^{3}	−17.11
10^{4}	−22.84
10^{5}	−28.53

Note that a negative $\Delta G^{\circ\prime}$ is related to a positive K_{eq} (and vice versa). At equilibrium, no Gibbs energy is available

Suppose the $\Delta G^{\circ\prime}$ for a reaction is $-10\,\text{kJ mol}^{-1}$, what would the equilibrium constant be?

$$\begin{aligned} R &= 0.0082898\,\text{kJ mol}^{-1}\,\text{deg}^{-1} \\ T &= 298\,\text{K} \\ RT &= 2.47\,\text{kJ mol}^{-1} \\ K'_{eq} &= e^{-(-10\,\text{kJmol})/2.47\,\text{kJmol}} \\ K'_{eq} &= e^{4.04} \\ K'_{eq} &= 56.8 \end{aligned}$$

In the above example a K'_{eq} of 56.8 exceeds 1.00, indicating that many more products to reactants are found at equilibrium. Most reactants have been converted to product (reactants $\rightarrow$ products); the reaction is spontaneous.

What would the equilibrium constant be if the $\Delta G^{\circ\prime}$ for a reaction is $+10\,\text{kJ mol}^{-1}$?

$$\begin{aligned} K'_{eq} &= e^{-(10\,\text{kJmol})/2.47\,\text{kJmol}} \\ K'_{eq} &= e^{-4.04} \\ K'_{eq} &= 0.0176 \end{aligned}$$

At a K'_{eq} of less then 1.00, few products and many reactants are found at equilibrium; this reaction is not spontaneous.

7.4 ΔG: Nonstandard Conditions

Conditions within a cell are not at all standardized to that of the laboratory (i.e., molar concentrations of reactants and products, 298 K, pH 7.0). Under nonstandard conditions, the change in Gibbs energy is symbolized as ΔG (not, $\Delta G^{\circ\prime}$). So how can the Gibbs energy of a biochemical reaction in a cell be determined when product and reactant concentrations may be completely different as compared with standardized conditions? Such a calculation requires the use of standard information about the chemical reaction ($\Delta G^{\circ\prime}$) along with the within-cell reactant and product concentrations (K'_{eq}) of the biochemical reaction (ΔG):

$$\Delta G = \Delta G^{\circ\prime} + 2.303RT \log K'_{eq}$$

To determine ΔG for a biochemical reaction within a cell, the first step is to determine $\Delta G^{\circ\prime}$ for the given chemical reaction under standard conditions. The next step is to measure the concentration of products and reactants inside the cell to determine the K_{eq} for the biochemical reaction.

As an example, under *standard conditions* (within the laboratory) a chemical reaction is completed as:

$$\begin{aligned}
\mathrm{A}+\mathrm{B} &\rightarrow \mathrm{C}+\mathrm{D}\\
[\mathrm{A}] &= 0.2\\
[\mathrm{B}] &= 0.2\\
[\mathrm{C}] &= 1.8\\
[\mathrm{D}] &= 1.8\\
K_{\mathrm{eq}} &= [\mathrm{C}][\mathrm{D}]/[\mathrm{A}][\mathrm{B}]\\
K_{\mathrm{eq}} &= [1.8][1.8]/[0.2][0.2]\\
K_{\mathrm{eq}} &= 81\\
\Delta \mathrm{G}^{\circ\prime} &= -2.303RT\log K_{\mathrm{eq}}\\
\Delta \mathrm{G}^{\circ\prime} &= (-5.688\,\mathrm{kJ\ mol}^{-1})(\log 81)\\
\Delta \mathrm{G}^{\circ\prime} &= (-5.688\,\mathrm{kJ\ mol}^{-1})(1.908)\\
\Delta \mathrm{G}^{\circ\prime} &= -10.85\,\mathrm{kJ\ mol}^{-1}
\end{aligned}$$

As $\Delta \mathrm{G}^{\circ\prime}$ indicates, this reaction is spontaneous.

Now imagine an identical reaction taking place in a cell. *Within a cell*, however, products and reactants are found to be different in concentration (nonmolar) as compared with the standard chemical reaction:

$$\begin{aligned}
[\mathrm{A}] &= 0.4\\
[\mathrm{B}] &= 0.4\\
[\mathrm{C}] &= 0.1\\
[\mathrm{D}] &= 0.1
\end{aligned}$$

Now the equilibrium constant is:

$$\begin{aligned}
K_{\mathrm{eq}} &= [\mathrm{C}][\mathrm{D}]/[\mathrm{A}][\mathrm{B}]\\
K_{\mathrm{eq}} &= [0.1][0.1]/[0.4][0.4]\\
K_{\mathrm{eq}} &= +0.0625
\end{aligned}$$

With different reactant and product concentrations the above reaction is not spontaneous ($K_{\mathrm{eq}} = +0.0625$). Recall however that the equation to determine the energy-exchange gradient for a biochemical reaction ($\Delta \mathrm{G}$) is different as compared with the standardized conditions of chemistry ($\Delta \mathrm{G}^{\circ\prime}$). In fact, both chemical and biochemical information is required:

$$\Delta \mathrm{G} = \Delta \mathrm{G}^{\circ\prime} + 2.303RT\log K'_{\mathrm{eq}}$$

if, $\Delta G^{\circ\prime} = -10.85\,\text{kJ mol}^{-1}$ and $K_{eq} = 0.0625$, and also, $2.303RT = 5.688$, then:

$$\Delta G = -10.85\,\text{kJ mol}^{-1} + (5.688)(\log 0.0625)$$
$$\Delta G = -10.85\,\text{kJ mol}^{-1} + (-6.85)$$
$$\Delta G = -17.7\,\text{kJ mol}^{-1}$$

In the above example the change in Gibbs energy is negative and so useful energy can be derived from this spontaneous cellular reaction ($\Delta G = -17.7\,\text{kJ mol}^{-1}$).

As has been demonstrated, reactant and product concentrations drastically affect the Gibbs energy availability of a given reaction. Within and without cells, conditions often change, varying reactant and product concentrations. Think of a muscle cell at rest and during exercise, for example, or any cell under fasting and feasting conditions. Figure 7.6 reveals how varying the reactant and product concentrations for a *single* biochemical reaction can affect Gibbs energy availability (review Figs. 7.1–7.4). Three different reactant (r) and product (p) concentrations are portrayed as indicated by the width of the two triangles at the bottom of Fig. 7.6.

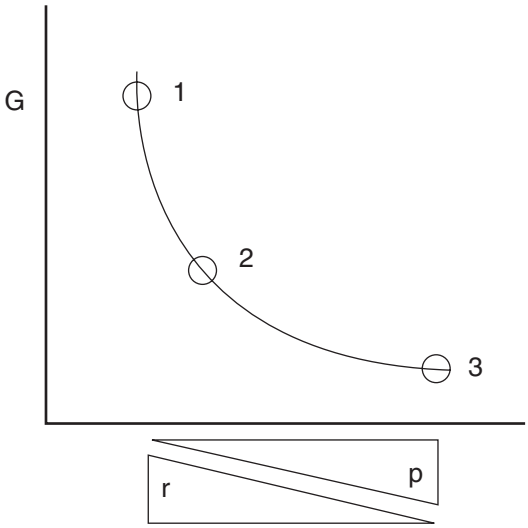


Fig. 7.6 In this example, a *curved line* portrays the Gibbs energy gradient and three different product:reactant slopes are *encircled*. Points 1 and 2 are both situated on a negative (downward) slope indicating spontaneity. The steepness of the slope identifies the size of the gradient. Slope 1 is far from equilibrium, where reactants greatly outnumber products; Gibbs energy availability is greatest here. Slope 2 at nonequilibrium reveals fewer reactants, more products, and a lower Gibbs energy availability as compared with slope 1. The line at point 3 reveals the reaction at equilibrium, where products outnumber reactants and the availability of Gibbs energy is zero. Gibbs energy availability is greatest when reactants (r) greatly outnumber products (p)

As will be demonstrated in the next section, reactant-to-product Gibbs energy gradients are not only exploited, but life takes an additional and active role in

maintaining or even building gradients – via the altering of product:reactant ratios – to optimize Gibbs energy availability. The "secret to life" is indeed a gradient.

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Part II
Bioenergetics

Chapter 8
Life's Currency: ATP

It is often stated, perhaps flippantly, that carbohydrates and fats are the fuel of cellular and physical work. But the energy held within these substrates is instead directly utilized to resynthesize the molecule ATP (adenosine triphosphate). Subsequently, it is ATP that provides the energy that allows cells to perform work. Cells could not labor against their immediate environment (and therefore survive) without ATP, the so-called "energy currency" of life.

8.1 ATP: Structure and Content

Given ATP's importance you will not find a lot of it within any living cell. At any moment the total amount of ATP within a muscle cell for example contains a rather meager supply, about 5.7 mmol of ATP per kilogram of fresh muscle (1). In fact, less then 10 g of ATP is contained within the whole human body at any given moment. Yet over the course of a day a resting human requires approximately their body weight in kilograms of ATP (2). Running a marathon also requires about a body weight's worth of ATP (3). Obviously, after eating, we do not make and store ATP to the extent that it doubles our body weight, then use that ATP throughout the day. It is apparent then that the moment-to-moment turnover of ATP – its incessant degradation and resynthesis – is rather extensive. ATP resynthesis via the aerobic and anaerobic metabolic pathways is a continuous, industrious, and life-engaging task.

A molecule of ATP ($C_{10}H_{16}N_5O_{13}P_3$) is shown in Fig. 8.1. Notice the four negative charges ($^{4-}$), providing ATP with its unique energy exchange qualities (Being negatively charged, ATP^{4-} is usually associated with the positively charged ion magnesium, forming the complex $MgATP^{2-}$. That complex is not shown; however magnesium's two positive charges (Mg^{2+}) bind two of ATP's negative charges).

The energy within ATP becomes available upon cleavage of its phosphate bond(s) and the subsequent reaction of these products with water, a process known as ATP

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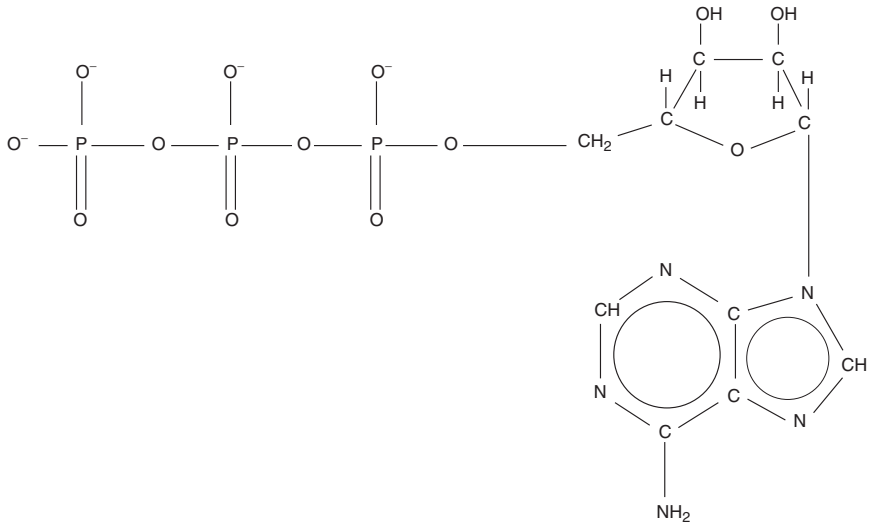

Fig. 8.1 In a neutral solution ATP exists as ATP^{-4}. Because like-charges repel, the adjacent negative charges invoke thermodynamic instability to the three bonded phosphates. In addition, the oxygen–phosphate double bonds continuously oscillate from top to bottom, causing oscillation of the negative charges as well and promoting what is called resonance stabilization. These two features – thermodynamic instability and resonance stabilization – ideally equip ATP for energy exchange purposes

hydrolysis:

$$ATP^{4-} + H_2O \rightarrow ADP^{3-} + HPO_4^{2-} + H^+ + \text{heat } (+\text{work})$$
$$ATP^{4-} + H_2O \rightarrow AMP^{2-} + 2HPO_3^{2-} + 2H^+ + \text{heat } (+\text{work})$$

One phosphate (HPO_4^{2-}) or two pyrophosphate ($2HPO_3^{2-}$) bonds can be broken and energy obtained during hydrolysis, resulting in adenosine diphosphate (ADP) and adenosine monophosphate (AMP), respectively. ATP often undergoes hydrolysis to perform some kind of cellular work. When work is performed heat loss is usually evident; the reaction by itself is exothermic.

8.2 ATP: Energy Exchange

Cellular metabolism is constantly producing and consuming protons (H^+) where consumption is denoted as an act of buffering. During these processes a good deal of heat is exchanged, none of which is directly related to mechanical work. A similar thermal appearance and disappearance scenario is found with the binding and unbinding of other ions such as calcium (Ca^{2+}) and magnesium (Mg^{2+}) with cellular proteins. For these reasons and more (composition of the solution and pH)

the enthalpy (ΔH) and Gibbs energy (ΔG) changes of ATP hydrolysis are heavily influenced by ATP's immediate surroundings.

When corrected for buffering, the standard molar enthalpy change (ΔH°) of ATP hydrolysis has been estimated at $-20\,\mathrm{kJ\,mol^{-1}}$ ($-4.8\,\mathrm{kcal\,mol^{-1}}$). Standard molar Gibbs energy change (ΔG°) has been estimated at $-31\,\mathrm{kJ\,mol^{-1}}$ ($-7.4\,\mathrm{kcal\,mol^{-1}}$) (4). At a standard temperature of 25°C (298 K) entropy changes (ΔS) would be $36.9\,\mathrm{J\,mol^{-1}}$. Altogether then, energy conservation for ATP hydrolysis is (note the units: kJ for ΔG and ΔH; J for ΔS):

$$\Delta \mathrm{G} = \Delta \mathrm{H} - T\Delta S$$
$$-31\,\mathrm{kJ\,mol^{-1}} = -20\,\mathrm{kJ\,mol^{-1}} - (298\,\mathrm{K})36.9\,\mathrm{J\,mol^{-1}}$$

As explained in the previous chapter, the Gibbs energy yielded by ATP hydrolysis within cells is dependent on the concentrations of [ATP] and [ADP], being greatest when reactants are *maintained* in greater concentration than are products; that is, when [ATP] is high and [ADP] low. Readers should note that these values vary slightly among references, also dependent on the laboratory from which they came:

$\Delta \mathrm{G} \approx -50\,\mathrm{kJ\ mol^{-1}}$ ($12\,\mathrm{kcal\ mol^{-1}}$) within a "typical" cell (5)
$\Delta \mathrm{G} \approx -64\,\mathrm{kJ\ mol^{-1}}$ ($15\,\mathrm{kcal\ mol^{-1}}$) in muscle at rest (6)
$\Delta \mathrm{G} \approx -55\,\mathrm{kJ\ mol^{-1}}$ ($13\,\mathrm{kcal\ mol^{-1}}$) in muscle during strenuous exercise (6)
$\Delta \mathrm{G} \approx -52$–$62\,\mathrm{kJ\ mol^{-1}}$ in muscle during anaerobic exercise (7)

How exactly is energy exchanged from ATP? One proposed hypothesis has it that the repulsion of the negatively charged Pi from ADP physically acts on a neighboring molecule or protein – a molecular "punch" so to speak – creating a conformational change of the recipient molecule or protein in the process. At the microscopic level this force performs actual mechanical work (8). It is of further interest that this "molecular pugilism" hypothesis appears to be the only existing explanation of the mechanism of how ATP coerces nonspontaneous reactions into becoming spontaneous.

8.3 ATP: Turnover Efficiency

ATP undoubtedly undergoes extensive turnover and because of this attempts have been made to estimate just which of the juxtaposed processes, ATP hydrolysis (utilization) or ATP resynthesis, is the more efficient. One review of the subject states that ~40% of heat loss occurs in the process of ATP utilization, with about 60% occurring during ATP resynthesis (4). To the contrary, it also has been stated that the energy available from ATP hydrolysis is used at close to 100% efficiency in a number of circumstances (8). Such relative statements are intriguing because of their diversity but it also must be kept in mind that from an absolute perspective, calculated enthalpy, Gibbs energy, and entropy values *are* far ranging under variable conditions. Moreover, a variation would be found in energy utilization (i.e., energy

Table 8.1 Efficiency (%) and source

ATP resynthesis	ATP hydrolysis	Reference
60% aerobic	49% muscle contraction	(9)
55% aerobic	–	(10)
36% anaerobic	–	
64% aerobic	41% muscle contraction	(11)
~67% aerobic	~ 40% mechanical work	(12)
56% glucose oxidation	20% glucose to fat storage	(13)
	11% glycogen storage	
49–52% fat oxidation	52% fat storage	
44% protein oxidation	4% protein synthesis	
	58% ion transport	
	26–35% mechanical work	
	65% aerobic (resting muscle)	(14)
	42% aerobic (fatigued muscle)	
60% aerobic	41–57% muscle contraction	(15)

Compare the above efficiencies with the following energy-exchange devices (from (16)): incandescent light, 5%; steam locomotive, 9%; gas engine, 25%; diesel engine, 35%; rocket engine, 48%; oil furnace, 65%

demand) by different types of ATP exchange devices that operate at different efficiencies; for example, ion pumps, muscle contraction, protein synthesis, etc.

The best estimations of metabolic efficiency are thought by some to take Gibbs energy considerations into account. Efficiency can indeed be defined by directly taking the actual work performed and dividing it by the direct amount of energy available (ΔG) to perform that work. But such methodology is not straight forward so that measurements of heat, oxygen uptake or nutrient intake have instead been used. Table 8.1 was created from sources that not only utilized several indirect measurement methodologies, but also employed several biochemical assumptions.

8.4 ATP Utilization (Energy Demand)

ATP is perhaps best known for its role in energy exchange to promote unfavorable biochemical reactions – as long as the Gibbs energy change of spontaneous ATP hydrolysis exceeds that of the nonspontaneous biochemical reaction. As an example, consider the phosphorylation of glucose. Upon entering a cell a phosphate (Pi) is attached to glucose at its sixth carbon (becoming glucose-6-phosphate). This phosphorylation prevents glucose from traversing back through the cell membrane and prepares it for further metabolic activity. The reaction and its Gibbs energy change is:

$$\text{Glucose} + \text{Pi} \rightarrow \text{glucose-6-phosphate} (\Delta G^{\circ\prime} = +13.8\,\text{kJ}\,\text{mol}^{-1})$$

The $+\Delta G^{\circ\prime}$ of glucose phosphorylation indicates a nonspontaneous reaction, but when coupled to ATP hydrolysis the reaction proceeds. To determine if ATP hydrolysis has the energy required to promote such a coupled reaction, the Gibbs

energy of the two chemical reactions are summed. If a negative Gibbs energy change is attained ($-\Delta$G), the reaction proceeds. The coupling of ATP hydrolysis to glucose phosphorylation is shown below (in cells an enzyme known as *hexokinase* is required):

Glucose + Pi → glucose-6-phosphate	$(\Delta G^{\circ\prime} = +13.8)$
ATP + H_2O → ADP + Pi	$(\Delta G^{\circ\prime} = -30.6)$
total	$\mathbf{(\Delta G^{\circ\prime} = -16.8\,kJ\,mol^{-1})}$

ATP is used in a multitude of roles that may include:

Biosynthesis: The cellular construction of fats, carbohydrates, and proteins from carbon-, hydrogen-, oxygen-, and nitrogen-containing compounds requires energy in the form of ATP. Biosynthesis, especially of complex proteins, is thought to be a costly process.

Molecular transport: ATP, with the help of cellular membrane proteins, fuels the export and import of materials and ions into and out of cells. Figure 8.2 reveals the actions of a sodium-potassium ion pump on the external bi-lipid membrane of a cell.

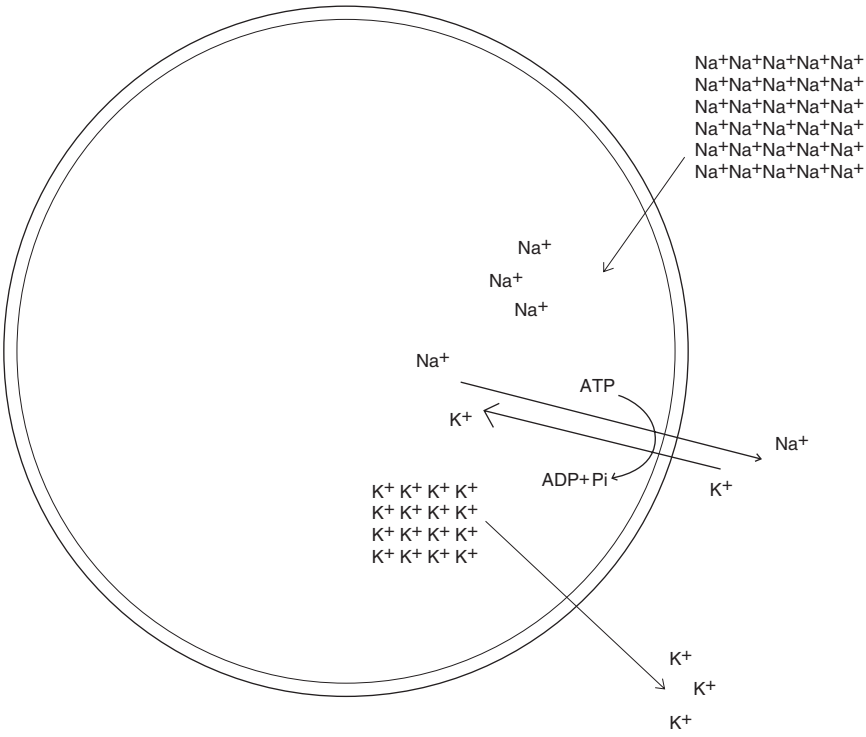

Fig. 8.2 Sodium [Na^+] and potassium [K^+] ion gradients are shown across a cells bilipid external membrane. The Na^+-K^+ ATPase (in black) is a cellular pump that spans the cell membrane and moves these ions against their respective gradients; energy in the form of ATP hydrolysis is expended to accomplish this process. A significant portion of a cell's total energy expenditure comes from the maintenance of ion gradients

The pump is known as a $Na^+ - K^+$ ATPase where the energy of ATP hydrolysis is used to move ions against their downhill gradients.

Intracellular signaling: Proteins known as kinases are triggered on and off by the actions of ATP. ATP itself can be converted into cyclic AMP, a molecule that signals a number of intracellular events that includes calcium transport.

Extracellular signaling (17): Nerve cells release molecules of ATP that can affect the metabolic actions of other cells. ATP from red blood cells influences the tone of smooth muscle cells that surround arteries and veins that in turn effects blood flow (18).

Motility: A highly organized network of protein pathways (also playing the role of cyto-skeleton) resides in cells that allow other protein molecular motors to literally "walk" along; ATP powers the locomotive process (19).

Ergogenic aid: It appears possible that ingesting ATP in tablet form may have ergogenic effects (though the mechanism of this effect is not understood) (20).

8.5 ATP Resynthesis (Energy Supply)

As will be demonstrated in greater detail in subsequent chapters, ATP undergoes resynthesis via several metabolic formats. Each of these three formats of metabolism is recognized here as an energy exchange device that couples the uphill (nonspontaneous) resynthesis of ATP from a variety of reactants:

aerobic respiration (21, 22):

$$ATP^{4-} + H_2O + \text{heat} \leftarrow ADP^{3-} + HPO_4^{2-} + H^+ (+\text{work})$$

anaerobic glycolysis (21, 22):

$$ATP^{4-} + H_2O + \text{heat} \leftarrow ADP^{3-} + HPO_4^{2-} (+\text{work})$$

creatine phosphate (CP) (21–24):

$$ATP^{4-} + H_2O \leftarrow ADP^{3-} + \text{creatine} - P^{2-} + H^+ (+\text{work})$$

Notice the discrepancies in the three methods of resynthesizing ATP: aerobic respiration consumes an inorganic phosphate (HPO_4^{2-} or Pi) and a hydrogen ion (H^+); anaerobic glycolysis consumes an inorganic phosphate but not a hydrogen ion; the breakdown of creatine phosphate (creatine-P^{2-}) does not produce as much heat as aerobic respiration and anaerobic glycolysis, nor does it consume an inorganic phosphate (Pi) but it does consume a hydrogen ion.

Because changes in pH (H^+ concentrations) help drive ventilation, the above information allows us to model the changes that occur with ventilation in respect to the utilization of the three formats of metabolic energy exchange. As an example, ATP hydrolysis results in an increase in H^+ production but aerobic respiration consumes these ions as part of ATP resynthesis. Based on this information it can be

surmised that the increase in ventilation during easy to moderately easy exercise is mostly due to neural mechanisms; the precise matching of ventilation rates with the metabolic rate is termed *hyperpnea*, when metabolic rate is measured solely as O_2 uptake. As exercise intensity increases, a greater rate of ATP hydrolysis is required with a concomitant increase in the rate of H^+ production. However, higher exercise intensities are fueled to some degree by anaerobic glycolysis that does not consume H^+; a build-up of H^+ subsequently takes place driving ventilation upward into a state of hyperventilation. It has traditionally been thought that H^+ comes from the buffering of lactic acid but this explanation is in reality somewhat unacceptable. Indeed, it is the anaerobically supported turnover of ATP, not lactic acid production per se, that is mostly responsible for changes in pH (21, 22). Hyperventilation has been used to identify the onset of anaerobic metabolism as a contributing factor to aerobic metabolic rates (25).

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Chapter 9
Metabolism as an Energy-Exchange Device

The metabolic breakdown of food is typically depicted as a spontaneous energy-releasing act of energy exchange (recall that the aerobic oxidation of glucose starts with seven molecules – $1C_6H_{12}O_6, 6O_2$ – and ends with $12 - 6H_2O, 6CO_2$). But the metabolic resynthesis of ATP requires energy and so is nonspontaneous. The metabolic biochemical pathways couple these two exchanges (Fig. 9.1). As an energy-exchange device, metabolism represents a biological machine of sorts, a marvel of engineering with moving parts and all.

Recall, $\Delta G^{\circ\prime}$ reveals Gibbs energy availability within a closed system under standard conditions, it is a descriptor of the force behind chemical reactions (Figs. 7.1–7.4). ΔG describes this *force* for nonstandardized individual biochemical reactions within cells. Single biochemical reactions are however often "stringed together" forming a continuous metabolic pathway where the biochemical product of one reaction becomes the reactant of another, then another, and so on until a final metabolic product is produced. Energy conversion takes place, from one form of chemical energy (glucose and fat) to another (ATP). In addition, energy transfer also occurs, being described as a *flow* from one place to another (from the start to the end of a metabolic pathway, and connecting intimately with every enzyme in between). From this perspective, a metabolic pathway is itself an open system comprised of linked-together individual biochemical open systems. Energy exchanges are demonstrated in the context of the kinetic interactions among these open systems entailing a coupling of forces and flows (1, 2). Energy exchanges within and without an active and open metabolic system (pathway) are costly in that during the process energy degradation and dissipation are irreversible (i.e., permanent) (1–3). Energy and materials are required to maintain a gradient that irreversibly expends energy. As long as a continuous supply of matter and energy are made available, life's energy exchanges flourish.

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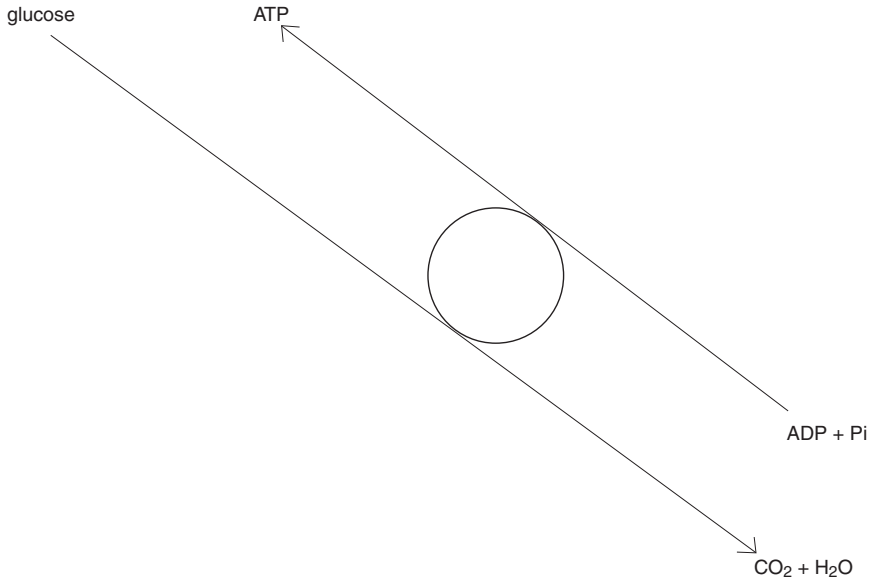

Fig. 9.1 The spontaneous (downhill) metabolic oxidation of glucose $\rightarrow CO_2 + H_2O$ is coupled to the nonspontaneous (uphill) resynthesis of ATP from ADP and Pi. Both exchanges result in the expenditure of energy.

9.1 Metabolic Power: Force and Flow

Aerobic metabolic pathways utilize oxygen; anaerobic metabolic pathways do not. As an energy-exchange device the operation of a metabolic pathway comes at the expense of Gibbs energy degradation, not *of* the system, but within the metabolic reactions catalyzed *by* the system (1). What does this mean? Consider the example of a two-stroke and four-stroke gasoline-powered engine. The energy contained within gasoline (as part *of* the system) is no different whether it fuels a two- or four-stroke motor. As energy-exchange devices, however, each engine converts the chemical energy of gasoline into mechanical force somewhat differently (energy exchange *by* the system). In similar fashion, energy exchange by the aerobic and anaerobic metabolic pathways also comes at a cost, but the ATP these pathways resynthesize (of the system) does not differ in terms of energy content.

An automobile engine helps convert the energy of gasoline into forward momentum. When idling the conversion into forward momentum does not take place, yet the engine still demands energy to maintain its operational status. A functional metabolism or metabolic rate also demands an incessant exchange of matter and energy throughout its system and likewise necessitates a continuous input of energy (Fig. 9.2).

Energy-exchange devices irreversibly consume energy at the expense of exchanging heat with the surroundings. The aerobic and anaerobic metabolic pathways are energy-exchange devices and as such produce heat as a part of *energy*

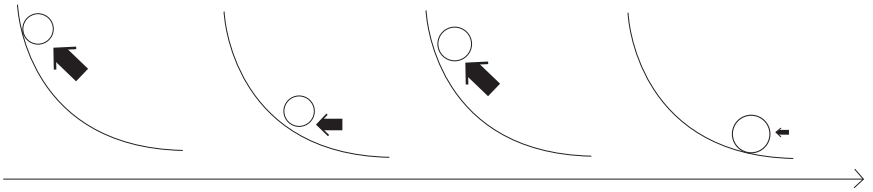

Fig. 9.2 Four independent biochemical reactions are portrayed as part of a complete metabolic pathway (each reaction requires a separate enzyme). The gradient for each reaction is displayed as a *curved line* (see Fig. 7.5). The forces and flows of metabolic power are demonstrated as follows: (1) force: the size of each of the four *thick short arrows* denotes the amount of energy required to maintain each biochemical reaction in nonequilibrium or far-from-equilibrium and (2) flow: the *long thin arrow* at the *bottom* of the figure reveals an organized flux of metabolic reactants and products within, through, and without the metabolic pathway, also with obligatory energy expenditure

conversion. In this regard heat can be used to quantify energy expenditure. However, bioenergetic descriptions of the metabolic pathways also must account for the forces and flows behind *energy transfer* too in which entropy also plays a role.

Recall that for closed systems emphasis is placed on the difference between the beginning and end points of energy exchange, not the path taken or the rate of exchange. To the contrary, Fig. 9.2 demonstrates fluxes throughout an open system where time and the extent of metabolic product formation must be taken into consideration. Simply put, metabolic forces and flows affect energy exchange and in-turn, energy expenditure. Metabolic forces and flows are aptly described in the context of exergy:

$$\partial G \partial \xi^{-1} = \text{exergy}$$

where ∂ = the rate of exchange, G = Gibbs energy ("force"), and ξ = the extent of metabolic product formation from reactants (product/reactant "flows") (4)

In a simplistic format:

$$\text{exergy} = \partial G$$

Exergy losses ($-\partial$G) – the degradation and dissipation of exergy in the generation of metabolic power – are founded as heat and entropy production, respectively (1, 2). This duality – heat and entropy production – is an important one, because in a closed system reaction, combustion in a bomb calorimeter, for example, internal energy conversion produces heat that diffuses to the surroundings and serves to increase the entropy of the environment. However, as Gibbs energy and heat (energy) undergoes transfer throughout an open metabolic pathway, internal entropy, along with heat production, is the result (1–3). A generalization is apparent: energy conversion from one form to another reveals heat production, energy transfer from one place to another can be better associated with an increase in entropy (i.e., positional entropy). When all metabolic energy exchanges are considered, energy is expended from the system as heat and entropy. Because internal and/or external conditions often change during metabolic energy exchange, the rates of work, heat, and entropy production may likewise differ discordantly (Fig. 9.3).

As Fig. 9.3 indicates, care must be taken when comparing systems where work may or may not be performed, heat is produced, and entropy may increase or

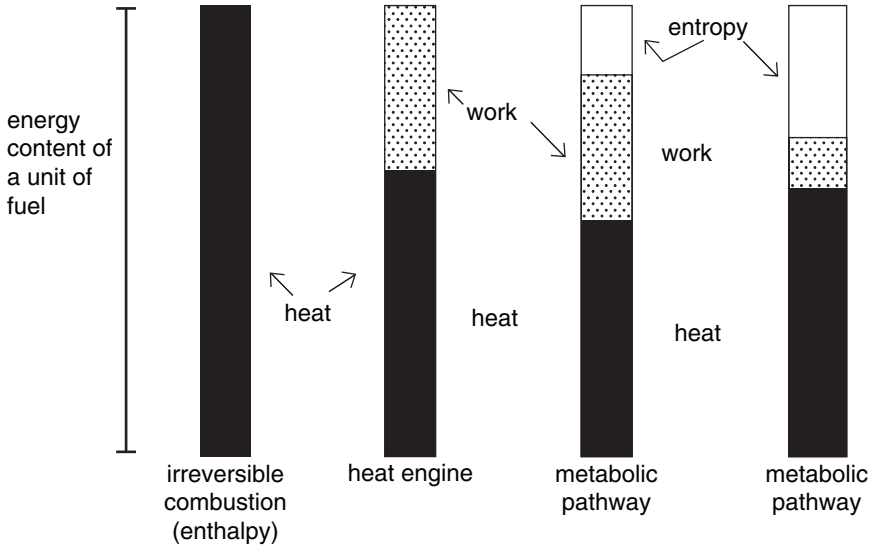

Fig. 9.3 From *left* to *right*: (1) A fuel undergoes complete and irreversible combustion in a closed system and all energy is expelled as heat, the enthalpy change (ΔH) indicates the internal energy content of that fuel (*left bar*). Because this heat is not useful it is thought to contribute solely to increasing environmental entropy. (2) A heat engine is able to transfer some thermal energy to work (*second bar* from *left*; work is reversible). (3 and 4) For these two open metabolic systems useful energy ($-\partial$G) is degraded as heat and entropy. Variance in the amounts of work, entropy and heat expended are dependent on internal and external conditions. Adapted from Hammerstedt and Lovrien (5)

decrease because metabolic energy expenditure, when quantified as work and heat production, is often absent the entropy component. Energy "costs" consist of the expenditure of both heat and entropy; heat as thermal energy, entropy as energy distribution or dispersion (It also must be recognized that there are dissenting opinions. For example, entire texts have been devoted to the notion that heat and entropy are one and the same (6). Here, heat and entropy are independently regarded as separate forms of energy, but they are no doubt related). Internal entropy production within a metabolic pathway (system) is always positive. However, the exchange of entropy with the surroundings can be positive, negative or zero (3). In fact, when exchange with the surroundings is considered, it was originally conceived that the metabolic system imports *negative entropy* (7).

9.2 Negative Entropy (?)

In his pocket-sized text, "*What is Life*?," Nobel-winning physicist Erwin Schrodinger (1887–1961) initiated discussion on the term he coined *negative entropy* (7):

> How does the living organism avoid decay? The obvious answer is: By eating, drinking, breathing . . . the technical term is metabolism. The Greek word [for metabolism] means change or exchange. Exchange of what? . . . everything that is going on in Nature means an increase of the entropy of the part of the world where it is going on. Thus a living organism continually . . . produces positive entropy – and thus tends to approach the state of maximum entropy, which is death. It can only keep aloof from it, i.e. alive, by continually drawing from its environment negative entropy. . . . What an organism feeds upon is negative entropy.

Much ado has arisen from Schrodinger's use of the term *negative entropy*. What exactly is meant by this? First and foremost, negative entropy is a concept that Schrodinger applied to open as opposed to closed systems. Our exchange of negative entropy with the environment suggests the consumption of concentrated energy (food for example). Negative entropy has also been thought of as stored energy (8). Others have characterized negative entropy (or negentropy) with system organization (9). More simply, entropy depicts useless not useful energy. Schrodinger's use of the term *negative entropy* likely came about with his understanding that entropy exchange often dictates Gibbs energy availability during energy transfer (10, 11). Thus, exergy degradation ($-\partial G$) perhaps represents a more rational explanation of the concept behind negative entropy exchange. Whichever the choice, within an open system, "The second law of thermodynamics requires that if there are any processes underway in the system, the quality of the energy in that system will degrade" (3).

The concept of exergy (negative entropy) is applied within this text in Chap. 10 to describe how nonspontaneous metabolic reactions are promoted and in Chaps. 12–16 to affectively separate anaerobic from aerobic energy exchange during the complete oxidation of glucose when a measurement of oxygen uptake is used to estimate energy expenditure. In the contemporary scientific literature, exergy dissipation and degradation describes the modus operandi of a myriad of open systems: river basins and atmospheric circulation (3), ecosystem design (3), resting metabolic rate (12), and a unified theory of animal locomotion (13) to name a few. The concept of exergy has been discussed for well over 50 years (1, 7, 8, 14). But even so, the contemporary use (or rather nonuse) of exergy conjures up Gibbs revelation of entropy when others found it "far-fetched, and. . . . obscure . . . " (15). This may begin to change however with the recognition that metabolic rates, when expressed as heat production *per volume of oxygen consumed*, often varies among living creatures to a much larger extent then previously believed (16), perhaps signifying the disparity among organisms in terms of energy expended as both heat and entropy (see Fig. 9.3, the metabolic pathways).

9.3 Dynamics of a Metabolic Pathway

Cells have traditionally been described solely in the context of aqueous pools of enzymes where reactants and products diffuse from enzyme-to-enzyme (17). This limited view may have arisen in part from the explosive developments in biochemistry to locate, isolate, and subsequently discover what does and does not influence

enzyme activity – many of these discoveries took place within the confines of a closed system (the test tube). As biochemistry was blossoming, cell biology was awakening. Cell biology is now undergoing an explosive growth of its own and with it has come new hypotheses that suggest cellular infrastructure and cellular dynamics as possible mechanisms of metabolic control (i.e., on and off mechanisms) and regulation (i.e., fine-tuning mechanisms). Reactants and products not only diffuse throughout cells, they also likely undergo an active and organized transport.

Cells are much more structured than what was previously thought. As an example, an intricate and highly modifiable arrangement of protein fibers known as the cytomatrix exists within each cell. These fibers certainly serve in the capacity of an internal skeleton but also appear to play a role in biochemical energy exchange. For example, the activity of *lactate dehydrogenase* (LDH; the enzyme that reduces pyruvate to form lactate) is almost doubled when in contact with actin, a chief protein of the cytomatrix (see Fig. 10.2) (18). Indeed, many of the eleven glycolytic enzymes have been found to not only associate with the cytomatrix but are organized in multienzyme associations whose aggregation also may influence metabolic rate (19, 20). Multiple enzymes in direct association with one another have been termed a *metabolon*, where metabolites are channeled from enzyme-to-enzyme-to-enzyme as part of a metabolic pathway. But not all enzymes are metabolons.

9.4 Intracellular Transport

It has been pointed out that a huge increase in the rate of ATP resynthesis, involving similarly large fluxes of metabolic reactants and products, often takes place with sometimes immeasurable changes in reactant–product concentrations between enzymes (21). Enzyme catalysts serve as the backbone of any metabolic pathway, being explicitly described in the context of a lock and key mechanism. The description is a precise one. Yet metabolism often is portrayed in terms of a random diffusion, occurring successfully because distances are so small on a molecular playing field. In a three-dimensional setting, however, the margin for error appears to be huge in how reactants or substrate (the key) would randomly and precisely diffuse into the active site (the key hole) of an enzyme again-and-again in strict fashion. Clearly, if the random diffusion of intermediate reactants and products was solely responsible for distributing metabolic materials from enzyme-to-enzyme then a build-up of intermediate metabolites would likely be found at various points throughout a diffusive-based system. Again, such accumulations are rarely seen.

The traditional concept of random diffusion does not appear to explain in entirety how substrate is transferred precisely from enzyme-to-enzyme along a metabolic pathway. Some scientists have concluded from the absence of amassed metabolic intermediates, "...that key control elements of energy-consuming and energy-yielding pathways must lie essentially external to the pathways per se..." (21). What and where are these external mechanisms? The answer may lie in the concept of intracellular flow (in addition to the presence of metabolons). And it is exergy (negative entropy) that empowers such a flow.

Contemporary hypotheses promote the idea that intracellular metabolites undergo convection or perfusion or channeling or streaming toward and away from enzymes along predetermined routes perhaps created by the cytomatrix (i.e., the cytoskeleton) (22–24). The idea of an orchestrated movement throughout the cellular cytoplasm is not new, though it is not clear to what extent proposed mechanism(s) contribute (whether the exact format is channeling, convection, perfusion or streaming, the primary focus here is in the concept of a "planned" and orderly transport). Cyclosis (also referred to as cycraplosis or cytoplasmic streaming) – the circulation of the cytoplasm – provides an excellent biological example of organized internal flow within eukaryotic plant cells. A similar scenario is possible within and throughout animal cells. If so, faster vs. slower metabolic rates may be based as much on cellular infrastructure and the dynamics of intracellular flow as on enzyme kinetics. It may also be possible that disease pathology and athletic performance are a direct result of the degree of presence or absence of metabolic power – forces and flows – throughout the aerobic and anaerobic energy-exchange pathways. In this regard, a life-form's metabolic rate is as much caused by internal biochemistry (e.g., enzyme function) as it is an act of engineering.

How exactly is metabolic power "fueled?" Only speculative answers can be provided at this time. Perhaps muscle contraction itself devotes at least some of its force production to the methodical displacement of intracellular metabolites; that is, the actual creation of an orderly intracellular current. In this context, the ΔG of ATP hydrolysis (ranging from -50 to $-64\,\mathrm{kJ\,mol^{-1}}$) may not be utilized in its entirety during chemo-to-mechanical energy conversion. Suppose a cycle or cycles of the actomyosin motor during muscle contraction is purposely dissipated to impart a kinetic flow throughout the metabolic pathways of muscle cells for example (see (25)). Flow may also be created by the operation of membrane pumps that require ATP to physically discharge ions: Na^+-K^+ ATPase, Ca^+ ATPase, etc. (the scenario may be fancifully compared with Fig. 2.4 where the efflux of energy and matter promotes another inward flux).

In resting cells the conformational changes in the enzymes that make-up the metabolic pathways may impart mechanical force to the system as a whole during spontaneous catalysis. Consider the force described in the physical repulsion of Pi from ADP during the hydrolysis of ATP (25). Enzymes too may physically "expel" their product from the active site. Mechanical work, a push, kinetic energy (a "flow"), is imparted to the product, the very demonstration of energy transfer. Dependent on the proximity of one enzyme to another, some of that energy may be expended as work by traveling to the next enzyme in-line of the metabolic pathway. Within cells distances are exceedingly small and so forces and flows would not need to be large, but they do need to be numerous and continuous. A conceptualization of cell size and distance is provided in Table 9.1.

Another hypothesis to explain the origin of metabolic power can be derived from the concept of dissipative structures, the result of open systems operating at non-equilibrium and far-from-equilibrium and the constant exchanges of energy and materials that are associated with these conditions (the term *dissipative structure* was coined by the Nobel laureate Ilya Prigogine, 1917–2003) (26). To begin the

Table 9.1 A conceptualization of cell size and distance

avg. cell size	20 μm
red blood cell	7 μm
Mitochondria	2 μm
Enzyme	10 nm
Glucose	0.9 nm
Water	0.2 nm

A millimeter is 1,000th of a meter; a micrometer is 1,000th of a millimeter; a nanometer is 1,000th of a micrometer; a picometer is 1,000th of a nanometer. Cells are small, their constituents even smaller. Miniscule mechanical forces due to minute internal movements and energy transfer are not only possible they are likely
Meter (m) – millimeter (mm) – micrometer (μm) – nanometer (nm) – picometer (pm).

description of a dissipative structure, conservation within an open system is applied; power in being equated with power out (26). As energy and materials are exchanged via a gradient that traverses an open system, an ongoing degradation of that gradient takes place and autocatalytic symmetry and self-organization result, a dissipative structure is born. The entropy of the dissipative structure is kept to a minimum in an open system (as opposed to a maximum within closed systems) (again, Schrodinger's concept of negative entropy comes to mind). Organization represents a concentration of energy – to maintain the gradient – as opposed to energy dispersal and it is well understood that a continuous cost incurs from a continuous concentrating of energy.

As a system moves into the realm of far-from-equilibrium (where many metabolic systems are thought to reside), energy is not only degraded it undergoes transfer (dissipation); the presence of steeper gradients increases energy flow and entropy production; on a larger scale consisting of system and surroundings, the increased entropy is exported to the surroundings (26). On a megascale, hurricanes and tornadoes – well-ordered structures by anyone's account – provide only two examples of how autocatalytic organization is created as imposed gradients are degraded at an accelerated rate (other examples include the growth and development of all animal life (9)).

Via personnel communication, Richard B. Kemp, now a retired Professor from Wales (Institute of Biological Sciences, Aberystwyth University), described internal cellular flow in terms of biological heat production decreasing the density of the cytosolic fluid surrounding the heat source and thereby creating a flow of cytosol toward the plasma membrane where heat is eventually released to the surroundings. The importance of the thermodynamic properties of water (27) again comes to mind (see also Fig. 2.3). Kemp also postulates that the cytoskeleton creates channels for this cytosolic convective heat flow. Mitochondria (aerobic metabolism) were, he goes on to explain, the principle source of heat within animals but the "compartmentalization" of glycolysis (anaerobic metabolism) may also contribute to intracellular flow (cytoplasmic streaming also is known to be affected by light exposure and pH). In Chap.6 a reference was provided by Schaarschmidt and colleagues

that the, "…heat produced inside the system…may be used for some irreversible processes" (28). Taken literally this statement suggests the conversion of metabolic heat into a convective current (or flow). Perhaps living cells are heat engines after all (!), operating not as a result of gas expansion but from changes in water density-volume relationships in response to metabolic heat production. The cost of this current may perhaps come from the disappearance of some metabolic heat.

Lastly, another example of the promotion of intracellular flow might entail the presence of an actual heart-like organelle within a cell, providing an internal convective current. But such a "pump" is yet to be discovered.

9.5 Time

Many physiological factors scale within living organisms: surface area, body volume, heart and lung size, and most importantly, from this text's standpoint, metabolic rate (Fig. 9.4).

Time itself scales with physiological size. Indeed, the term *power* (e.g. metabolic power) contains a temporal component. Relationships among body size in comparison with heart rate, breathing rate and glucose and amino acid turnover have been reported for animals as small as mice and as large as elephants (30, 31).

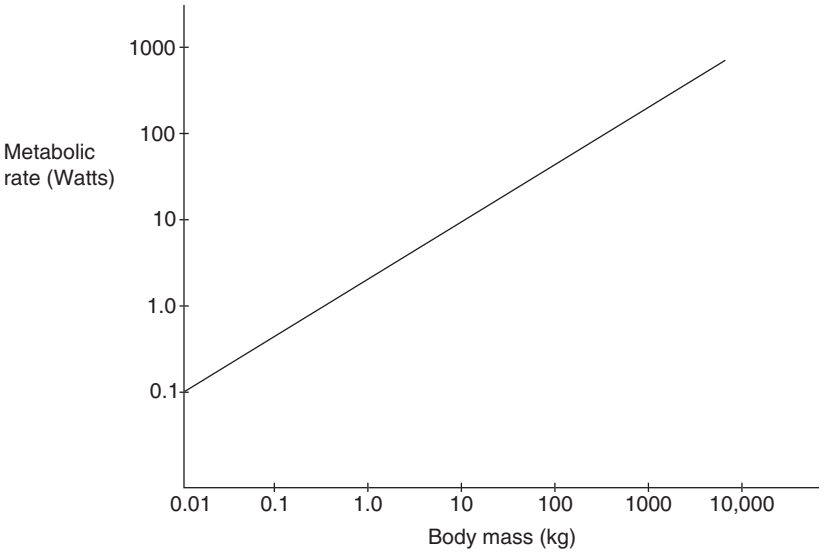

Fig. 9.4 Whether a mouse or an elephant, most of all animal life has an estimated metabolic rate, when measured as oxygen uptake, that falls along a straight line (on a logarithmic scale). The slope of this line indicates that for every 100% increase in body mass metabolic rate increases by about 68% (29). This relationship may not be so straight forward because anaerobic metabolism is not accounted for, nor is the oxygen utilized in biochemical reactions other than aerobic ATP resynthesis (16). Also absent are actual heat measurements and calculation of the entropy (26). Adapted from Schmidt-Nielsen (30)

Schmidt-Nielsen has elegantly explained temporal relationships in the context of the beating mouse and elephant heart (30). The mouse heart beating 600 times every minute will, over its 3-year lifespan, undergo ∼800 million total contractions. At 30 beats min^{-1} the elephant's heart also appears to undergo a similar amount of total contractions over its lifespan, taking 40 years to do so. That relative relationship has been interpreted in the context of physiological time, not clock time.

While the difference between a 3-year-mouse and 40-year-elephant lifespan is readily understood by human observers (who may live 70+ years), so is the notion of a single "natural" lifetime by the creatures that live them. Thus, from birth to natural death, physiologic time is a relative concept. Bioenergetics also has been interpreted in the context of physiological time. Similar to the total lifetime heart beats allotted for mice and elephants, total energy usage per unit body mass also appears constant over a species lifespan. If this is true then perhaps entropy per unit body mass also is a constant (under resting conditions) and a universal statement can be made that all life forms, big or small, strive to maximize metabolic efficiency by minimizing internal entropy (keep in mind this statement represents energy expended over a life-time, not energy expended per volume of oxygen consumed) (12). More specifically, life's inherent energy-exchange mechanisms – aerobic and anaerobic metabolism – appear to optimize exergy degradation and dissipation.

9.6 Exergy Synopsis

Energy costs within an open system are founded as: (1) the inefficient exploitation of spontaneous energy exchange, (2) the maintenance of metabolic force – energy gradients – by the continuous input of energy, and (3) the expense of maintaining an organized flow of energy and materials throughout a metabolic pathway (an act of engineering in addition to biochemical enzyme function). Useful work is performed throughout a metabolic pathway; heat and entropy are independently expended as a result. The "secret to life" may reside in the efficient-as-possible exploitation of exergy. For a living organism, death coincides with the disappearance of an energy-exchange gradient and the absence of metabolic power.

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Chapter 10
Anaerobic Metabolism

Under normal conditions glucose and fat oxidation within the metabolic pathways "fuels" ATP resynthesis (protein plays a limited role as a fuel). Glucose is unique because unlike fat its energy content is exploited by anaerobic metabolism in addition to aerobic metabolism. Fat oxidation is completely aerobic. Anaerobic metabolism, as its name implies, does not involve oxygen. However, the products of anaerobic metabolism – pyruvate and lactate – can undergo complete oxidation aerobically; but that is a later story (Chap. 11). In fact, biochemistry was a borne anaerobic baby and grew to become an aerobic adult. Let us start from the beginning . . .

10.1 A Brief History of Anaerobic Biochemistry

For literally thousands of years, prevailing thought held that heat was a prerequisite for life. It was Jean Baptiste van Helmont (1577–1644) who declared things the other way around: life produced heat. The warmth rising from the fermentation of wine – the splitting of glucose to form alcohol – was cited as part of his proof. Louis Pasteur (1822–1895) directed his talents toward a more complete investigation of alcohol production. Pasteur recognized anaerobic fermentation as an organized biological process dedicated to living organisms, not an act of chemical disintegration as thought by others at the time. Eduard Buchner (1860–1917) later demonstrated that fermentation could take place within both living yeast and the lifeless test tube (he was awarded the 1907 Nobel Prize for this). It became understood that glucose breakdown involved the actions of several enzymes, the catalysts of life's biochemical reactions; multiple reactants and products were produced along the metabolic pathway of glucose breakdown . . . but that was not all. A rather monumental understanding of metabolism was presented by Arthur Harden (1865–1940) and William Young (1878–1942), who first recognized the importance of inorganic phosphate (Pi) not as a part of ATP, but as part of the fermentation process.

In organisms other than yeast, it became recognized that a similar type of fermentation took place, but clearly, animal cells did not produce alcohol! The biochemical

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degradation of glucose in animal cells stopped one step short of alcohol production, instead the end product was found to be lactic acid. Suffice to say that once completed, the elucidation of glucose splitting – termed *glycolysis* (glyco = glucose; lysis = to split) – had not only made history but initiated the science of biological chemistry. As stated by the author of one well-known biochemistry text, "... the development of biochemistry and the delineation of this pathway went hand in hand" (1). Biochemistry indeed had an anaerobic birth. The anaerobic breakdown of glucose within your body's cells is now recognized with names that include substrate-level phosphorylation, anaerobic metabolism, and the Embden–Meyerhoff–Parnas pathway (Gustav Embden, 1874–1933; Otto Meyerhoff, 1884–1951; Jacob Parnas, 1884–1949).

10.2 The Glycolytic Gradient

Glycolysis with its associated phosphate (Pi) shifts and transfers takes place in the cellular cytoplasm as a 10- and 11-step chemical-to-chemical energy exchange (1, 2). The gradient begins with one molecule of glucose and ends with two molecules of pyruvate or lactate (1glucose → 2pyruvate or 2lactate). Two ATPs are needed to prep the reaction as it takes place within a cell. Ten enzymatic steps result in pyruvate formation (also known as "aerobic" glycolysis); an additional eleventh enzyme leaves lactate as the final product (also known as anaerobic glycolysis). With glucose as substrate, glycolysis, whether aerobic or anaerobic, resynthesizes four ATPs overall, resulting in a net production of two ATPs per glucose molecule or moiety.

Muscle stores glucose in the form of glycogen (glycogen being the predominately used carbohydrate substrate within working skeletal muscle). Glycogen degradation is termed *glycogenolysis*, resulting in the resynthesis of three ATPs. The starting points of glucose and glycogen degradation differ but the end products are the same. The glycolytic pathway is shown in Fig. 10.1.

Many biochemistry texts, when reporting the individual thermodynamic properties of each of the steps of glycolysis, have a tendency to report only Gibbs energy changes and for good reason (as opposed to enthalpy and entropy changes). Gibbs energy changes indicate the spontaneity and the amount of available energy from a given reaction, both of which represents invaluable information (1). Glycolytic Gibbs energy changes (of the system) under standard conditions ($\Delta G^{\circ\prime}$) and physiological conditions (ΔG) are typically displayed to portray the glycolytic gradient; from concentrated energy as glucose, to more distributed energy as pyruvate.

As stated over 30 years ago by Minakami and de Verdier, "Data on enthalpy changes of [individual] glycolytic reactions are difficult to find in the literature" (3); the same was true regarding entropy. Such difficulty apparently served to motivate these investigators to measure and calculate the respective enthalpy (ΔH), entropy (ΔS), and Gibbs energy (ΔG) changes of all the independent glycolytic reactions under physiological conditions (see Table 10.1). It needs to be noted that the values

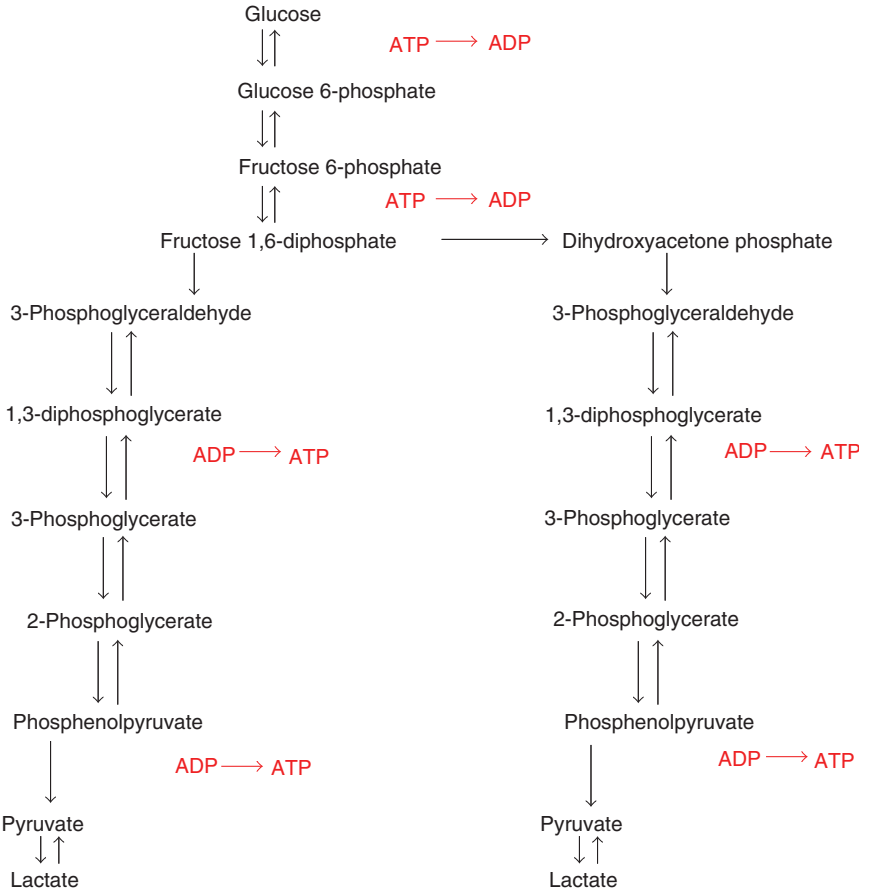

Fig. 10.1 The *arrows* in the figure (in fact most figures where a metabolic pathway is represented) usually indicate forward and/or reverse directional capabilities of a given reaction. In addition, the overall start-to-finish dynamics of an active metabolic pathway also needs consideration. Reactants and products of each individual reactions are provided (enzymes are not shown). Glucose itself is split into two at reaction no. 4. Phosphate (Pi) shifts and transfers occur throughout much of the glycolytic pathway

listed in Table 10.1 represent a compilation of individual closed-system reactions (using red blood cells, erythrocytes) (also, Table 10.1 starts with one-half glucose and ends with one pyruvate or lactate molecule).

Instead of piecing together individual reaction steps, an over-all start to finish measure also can be taken to determine the molar enthalpy changes (ΔH) for glucose-to-lactate conversion, that is, the overall glycolytic reaction. For example, Gnaiger reported glucose-to-lactate enthalpy changes ranging from -70 to $-80\,\mathrm{kJ\,mol^{-1}}$; with glycogen as a starting point the overall enthalpy change ranged from -71 to $-81\,\mathrm{kJ\,mol^{-1}}$ (3) (the value of -80 to $-81\,\mathrm{kJ\,mol^{-1}}$ exquisitely matches that of Table 10.1 when doubling the enthalpy change of one-half the

Table 10.1 Closed-system thermodynamic parameters of one-half glycolysis

Reaction	Enzyme	ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})	ΔS (kJ mol^{-1})
1. 0.5glucose + 0.5ATP → 0.5glucose 6-phosphate + 0.5ADP + 0.5H^+	Hexokinase	−13.8	−20.9	+7.4
2. 0.5glucose 6-phosphate → 0.5fructose 6-phosphate	Phosphoglucose isomerase	+4.8	+0.2	+4.6
3. 0.5fructose 6-phosphate + 0.5ATP → 0.5fructose 1,6-bisphosphatase + 0.5ADP + 0.5H^+	Phosphofructokinase	−13.8	−13.0	−0.8
4. 0.5fructose 1,6-bisphosphate → glyceraldehyde 3-phosphate	Aldolase	+20.9	−0.4	+21.3
4. 0.5fructose 1,6-bisphosphate → dihydroxyacetone phosphate	Aldolase	?	?	?
5. dihydroxyacetone phosphate → glyceraldehyde 3-phosphate	Triose phosphate isomerase	?	−2.5	?
6. glyceraldehyde 3-phosphate + Pi + NAD^+ → 1,3-bisphosphoglycerate + NADH + H^+	Glyceraldehyde 3-phosphate dehydrogenase	−2.9	−1.0	−1.9
7. 1,3-bisphosphoglycerate + ADP → 3-phosphoglycerate + ATP	Phosphoglycerate kinase	−5.4	+ 1.3	?
8. 3-phosphoglycerate → 2-phosphoglycerate	Phosphoglyceromutase	0.0	−0.6	+0.6
9. 2-phosphoglycerate → phosphoenolpyruvate + H_2O	Enolase	+14.6	−1.3	+15.9
10. phosphoenolpyruvate + ADP + H^+ → pyruvate + ATP	Pyruvate kinase	0.0/+4.4	−15.5/−53.7	+15.5/ +62.6
11. Pyruvate + NADH + H^+ → lactate + NAD^+	Lactate dehydrogenase	−44.4/−40.0	0.0/-53.7	−44.4/ +18.2

Adapted from (1, 3).

Table 10.2 Thermodynamics of two overall glycolytic reactions (from (5))

Reaction	ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})	ΔS (kJ mol^{-1})
0.5glucose → pyruvate ("aerobic" glycolysis)	+4.4	−53.7	+62.6
0.5glucose → lactate (anaerobic glycolysis)	−40.0	−53.7	+18.2

glycolytic reaction). The enthalpy changes of any reaction are heavily influenced by the different mediums or surroundings where the events are recorded: muscle cells, intestinal cells, nerve cells, liver cells, test tubes, Petri dishes, etc. In pursuit of a proper acid–base balance, heat exchanges for an identical reaction or series of reactions (glycolyisis) may differ between and even within cells. Imagine those acid–base differences occurring between resting and exercising skeletal muscle for example. Including the heat associated with acid neutralization, di Prampero et al. measured the glycogen-to-lactate enthalpy change at 76 kJ mol^{-1}; when acid–base changes were accounted for and eliminated from the overall enthalpy changes, the glycogen-to-lactate enthalpy change was −64 kJ mol^{-1} (4).

Overall, entropy increases ($+\Delta S$) as glucose is degraded to pyruvate but the reduction of pyruvate to form lactate results in a negative entropy change ($-\Delta S$) (5) (Table 10.2). This suggests lactate as acquiring a greater structure or order as compared with pyruvate. The acknowledgement of entropy and enthalpy changes in addition to Gibbs energy allows for a more complete interpretation of biological energy expenditure. As will be demonstrated in the next section (Sect. 10.3), the enthalpy and entropy exchanges of glycolysis as glucose-to-pyruvate (aerobic glycolysis) and as glucose-to-lactate (anaerobic glycolysis) suggests the presence of two distinct overall reactions and, when recognized as such, provides a valuable tool in the estimation of aerobic and anaerobic contributions to whole-body energy expenditure.

As shown, Table 10.1 is incomplete and thus needs to be interpreted with caution (see missing thermodynamic values for reactions 4, 5, and 7). Beyond the absence of data, some glycolytic reactions appear to be nonspontaneous under physiological conditions. One such reaction, a phosphate transfer, is shown below, the seventh reaction of glycolysis:

$$1,3\text{-bisphosphoglycerate} + \text{ATP} \rightarrow 3\text{-phosphoglycerate} + \text{ATP} (\Delta G = +1.3)$$

While having a (nonspontaneous) ΔG of + 1.3 kJ mol^{-1}, it must be concluded that the reaction does indeed take place within cells, otherwise no living organism on earth would be able to exploit glycolytic energy exchange, considered one of the oldest metabolic pathways on our planet (6). How, with a positive ΔG, is a nonspontaneous reaction promoted into spontaneity? The input of energy is the logical solution. Recalling those forces and flows that are inherent to an open metabolic system, metabolic power likely promotes the reaction in the forward direction (Fig. 10.2).

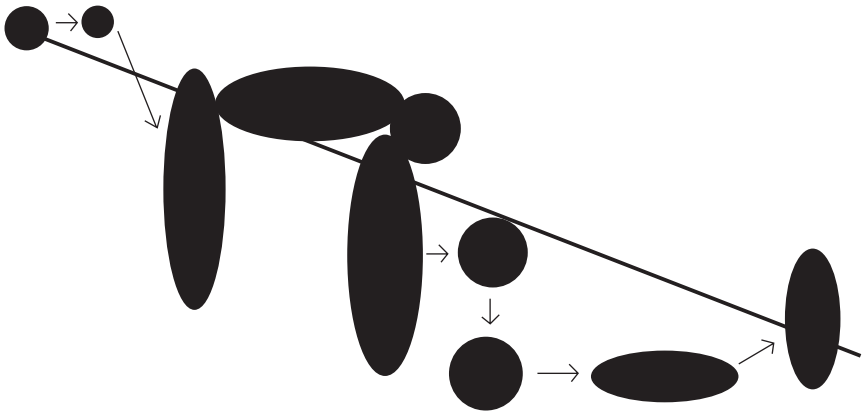

Fig. 10.2 A depiction of anaerobic glycolytic enzyme–enzyme channeling and perfusion/streaming/convection as a composite of metabolic power (forces and flows). The *thick diagonal line* represents an actin filament, part of the cell's cytoskeleton. The *circles and ellipses* represent each of the ten glycolytic enzymes; some are attached to and affected by actin, while others are not. Enzymes in direct contact with each other represent enzyme–enzyme channeling (a metabolon). The *arrows* portray enzyme-to-enzyme perfusion/streaming. Glycolysis starts at hexokinase (*top left circle*) and ends at pyruvate kinase (*bottom right ellipse*) (modified from Bereiter-Hahn et al. (7)

10.3 Glycolytic Enthalpy and Entropy

Glycolysis is activated at the *onset* of muscle contraction, perhaps by the sudden increase of intracellular calcium (Ca^{2+}) (8, 9). Arguments have been made concerning kinetic (ADP concentration) vs. thermodynamic (ΔG of ATP hydrolysis) control of the metabolic pathways (10). These arguments will not be settled here though it should suffice to say that metabolic control appears to fluctuate between sites of ATP utilization and ATP resynthesis: from actomyosin during low-to-moderate exercise to sites of ATP resynthesis at higher exercise intensities, respectively (11). Biochemical activity in working muscle may speed up some 3,000-fold upon the arrival of a muscle's action potential (9). So too must the impending enthalpy and entropy changes of this increase in metabolic activity. As mentioned earlier, the scientific literature reveals that the energy exchanges associated with glycolysis have mostly been interpreted in terms of lactate rather then pyruvate production: anaerobic glycolysis as opposed to "aerobic" glycolysis, respectively. This needs to be well recognized because the thermodynamics of anaerobic glucose-to-pyruvate formation are different from that of glucose-to-lactate formation (Tables 10.1 and 10.2).

If the thermodynamic parameters in Table 10.2 are correct, then the metabolic breakdown of glucose-to-pyruvate results in the net flux of heat (energy) to rather than from the system; the enthalpy change is small ($\Delta H = 4.4\,kJ\,mol^{-1}$). Note also the rather considerable change in overall entropy when pyruvate as opposed

to lactate is formed; $62.6\,\mathrm{kJ\,mol^{-1}}$ vs. $18.2\,\mathrm{kJ\,mol^{-1}}$, respectively. When lactate as opposed to pyruvate is the end product of glycolysis, a rather large change in enthalpy is seen: heat (energy) is exchanged from the system to the surroundings ($\Delta\mathrm{H} = -40.0\,\mathrm{kJ\,mol^{-1}}$). Entropy actually decreases ($\Delta S = -44.4\,\mathrm{kJ\,mol^{-1}}$) with the reduction of pyruvate to form lactate: glucose-to-pyruvate, $\Delta S = 62.6\,\mathrm{kJ\,mol^{-1}}$; glucose-to-lactate, $\Delta S = 18.2\,\mathrm{kJ\,mol^{-1}}$. Based on this information the largest amount of heat loss during glycolysis is with the reduction of pyruvate to form lactate, "justifying the interpretation that in most cases heat is produced only by lactate formation…" (3). Less heat (energy) is exchanged with the overall metabolic degradation of glucose-to-pyruvate. Moreover, the overall enthalpy change with pyruvate as the end product is positive, indicating heat (energy) flow toward the system, perhaps suggestive of the conversion of this energy to intracellular flow (perfusion/streaming/convection) with a concomitant increase in entropy. In Chap. 12, it will be demonstrated that both the enthalpy and entropy changes of the glucose-to-pyruvate and glucose-to-lactate reactions need to be taken into consideration when cellular and whole-body energy expenditure fueled by glucose oxidation is accounted for as a measurement of oxygen uptake.

Matter and energy are continuously moving into, through, and out of metabolic systems; energy is expended in the process. A working metabolism thus involves scalar fluxes that by definition entail units of quantity (e.g., mass or volume). The flux of heat in scalar (not vector – magnitude and direction) terms has been appropriated to the study of energy expenditure because biochemical reactions invoke the movement of energy (heat) throughout the metabolic (open) system (4, 12, 13). Both acts of ATP turnover, glycolytic ATP resynthesis along with the ATP hydrolysis of muscle contraction, produce heat (energy) that is irreversibly discarded (expended) from the system (14). However, in the context of metabolic power, in terms explicit to heat exchange (possible *conversion* into an organized intracellular current and *transfer* throughout the metabolic system or biochemical pathway), increases in entropy are the result (4, 12, 13).

Environmental heat and entropy increase as a result of biological energy exchange (15, 16). The reactions presented in Table 10.2 suggest that the overall breakdown of glucose-to-pyruvate is entropy driven ($\Delta S = +62.6\,\mathrm{kJ\,mol^{-1}}$). To the contrary, the overall breakdown of glucose-to-lactate appears to be driven primarily by a large overall enthalpy change ($\Delta\mathrm{H} = -40\,\mathrm{kJ\,mol^{-1}}$).

10.4 "High-Energy" Phosphate Buffering

At times energy demand within muscle exceeds that of glycolytic ATP supply. Under these conditions other "high-energy" phosphate molecules act as a buffer to rapidly resynthesize ATP, keeping ATP levels high (thereby preventing a drop in the ΔG of ATP; "high energy" is placed in quotes because the energy availability depends on [ATP] and [ADP] concentrations; at equilibrium ATP has no available

energy; see Fig. 7.5). "High-energy" phosphate exchanges are considered a part of the anaerobic metabolic system. Creatine phosphate or phospho-creatine (PC), for example, instantaneously phosphorylates ADP via the enzyme *creatine kinase*:

$$CP + ADP + H^+ \rightarrow Cr + ATP$$

The reaction does not evolve heat to the extent that respiration and glycolysis do during ATP resynthesis (17, 18). It also is of interest that protons (H^+) are consumed in this reaction. Thus, at the very onset of intense muscle contraction when PC stores are heavily utilized, metabolic heat production is minimal and pH can momentarily rise as the muscle undergoes slight alkalosis (19).

Creatine phosphate is stored in muscle at about 3–4 times the concentration of ATP, but even so it is still not a lot. Muscle PC levels are high enough to fuel several seconds of all-out physical work. Power output drops precipitously as PC stores fall. As will be demonstrated later, the PC that is expended during exercise undergoes restoration exclusively via aerobic metabolism in the recovery from exercise (20). This must be taken into consideration when estimating energy expenditure during and after intense exercise (Chap. 16).

As intense muscle contraction continues and PC concentrations continue to approach depletion, the union of two ADP molecules also resynthesizes ATP:

$$2ADP \rightarrow ATP + AMP + heat$$

AMP is adenosine monophosphate. The enzyme for this reaction is *myokinase*.

The "high-energy" phosphates are a finite anaerobic energy source; when nearly depleted, fatigue sets in and muscle contraction ceases.

10.5 Anaerobic "Speed"

All of the ATP resynthesizing metabolic pathways appear to be activated upon the initiation of muscle contraction (21). It is important to note however that it takes time, several minutes, for aerobic metabolism to reach a maximum rate, while the high-energy phosphate PC achieves maximal rates of ATP resynthesis almost instantly and glycolytic rates take but a second or two to operate at maximum velocity. Maximal power output by muscle is accelerated only for about 10–20 s before declining, suggesting that the rate of anaerobic metabolism may be a potential factor in that decrease (see Fig. 10.3).

The rate of ATP resynthesis has been estimated at 60.0 μmol ATP per gram of wet tissue weight per minute for anaerobic glycolysis, and for the PC and ATP stores 96–360 μmol ATP per gram of wet weight per minute (in comparison the aerobic oxidation of fat and glucose resynthesizes ATP at 20 and 30 μmol ATP per gram of wet weight per minute, respectively) (23). The best experiments to induce rapid metabolic rates involve exercise with skeletal muscle undergoing contractions at high-power outputs. Some researchers have used electrical stimulation of muscle to

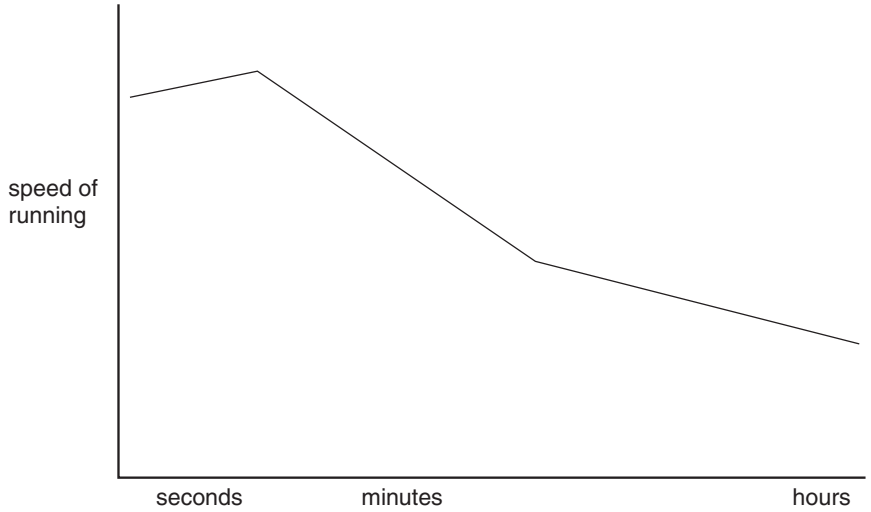

Fig. 10.3 This logarithmic plot of running speed and time reveals three distinct linear slopes. It has been proposed that the three separate regression lines are indicative of ATP resynthesis contributions by the three metabolic systems: ATP, PC stores (seconds), anaerobic glycolysis (minutes), and aerobic respiration (minutes to hours). Adapted from McGilvery (22)

enhance the contractile effort. To obtain an estimation of anaerobic metabolic rates, a small biopsy is rapidly excised from the muscle that underwent contraction and is quickly frozen. The rapid freezing technique halts all biochemical reactions within the biopsy sample and the contents are then analyzed to determine the extent of their contribution during a given time period (see Table 10.3).

Clearly the greatest contributions to energy expenditure by anaerobic metabolism occur with intense and brief activity. The flow of metabolic reactants and products through the glycolytic metabolic pathway is nothing less than remarkable under these conditions, with net flux reported to be several hundred-fold greater than the rest (26). At such velocities however a compromise is reached because increases in power – including metabolic power – come at an expense. Keep in mind that anaerobic glycolysis generates only two ATPs when beginning with a single glucose moiety, so that many, many glucose moieties are needed (coming from

Table 10.3 ATP resynthesis rates – millimoles of ATP per kilogram of dry muscle per second

Exercise	Duration	PC	Glycolysis	Reference
Electrical stimulation	1.28 s	9.0	2.0	(24)
	2.56 s	5.0	5.3	(24)
	3.0 s	5.0	2.8	(24)
Cycling (140 rpm)	10 s	4.4	9.3	(25)
	30 s	0.7	6.5	(25)

glycogen) to provide a large amount of ATP. As will be shown in the next chapter, aerobic metabolism resynthesizes 17 times the ATP per molecule of glucose than does anaerobic glycolysis. A trade-off arises: efficient ATP supply or high-power output. Gnaiger has elegantly categorized this dichotomy in stating that, "maximal values of both (ATP supply and power output) cannot be achieved simultaneously" (27). In this regard, biological organisms have an apparent "metabolic choice" when attempting to sustain muscle contractions, accelerated glucose or glycogen breakdown coupled with rapid but limited anaerobic ATP supply (two ATPs per glucose molecule) or slower glucose or glycogen breakdown coupled to a more abundant aerobic ATP supply (36 ATPs per glucose molecule). Athletes, human or not, utilize anaerobic metabolism to supply the energy demands of strength-, speed- and power-related activities.

As fast as use of the ATP, PC stores and anaerobic glycolysis are it is apparent that working muscle never relies solely on a single metabolic system. At the initiation of any type of contraction, activation of both anaerobic metabolic pathways and the aerobic metabolic pathway takes place. Taking the concept that all metabolic systems operate simultaneously to the extreme, Shulman and Rothman have proposed the *glycogen shunt* hypothesis (28). Under the strict condition of easy to moderately intense rhythmic (pulsatile) muscle contraction, they propose that PC is broken down to resynthesize ATP within the first 15 ms of contraction. In the remainder of the contractile phase lasting from 15 to 100 ms, PC is resynthesized from glycogenolysis and glycolysis. The last phase of the glycogen shunt hypothesis takes place in the recovery phase of a rhythmic contraction and involves the rapid resynthesis of glycogen via glucose from the bloodstream and mitochondria's aerobic metabolic pathways (Chap. 11).

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Chapter 11
Aerobic Metabolism

No less than three different types of gradients make up respiration, representing the aerobic energy-exchange devices. Respiratory gradients are created, maintained, and exploited within mitochondria through the use of membranes. As will be shown, membrane-oriented energy exchange gradients differ tremendously as compared with anaerobic substrate-level phosphorylation. Membranes are constructed of lipid bilayers that act as a barrier separating areas of high (concentrated) energy from lower (dispersed) energy. Such separation defines the word gradient (a difference over a distance).

11.1 Mitochondria

Mitochondria are a double-membrane organelle once thought to be a type of ancient bacteria that began a symbiotic relationship with eukaryotic cells several billion years ago (mitochondria have an independent albeit limited DNA separate from that of the cells nucleus) (1–3). Taken literally this means that every cell in your body is composed of at least two life forms (in fact, several of your cell's organelles are thought to have originated as separate life forms). First seen as having a bean-shaped appearance, mitochondria were also found to congregate in those areas of the cell that require a sustained and or large energy (ATP) supply (4, 5), around a muscles contractile apparatus for example (6). It is now apparent that the membranes of a few mitochondria actively spread as a reticulum throughout a cell, amassing at sites of high energy demand (the surface area of a single mitochondria must be incredibly extensive). Far from having the sole role of primary energy supplier, mitochondria are important in cell signaling, the biosynthesis of iron compounds, calcium control within the cell, and apoptosis (programmed cell death). Figure 11.1 portrays a mitochondrian in a traditional bean-shaped form.

Depending on the cell type, mitochondria may occupy a volume of 1–50% of a cell's interior. The type and amount of structures found within a cell speaks loudly to what the primary function of a cell is. To place this in perspective, the zoologist

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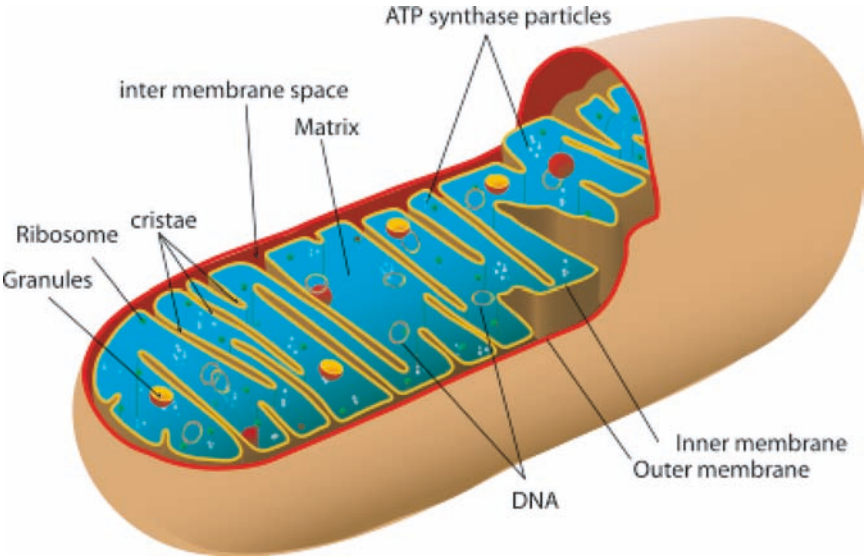

Fig. 11.1 A traditional pill-shaped portrait of a single mitochondrion is shown. Much of mitochondrial metabolism occurs within the mitochondrial matrix (where the enzymes of the Krebs cycle and fat oxidation are found) and the inner mitochondrial membrane (where electron transport chain resides) (Courtesy of Mariana Ruiz Villarreal, http://commons.wikimedia.org/wiki/Image:Diagram_of_an_animal_mitochondrion.svg)

Peter W. Hochachka (1937–2002) surmised that in a muscle cell, for example, three components make-up or fill the majority of the cells internal space: the sarcomere (the contractile apparatus), the sarcoplasmic reticulum (a double-membrane structure that contains the calcium needed to promote muscle contraction), and the mitochondria themselves (to supply the energy demands of contraction) (7). Fast twitch (white) muscle – the muscle of sprinters – is considered to be mostly anaerobic, containing perhaps a 1% volume of mitochondria but a drastically larger percentage of sarcoplasmic reticulum. Slow twitch (red) muscle – the muscle of long distance runners – is highly aerobic, whose volume is perhaps 50% filled by energy-producing mitochondria.

Mitochondria's outer membrane is roughly 50% protein and 50% lipid; it is an extremely porous structure that perhaps contributes to the mitochondrion's overall shape (8). The inner membrane has a protein content of almost 80% and is highly selective in its allowance of material exchange. The aerobic energy gradients are all found within or enclosed by this inner membrane (Fig. 11.1).

11.2 Krebs Cycle: Gradient 1

The aerobic biochemistry of substrate degradation is recognized by the metabolic pathway known as the Krebs cycle (named after its founder Hans Krebs,

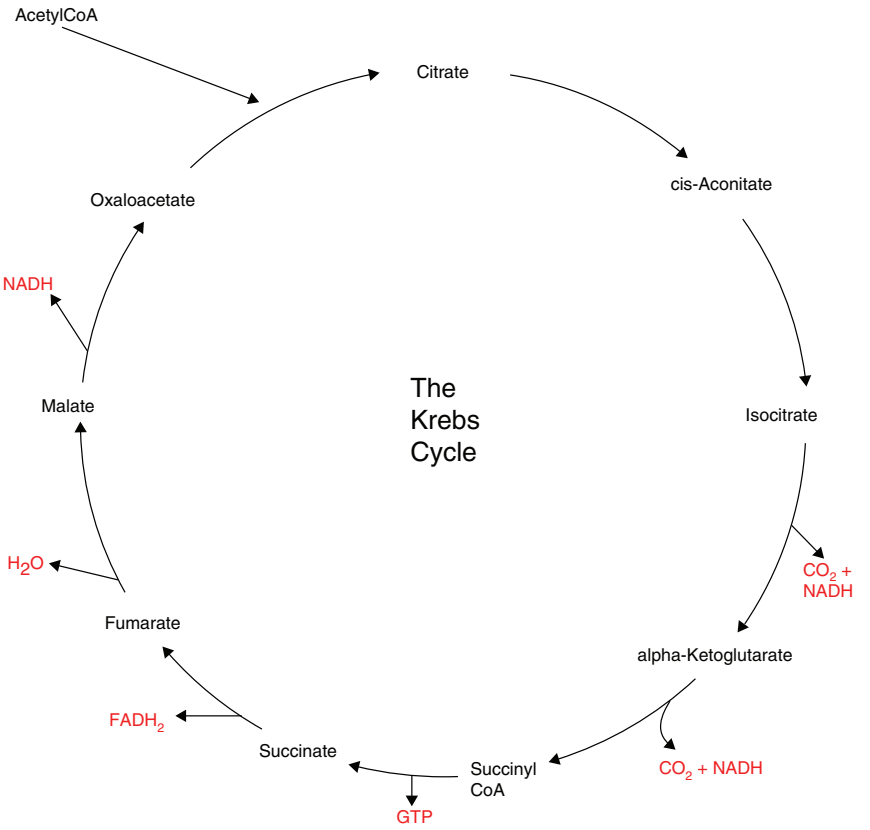

Fig. 11.2 The reactions of the Krebs cycle take place deep within the mitochondrial matrix, surrounded by the inner mitochondrial membrane. Acetyl co-enzyme A (CoA) enters the cycle from the *top right-hand corner*. Reactants are shown but the enzymes associated with these reactions are not (see Table 11.1). Products of the Krebs cycle are given in *red*. The purpose of the Krebs cycle is to supply the electron transport chain (ETC) with reducing equivalents

1900–1981). This pathway also is known as the citric acid cycle and the tricarboxylic acid cycle. As shown in Fig. 11.2, the Krebs cycle does indeed operate in a cyclical format: its end-product oxaloacetate condenses with the entrance reactant acetyl co-enzyme A (CoA) to begin the cycle:

While typically represented in a cyclical format, it is understood that the Krebs cycle is a metabolic energy-exchange device with a higher-energy starting point and a lower-energy ending point. Thus, the metabolic pathway that is the Krebs cycle represents an energy-exchange gradient (Fig. 11.3).

ATP is not resynthesized in the Krebs cycle, though one act of substrate level phosphorylation is present that produces GTP (an ATP equivalent). The purpose of the Krebs cycle instead is to strip hydrogen ions (H^+) and electrons (e^-) from substrate, providing them to two specialized carriers: (1) nicotinamide adenine dinucleotide (NAD^+) and (2) flavin adenine dinucleotide (FAD). During one "spin"

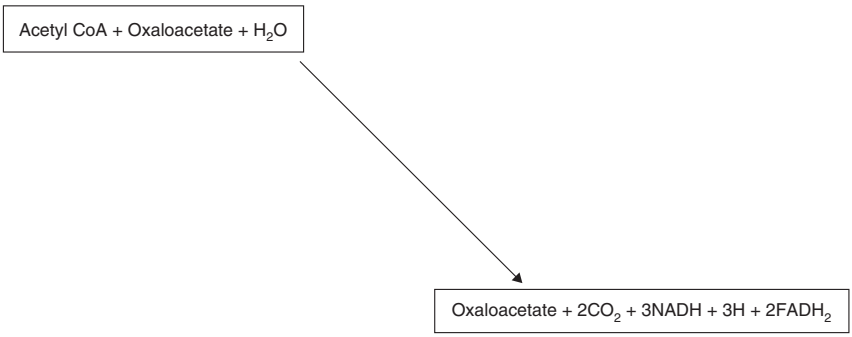

Fig. 11.3 Note that the initial reactants are fewer in number than the final products. These criteria hint that overall, the Krebs cycle gradient represents a spontaneous process

of the Krebs cycle, three NAD^+ and one FAD are required; two molecules of carbon dioxide (CO_2) are also formed and released. The nine enzymatic reactions of aerobic oxidation are provided in Table 11.1 (9).

The aerobic oxidation of substrate begins with the entrance of two carbon units into the Krebs cycle. Each 2-carbon unit is attached to a molecule called coenzyme-A (CoA). The linkage between the 2-carbon unit and CoA occurs via a "high-energy" thioester bond (sulfur linkage – S) to form acetyl CoA (some scholars think that the "high-energy" thioester bond predated ATP in the very first life forms on planet earth) (Fig. 11.4).

The 2-carbon unit of acetyl CoA condenses with the 4-carbon molecule oxaloacetate that is found as the last product of the Krebs cycle. The 6-carbon product

Table 11.1 Krebs cycle reactions (closed system), $\Delta G^\circ (\mathrm{kJ\,mol^{-1}})$

Reaction	Enzyme	ΔG°
1. Acetyl CoA + oxaloacetate + H_2O → citrate + CoA + H^+	Citrate synthetase	−31.4
2. Citrate → *cis*-aconitate + H_2O	Aconitase	+8.4
3. *Cis*-aconitate + H_2O → isocitrate	Aconitase	−2.1
4. Isocitrate + NAD^+ → α-ketoglutarate + CO_2 + NADH	Isocitrate dehydrogenase	−8.4
5. α-ketoglutarate + NAD^+ + CoA → succinyl CoA + CO_2 + NAD^+	α-ketoglutarate dehydrogenase	−30.1
6. Succinyl CoA + Pi + GDP → succinate + GTP + CoA	Succinyl CoA synthetase	−3.3
7. Succinate + FAD → fumarate + $FADH_2$	Succinate dehydrogenase	0
8. Fumarate + H_2O → L-malate	Fumarase	−3.8
9. L-malate + NAD^+ → oxaloacetate + NADH + H^+	Malate dehydrogenase	+29.7
		−41.0

Note that only standard Gibbs energy values are provided (ΔG°). Evidence suggests that the Krebs cycle enzymes are associated as a metabolon that channels substrate from enzyme-to-enzyme (10, 11). Table adapted from (9).

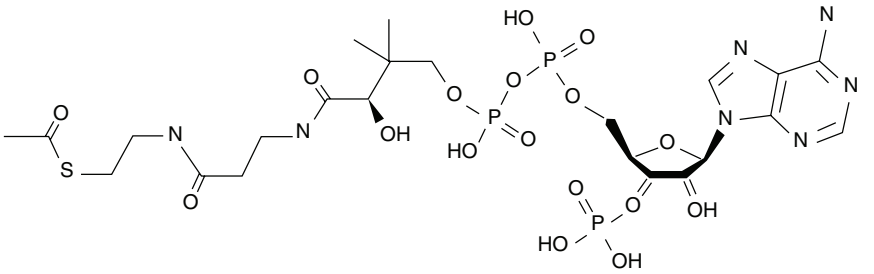

Fig. 11.4 A molecule of acetyl Co-A is shown. In this format, 2-carbon units begin the aerobic oxidation process. In this figure, the 2-carbon unit is located at the extreme *left* of the molecule, where one carbon forms a bond with sulfur (S)

formed from this reaction also provides another name to this cycle, the *citric acid cycle*. Recall that anaerobic glycolysis can only use glucose as substrate. Mitochondrial oxidation is unique in that two carbon units can be derived from glucose, fats, or proteins (amino acids). Moreover, carbohydrate substrates are oxidized much more completely, resynthesizing 18× more ATP as compared with anaerobic glycolysis, making mitochondria an ideal energy-exchange device within cells.

As substrate is oxidized in the Krebs cycle, NAD^+ and FAD are subsequently reduced; NAD^+ accepts one hydrogen ion (H^+) and two electrons ($2e-$) to become NADH; FAD is reduced by accepting $2e-$, 1 H^+, and one hydride ion ($:H^-$) to become $FADH_2$ (a hydride ion is a hydrogen atom that has two as opposed to one electron, hence the negative charge). Once reduced, NADH and $FADH_2$ deliver electrons to the electron transport chain (also known as the respiratory chain).

11.3 Electron Transport Chain: Gradient 2

The electron transport chain (ETC) represents another type of gradient that begins the two-part process of oxidative phosphorylation; this gradient is located within the lipid bilayer of the inner mitochondrial membrane. The word *oxidative* describes the association of the electron carriers with oxygen (phosphorylation is described later where ATP undergoes re-synthesis). Oxygen's attraction for electrons is great, providing the impetus for a gradient. As a metabolic gradient, oxidative phosphorylation describes driving forces that are exploited for useful purposes. Toward the top of the gradient are the electron carriers NADH and $FADH_2$, oxygen (O_2) is found at the bottom of the gradient (note that oxygen is not a part of the Krebs cycle, it is only found in the ETC) (Fig. 11.5).

NADH and $FADH_2$ enter the ETC at different places so that the attraction or electronegativity of oxygen for the electrons carried by NADH and $FADH_2$ is different. The electrical charge between NADH entering at the top of the ETC and oxygen at the bottom has been measured at 1.14 V ($\Delta G^\circ = -220\,\mathrm{kJ\,mol^{-1}}$). $FADH_2$ enters the ETC at a lower point than does NADH, and so the energy differential is slightly less than that of NADH ($\Delta G^\circ = -200\,\mathrm{kJ\,mol^{-1}}$).

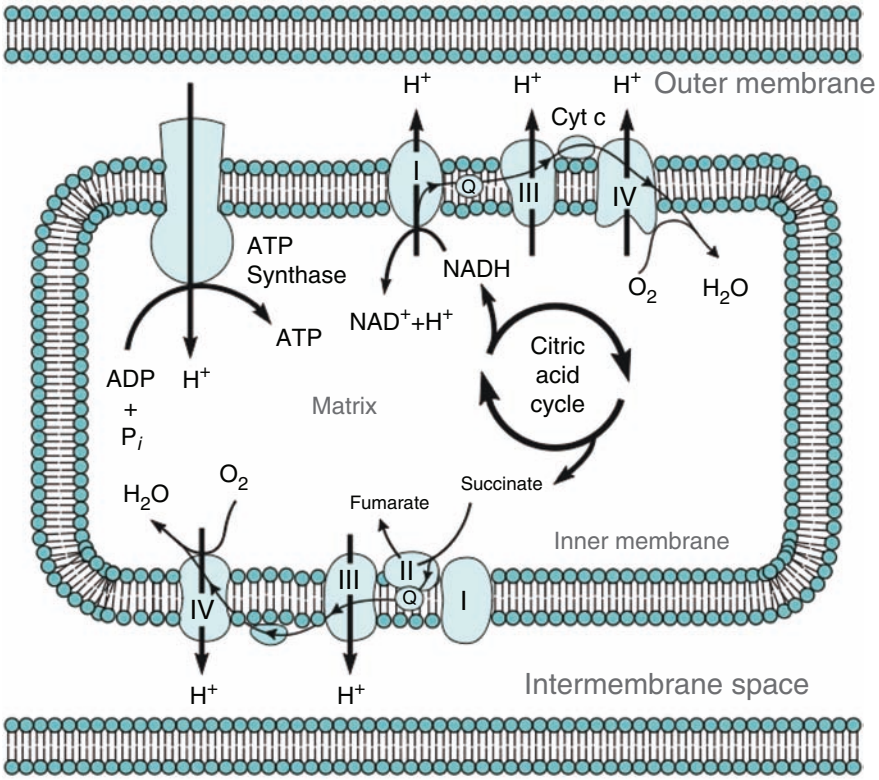

Fig. 11.5 The electron transport chain (ETC) is depicted above within the mitochondria's inner membrane as I, Q, III, Cyt c, IV. Hans Krebs' Citric Acid Cycle supplies electrons to the ETC. An ATPase is also shown. Overall ΔG° spanning the complete ETC is $-220\,\mathrm{kJ\,mol^{-1}}$ (9). Oxygen is reduced with both electrons and protons to form water (courtesy of Tim Vickers, http://commons.wikimedia.org/wiki/Image:Mitochondrial_electron_transport_chain%E2%80%94-Etc4.svg)

The word *phosphorylation* describes the attachment of Pi to ADP, but similar to the Krebs cycle, actual ATP resynthesis is not directly associated with the ETC. The energy exchange of electron transfer is instead made available to pump protons (H^+) from one side of mitochondria's inner membrane to another. As a result, a proton-motive force is created.

11.4 Proton-Motive Force: Gradient 3

Humans and animals (including scientists!) often learn by example. But this is not always the case. Take for instance the birth of biochemistry where glycolysis was

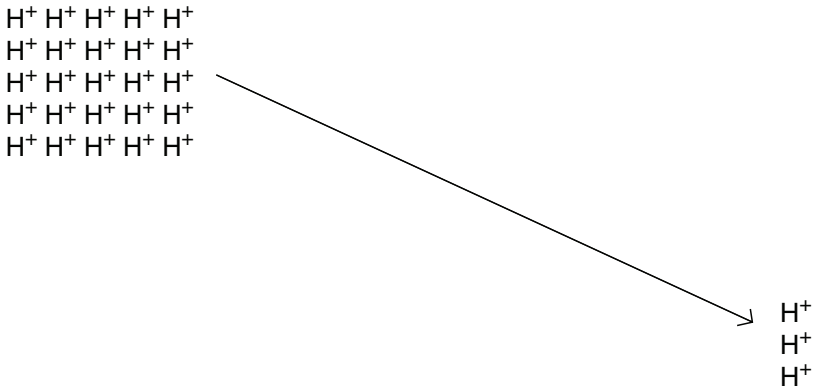

Fig. 11.6 The proton-motive gradient invokes a force, what Peter Mitchell described as chemiosmosis. This is the third gradient of aerobic energy exchange (the Krebs cycle and ETC representing the other two gradients)

discovered as a form of substrate-level phosphorylation in the re-synthesis of ATP. From such a perspective it would appear natural to search for a similar means in the quest to uncover the mitochondrial mechanism of ATP resynthesis. Based on this line of reasoning, it was thought that mitochondrial proteins (enzymes) were directly involved in phosphate (Pi) shifts and transfers, just as they were for anaerobic glycolysis. Mitochondria were discovered as the source of aerobic metabolism in the mid-1940s and subsequently dissected to reveal anatomical structure in the 1950s. Biochemical analyses followed suite. Many proteins were found, yet the search for the mechanisms of aerobic substrate-level phosphorylation proved futile, they simply were not there. A novel approach to aerobic energy exchange was seemingly called for. In 1961 a scientist by the name of Peter Mitchell (1920–1992) came up with a hypothesis that even today is still referred to as a radical mechanism of ATP resynthesis. Over the years disproof of his idea was never found; he was rewarded with a Nobel Prize in 1978.

Mitchell elucidated how electron transfer within the ETC provided the energy to physically pump protons (H^+) from the inside to the outside of the inner mitochondrial membrane. With this pumping a buildup of H^+ takes place, being greater on the outside as compared with the inside of the mitochondrial inner membrane. For every pair of electrons provided by NADH, 10 H^+ are pumped; for every pair of electrons provided by $FADH_2, 6H^+$ are pumped (10). A gradient is created that is both chemical (H^+) and electrical (charge separation across a membrane) in nature (Fig. 11.6).

Residing across the inner mitochondrial membrane is a protein-derived proton portal known as mitochondrial ATPase. The buildup of hydrogen ions created by the ETC literally "fall" down their gradient through this portal and the energy exchange of this transfer is captured by the ATPase to resynthesize ATP from ADP and Pi. In

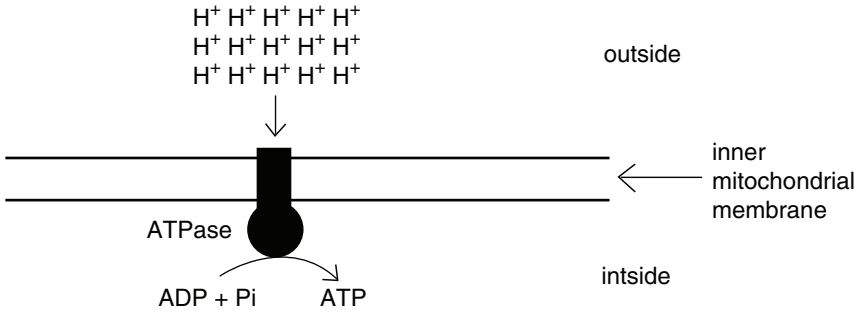

Fig. 11.7 The mitochondrial ATPase is shown in *black* above spanning the inner mitochondrial membrane. Mitochondrial ATPase is a rotary engine of sorts whose protein components spin as protons pass through. This rotational energy is captured and utilized to resynthesize ATP from ADP and Pi

reality, H^+ do not pass through the membrane in a linear fashion but instead travel along a complicated pathway created by the protein structures of the mitochondrial ATPase (12, 13). At least two H^+ pathways are present in the mitochondrial ATPase; one that is associated with the degradation of the proton-motive force, the other with the reduction of oxygen to form water (13). Current evidence suggests that passage of 3 H^+ through the mitochondrial ATPase is required for each ATP resynthesized (see Fig. 11.7).

The passage of protons down the chemiosmotic gradient is said to be tightly coupled when each H^+ travels through the mitochondrial ATPase. However, as with most energy-exchange devices this coupling is not perfect (inefficient) and the chemiosmotic gradient is no exception. Membranes are not perfect barriers. When protons traverse the inner mitochondrial membrane without resynthesizing ATP, respiration is said to be uncoupled. In some tissues this is a natural phenomenon, producing heat rather then ATP in the process. Brown adipose tissue (BAT) for example, found in small mammals and infant (but not adult) humans, acts as a type of furnace producing heat for protection from the cold. The presence of specific proteins called uncoupling proteins (UCPs) seems to on the one hand encourage inefficiency in terms of ATP production; on the other hand, in terms of heat output rather than heat loss, this is an effective mechanism.

11.5 The Creatine Phosphate Shuttle

The ATP that undergoes resynthesis within mitochondria is not the ATP that undergoes hydrolysis in other areas of the cell. In muscle, for example, a shuttle system is thought to exist between the sites of energy supply (i.e., mitochondria) and energy demand (e.g., the muscle sarcomeres) – the creatine phosphate (CP) shuttle – to help maintain high levels of ATP and low levels of ADP at both sites (14). Recall that it

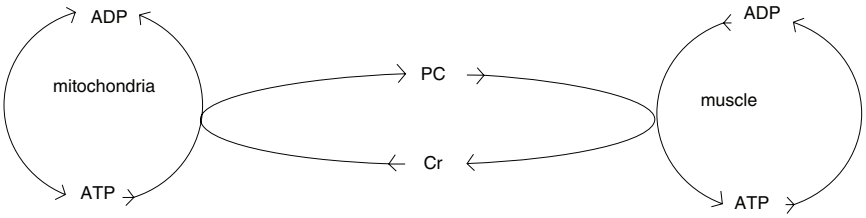

Fig. 11.8 The creatine phosphate shuttle. In this scenario the two energy-exchange devices – mitochondria and muscle – are separated in an apparent attempt to minimize the effect one system has on the other while matter and energy fluxes continuously take place within and without both. Adapted from (14)

is critical to the Gibbs energy availability of ATP to maintain high [ATP] and low [ADP] concentrations (see Fig. 7.5). Also recall that the two systems, mitochondrial energy exchange and muscle contraction energy exchange, are open systems. The CP shuttle is hypothesized to act as a buffer between the two systems, possibly preventing drastic changes in both systems from taking place in response to those fluxes taking place within and without any one system (Fig. 11.8). ATP undergoes hydrolysis at the myosin–actin interface of the sarcomere forming ADP and Pi. That ADP is immediately re-phosphorylated by CP. The left-over creatine (Cr) is shuttled to the mitochondria where ATP re-phosphorylates Cr to form CP.

11.6 ATP Tally

Net ATP resynthesis is now derived from the complete anaerobic and aerobic oxidation of glucose (Table 11.2) (15).

Table 11.2 ATP resynthesis from anaerobic and aerobic sources

Source	Metabolism	ATP
Substrate-level phosphorylation	Glycolysis	2
$2NADH + H^+$	Glycolysis	4
$2NADH + H^+$	Pyruvate – acetyl CoA	6
Substrate-level phosphorylation	Krebs cycle	2
$6NADH + H^+$	Krebs cycle	4
2FADH2	Krebs Cycle	18
		36

The values are estimates and vary slightly depending on the source (the exact amount of ATP resynthesized in regard to the amount of oxygen consumed likely varies slightly among cell types and under different conditions (e.g., the extent of uncoupling proteins differs among cells) (adapted from (15)).

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Part III
Metabolism

Chapter 12
Aerobic Energy Expenditure

The best measures of energy exchange require detailed analyses of all matter and energy entering, staying within, and leaving a system. As the term implies however, *energy expenditure* focuses only on what is leaving the system and, concomitantly, what is gained by the surroundings (environment). The differences between closed and open systems have been detailed throughout this text. From the standpoint of a closed system, for example, heat (energy) *added to the system* from the surroundings was given a positive sign ($+\Delta$H). Heat (energy) leaving or *subtracted from a closed system* to the surroundings is given a negative sign ($-\Delta$H). As related to an open system however the vantage point is reversed (think Schrodinger's negative entropy); energy expended *from the system* and being *added to the surroundings*. Energy expended from an open system and added to the surroundings can be given a positive sign ($+$).

12.1 Combustion, Respiration, and Heat

The enthalpy (ΔH) of glucose oxidation (closed-system combustion) was provided in previous chapters as being subtracted from the system, hence the negative sign:

$$C_6H_{12}O_6 + 6O_2 = -2,802\,\text{kJ}\,\text{mol}^{-1}$$

This reaction can also be rewritten to reveal the heat produced, not lost, by the oxidation of glucose within an open biological system (1). Notice that the negative sign of the enthalpy change below has been replaced by a positive sign to denote energy expenditure to the surroundings:

$$C_6H_{12}O_6 + 6O_2 = +2,802\,\text{kJ}\,\text{mol}^{-1}\ (669\,\text{kcal}\,\text{mol}^{-1})$$

Heat is a product of oxidation; with no work being performed, heat represents both enthalpy change and energy expenditure. The oxidation of palmitate (palm oil), a

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prototypical fat, is (1):

$$C_{16}H_{32}O_2 + 23O_2 = +10{,}040\,\text{kJ}\,\text{mol}^{-1}\ (2{,}398\,\text{kcal}\,\text{mol}^{-1})$$

Palmitate (palmitic acid) is a 16-carbon fatty acid; fatty acids range from 1 to 30 carbons in length.

Heat and oxygen uptake have been well studied in a variety of academic arenas. The biological and fire sciences are two examples. Yet as diverse as metabolic respiration and combustion may at first appear, it has been known since the late eighteenth century that the heat and gases exchanged, be they a product of respiration or combustion, are identical.

"la respiration est donc une combustion" Antoine Lavoisier (1743–1796)

Lavosier's statement is a rather remarkable one considering it was made well over 200 years ago; he has not yet been disproven (nor should he ever be). Scientists built upon this reasoning by recognizing that the oxidation of carbohydrate (glucose) and fat – be it by combustion or respiration – was different per molecule of oxygen consumed: Carbohydrate results in greater heat production as compared with fat. This concept was originally interpreted in terms of substrate efficiency, "... pure carbohydrate combustion is approximately 12% more efficient than pure fat or, pure fat is approximately 11% less efficient than pure carbohydrate according to the basis of comparison" (2). It needs to be well recognized that this statement, taken from a 1928 article in *The Journal of Nutrition*, came from scientists who aptly measured gas and heat exchanges, yet made no calculations of entropy exchange from system to surroundings. Indeed, biochemical energy exchange pathways were not yet known. If heat and entropy are considered different forms of energy, then a measurement of heat alone does not account for changes in entropy. Consider glycolysis with either pyruvate (entropy driven) or lactate (enthalpy driven) as an end product (see Table 10.2). As was demonstrated previously, a metabolic pathway – aerobic or anaerobic – is an energy-exchange device that adheres to the second law of thermodynamics and thus operates with a degree of inefficiency; it is not a heat engine, but environmental heat and entropy increases are the result.

12.2 Thornton's Law: Combustion

In 1917, William Thornton published his study of heat and oxygen uptake during the combustion of a variety of organic fuels. The results revealed a relationship so straight forward that it became known as Thornton's Law (or Thornton's rule) (3). As depicted by Thornton, the heat (energy) production of most combusted fuels is remarkably consistent when expressed per unit of oxygen consumed, with most data points falling within $\pm 5\%$ of a line of best fit (Fig. 12.1).

While Thornton depicted the combustion of gas, the same rule applies to liquids and solids (4–6). Oxygen has a high electronegativity and hence a strong attraction for electrons. As oxygen "grabs" electrons (more appropriately, electrons are shared

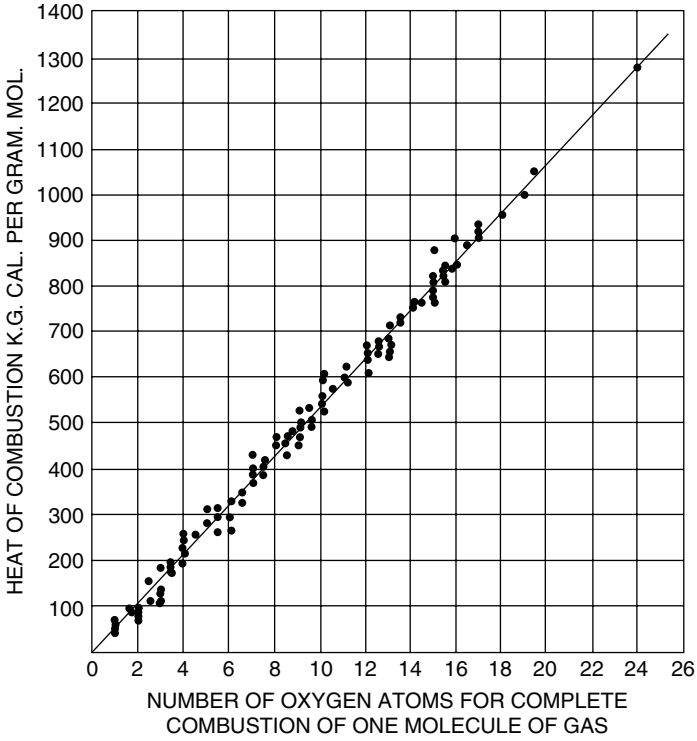

Fig. 12.1 "... when combustion is complete with one oxygen atom the heat set free, irrespective of bonds is 52.4 calories per gram molecule of combustible gas, when with two atoms 105.9, with three 158.59." This figure and quote were taken from Thornton's original paper (3)

when carbon binds to oxygen as CO_2 and hydrogen binds to oxygen as H_2O) from a fuel during combustion, a similar amount of heat is released regardless of the source of those electrons: Similarity falls within $\pm 5\%$ of a line of best fit (scholars will note this 5% figure as identical to the error associated with statistical analysis at $p < 0.05$). Oxygen appears to make little distinction as to where electrons are obtained during combustion; heat production per electron transfer appears relatively similar whether those electrons come from wood, coal, alcohol, fat, glucose, etc. Predicted heat production during electron transfer from substrate to oxidant was standardized by Thornton's line of best fit (Fig. 12.1) (4):

$$-111\,\mathrm{kJ\,mol^{-1}} \text{ of electrons}$$

The variance about the line of best fit that is seen as electrons are transferred to oxygen from different fuel sources is largely dependent on the *proportion* of the types of bonds within the reactant molecules: carbon–carbon, carbon=carbon, carbon=oxygen, hydrogen–carbon=oxygen, and carbon–oxygen–hydrogen (−, single; =, double). The larger the molecule the more proportional the types of bonds

tend to be. For smaller molecules, this proportionality tends to deteriorate, revealing a greater variability in oxygen uptake–heat production relationships. As an example, the carbon–hydrogen bond (C—H) comprises 62% of palmitate and 32% of glucose (recall in Chap. 5 that enthalpy changes, ΔH, are calculated based on the enthalpy of formation, and so while the bonds formed with CO_2 and H_2O production are not different, the starting points are). If the relative amount of C—H bonds were similar between fats and carbohydrates, less absolute distinction would be found among their respective heats of combustion during oxidation.

Actual heat production per mole of electron exchange is provided for palmitate and glucose below revealing a 6% difference between the two (4):

$$\text{Palmitate} = \sim 109\,\text{kJ}\,\text{mol}^{-1}\ (26.154\,\text{kcal}\,\text{mol}^{-1})$$
$$\text{Glucose} = \sim 116\,\text{kJ}\,\text{mol}^{-1}\ (27.697\,\text{kcal}\,\text{mol}^{-1})$$

The number of electrons transferred for glucose and fat oxidation is shown below:

Glucose

$$C_6H_{12}O_6 + 6O_2 \rightarrow 24e^- + 24H^+ \rightarrow 6CO_2 + 6H_2O$$

Palmitic acid

$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 92e^- + 92H^+ \rightarrow 16CO_2 + 16H_2O$$

If the measured heat production per mole of oxidized glucose (2,802 kJ) and fat (10,040 kJ) is compared with the heat (energy) equivalent of electron transfer per substrate (palmitate = $\sim$109 kJ mol^{-1}; glucose = $\sim$116 kJ mol^{-1}) and the heat production of standard electron transfer ($-$111 kJ mol^{-1} of electrons), then it can be seen how precise these respective measures and estimates are: $\pm$5%, within, not between substrates):

Glucose

$$24e^- \times 116\,\text{kJ (actual)} = 2{,}784\,\text{kJ (a 0.6\% difference compared with 2,802 kJ)}$$
$$24e^- \times 111\,\text{kJ (standard)} = 2{,}664\,\text{kJ (a 4.9\% difference compared with 2,802 kJ)}$$

Palmitic acid

$$92e^- \times 109\,\text{kJ (actual)} = 10{,}028\,\text{kJ (a 0.1\% difference compared with 10,040 kJ)}$$
$$92e^- \times 111\,\text{kJ (standard)} = 10{,}212\,\text{kJ (a 1.6\% difference compared with 10,040 kJ)}$$

Scientists however do not directly measure electron transfer during either combustion or biological respiration. Instead, a measure of oxygen is made whose relationship to energy expenditure is estimated as an oxycaloric equivalent (4, 6):

$$-450\,\text{kJ}\ (\pm 5\%)\,\text{mol}\ {O_2}^{-1}$$

The difference between 109 kJ (palmitate oxidation) and 116 kJ (glucose oxidation) is 6%. This variance increases to over 7% when expressed per mole of oxygen. From a statistical point of view, an acceptable error of within $\pm$5% sets a rather

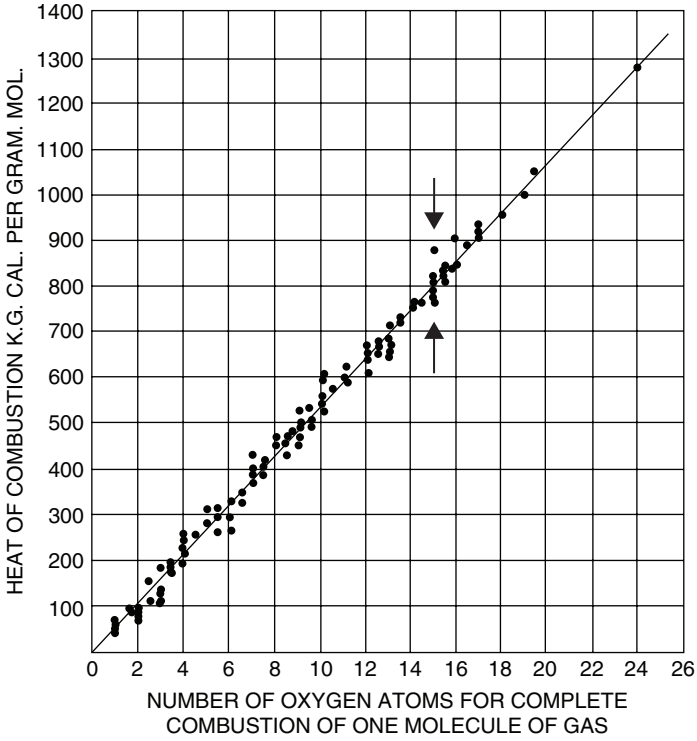

Fig. 12.2 A relatively large difference (e.g., 7%) in heat production per unit oxygen consumed is portrayed for two respective data points (e.g., glucose and fat). Yet both data points also fall within 5% of the line of best fit. Two interpretations are apparent. The two data points appear different in comparison to each other. But they are similar when compared with the line of best fit (modified from (3))

strict boundary, so that while small, a 6 or 7% variance can be considered significant. Thornton's rule along with the oxygen-based data of fat and glucose oxidation and heat production poses an interesting dilemma. Are glucose and fat oxidation significantly different in regard to the heat produced per the proportion of bond types within each molecule or should they be regarded as similar because they each fall within ±5% of the line of best fit (Fig. 12.2)? In fact, both statements are correct.

12.3 Respiration and Energy Expenditure

As Lavoisier indicated over 200 years ago, respiration and combustion are similar processes in regard to heat production and oxygen consumption (they are dissimilar in terms of the rate of the reaction; respiration being a slowed down version of combustion). The oxycaloric equivalent for respiration is (7):

$$-470\,\text{kJ}\ (\pm 5\%)\,\text{mol}\ {O_2}^{-1}$$

The $-20\,\mathrm{kJ\,mol\,O_2}^{-1}$ (4%) difference between combustion (at $-450\,\mathrm{kJ\,mol\,O_2}^{-1}$) and respiration (at $-470\,\mathrm{kJ\,mol\,O_2}^{-1}$) results from the medium of living tissue that surrounds the metabolic pathways. Acid–base reactions for example are associated with heat exchange, but they are not associated directly with energy expenditure (7). As with the combustive oxycaloric equivalent, the respiratory oxycaloric equivalent of $-470\,\mathrm{kJ\,mol\,O_2^{-1}}$ is remarkably consistent (±5%) for a variety of tissues undergoing full aerobic respiration. Based on measurements of cell cultures, a more exacting portrayal of glucose and palmitate oxidation via respiration reveals a difference of 7.5% (7):

Glucose and glycogen

$$-469\,\mathrm{kJ\,mol\,O_2}^{-1}$$

Palmitate

$$-434\,\mathrm{kJ\,mol\,O_2}^{-1}$$

Regarding biological energy exchange, the actual measurement of liters (volume) rather than moles (amount) of oxygen is often used to estimate energy expenditure (kJ). At a single standard temperature and pressure, one mole of gas has a volume of 22.4 L producing the following conversions for the above oxycaloric values:

Glucose and glycogen

$$-469\,\mathrm{kJ\,mol\,O_2}^{-1}/22.4\,\mathrm{mol\,L}^{-1} = 20.9\,\mathrm{kJ\,per\ liter\ of\,O_2}$$

Palmitate

$$-434\,\mathrm{kJ\,mol\,O_2}^{-1}/22.4\,\mathrm{mol\,L}^{-1} = 19.4\,\mathrm{kJ\,per\ liter\ of\,O_2}$$

A question was asked earlier concerning the difference or similarity with the heat produced by glucose and fat oxidation. Combustion scientists might view similarity (6). Exercise physiologists and nutritionists may take a contrary stance where the electron exchange from substrate to oxygen focuses not on similar heat production but instead on what is seen as a fundamental difference between fat and carbohydrate oxidation (2). These values are typified in nutrition and exercise physiology texts as:

Fuel	**Conversion**
Fat	$1\,\mathrm{L\ O_2} = 19.6\,\mathrm{kJ}$
Glucose	$1\,\mathrm{L\ O_2} = 21.1\,\mathrm{kJ}$

With fat having less heat produced per liter of oxygen consumed, is this difference indicative of glucose being a more efficient substrate as compared with fat as was suggested many decades ago, the difference being solely the result of their differing enthalpies of bond formation? In fact, enthalpy differences are only part of the answer. Succinctly put, the biological oxidation of glucose also differs from that of fat because there is an anaerobic energy exchange component to glucose but not fat metabolism. As will be demonstrated, metabolic heat and entropy exchange both need to be considered to better account for the discrepancy.

12.4 Heat and Gas Exchange

The equations below demonstrate heat production and gas exchange for glucose (top) and palmitate (bottom) oxidation:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2 + \sim 2{,}802\,\text{kJ}$$
$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16H_2O + 16CO_2 + \sim 10{,}040\,\text{kJ}$$

The fatty acid palmitate is a much larger molecule as compared with glucose, having 10 more carbon atoms (C), 20 more hydrogen atoms (H), and 4 less oxygen atoms (O). Based on size difference alone, it takes 17 more molecules of oxygen (O_2) to oxidize a molecule of palmitate as compared with glucose, and 10 more molecules of carbon dioxide (CO_2) are formed with palmitate.

The size difference between glucose and fat molecules can be eliminated when expressing biological oxidation (gas exchange) as a ratio. Comparisons between biological glucose and fat oxidation are usually presented in the context of the ratio of carbon dioxide produced to oxygen consumed; this is known as the respiratory quotient or RQ:

$$RQ = CO_2/O_2$$

For glucose:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2$$
$$RQ = 6CO_2/6O_2$$
$$RQ = 1.00$$

For palmitate:

$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16H_2O + 16CO_2$$
$$RQ = 16CO_2/23O_2$$
$$RQ = 0.70$$

Notice that the RQ is dimensionless; no units are attached (it is a simple ratio and not based on the size of the molecules being oxidized). At first glance it may appear that fat requires more oxygen to undergo oxidation as compared with glucose. It must be recognized however that within cells glucose and glycogen are first broken down anaerobically by the glycolytic metabolic pathway to form two 3-carbon molecules (either pyruvate or lactate). But only 2-carbon products can be further oxidized via aerobic respiration. Prior to pyruvate's entrance into the Krebs cycle a decarboxylation must take place, whereby a carbon dioxide molecule is evolved (as part of the pyruvate dehydrogenase or PDH reaction). To the contrary, fat molecules are degraded 2-carbon units at a time during oxidation. From the perspective of the volume of oxygen consumed, less carbon dioxide is evolved with fat oxidation because fatty acids are broken down into 2-carbon molecules not 3-carbon molecules (as is glucose and glycogen). Taken in the context of the RQ then, fat oxidation does not require more oxygen during oxidation as compared with glucose.

When oxygen uptake and carbon dioxide production are at steady-state rates, the RQ is a powerful tool that enables us to distinguish substrate disappearance during respiration, be it fat or glucose or combinations of both (8, 9) (see Table 12.1). In resting humans the RQ tends to be low, usually near the 0.70 figure, indicating the predominate utilization of fat as a fuel. As exercise intensity rises, glycogen becomes the predominant fuel within working muscle. With total carbohydrate utilization an RQ of 1.00 is observed (when measured at the mouth, hyperventilation and/or the release of any stored carbon dioxide causes an increase in carbon dioxide production that is not related to immediate metabolic respiration and the ratio of CO_2/O_2 exceeds 1.00 (the recovery from exercise is a wonderful example of this); when measured at the mouth the RQ is known as the respiratory exchange ratio or RER).

At an RER of 0.70 an oxygen uptake to energy expenditure conversion has been widely published and universally accepted for fat oxidation as:

$$1\,\text{L of } O_2 = 19.6\,\text{kJ}$$

At an RER of 1.00 the oxygen uptake to energy expenditure conversion for glucose oxidation is recognized as:

$$1\,\text{L of } O_2 = 21.1\,\text{kJ}$$

Per liter of oxygen consumed, the heat production of glucose oxidation (at 21.1 kJ) exceeds that of fat (at 19.6 kJ) by 1.5 kJ or more than 7%. These values are correct. So again, why do they differ by more than an accepted range of $\pm 5\%$?

12.5 Aerobic Energy Expenditure as Heat and Entropy

Oxygen uptake to energy expenditure conversions as represented by the RER are not an indication of the efficiency of the substrate per se. The fact that glucose oxidation evolves more heat per mole of oxygen consumed does not indicate that it is a more efficient a fuel as compared with fat. Nor does it mean that when ATP resynthesis is expressed as a phosphorylation to oxygen ratio (P/O ratio), glucose oxidation by mitochondria (where P/O = 2.7) has a greater phosphorylation potential than fat oxidation (where P/O = 2.3). If nutritionists and exercise physiologists accepted a standard oxygen uptake to heat exchange factor for aerobic energy expenditure as depicted by Thornton's law and acknowledged the distinct enthalpy *and* entropy changes of glucose-to-pyruvate and glucose-to-lactate breakdown, then a hypothesis can be promoted that perhaps better describes metabolic energy expenditure, or in the very least enables a separation of anaerobic energy expenditure from aerobic energy expenditure. Simply put, energy expenditure derived from the RER provides as much information concerning the presence of the aerobic and anaerobic *metabolic pathways* as it does about the *substrate* being oxidized.

For the moment let us accept measured energy exchange per amount of oxygen consumed at -470 kJ ($\pm 5\%$) per mole of O_2. This all-aerobic conversion factor (i.e.,

Thornton's law) can also be interpreted as (10–12):

$$1\,\text{L of } O_2 \approx 19.6\,\text{kJ}$$

With the above oxygen to heat conversion in mind, recall six basic energy exchange tenets as they relate to biological metabolism:

1. Energy expenditure results from energy exchange. Energy exchange is a composite of energy conversion (from one form to another with heat production) and energy transfer (from one place to another, increasing overall entropy).
2. Glucose and glycogen oxidation involves anaerobic energy exchange as substrate-level phosphorylation and aerobic energy exchange as mitochondrial respiration at 21.1 kJ per liter of O_2.
3. Fat oxidation involves only mitochondrial respiration at 19.6 kJ per liter of O_2.
4. Aerobic (mitochondrial) metabolic heat production is relatively large (13). A large metabolic heat production as a part of anaerobic glycolysis (substrate-level phosphorylation with lactate production) is also apparent for glucose-to-lactate degradation. However, aerobic glycolysis (substrate-level phosphorylation with pyruvate production) consists of a rather small amount of exchanged heat (14). The degradation of glucose-to-lactate is enthalpy driven; the degradation of glucose-to-pyruvate is entropy driven (14).
5. When the consumption of a volume of oxygen is used to estimate metabolic energy expenditure part of the 1.5-kJ difference between glucose and fat oxidation results in part from their respective enthalpies of bond formation ($\pm 5\%$).
6. Overall entropy increases as a result of metabolic power production (15–17).

Based on heat measurements alone it is apparent that the energy exchanges associated with metabolic substrate-level phosphorylation are not measured in full when pyruvate as opposed to lactate is the end product of glycolysis. When lactate is produced the heat evolved does account for glycolytic ATP resynthesis. Consider also that 2 or 3 ATPs are resynthesized via anaerobic substrate-level phosphorylation from glucose and glycogen, respectively; 32–33 ATPs are resynthesized via the aerobic mitochondrial oxidation of glucose and glycogen, respectively:

$$\text{2–3 ATP glycolysis} + \text{32–33 ATP aerobic oxidation} = \text{34–36 total ATPs}$$

When expressed in relative terms, anaerobic ATP resynthesis from glucose and glycogen oxidation (on average) represents $\sim 7\%$ of the total. The relative difference between 21.1 kJ (glucose oxidation) and 19.6 kJ (fat oxidation) is also $\sim 7\%$. This similarity need not be considered mere coincidence. Instead, these 7% differences can be interpreted as being very much related. Clearly, glycolytic substrate-level phosphorylation is an inefficient energy exchange process whether the end product is pyruvate or lactate. But accountability originates from different sources dependent on the glycolytic end-product: pyruvate or lactate, respectively associated with greater entropy or heat. When energy expenditure is interpreted as a heat measurement, how can the entropy component of glucose-to-pyruvate degradation be accounted for? From the perspective of metabolic energy expenditure (from the

system to the surroundings), *with Gibbs energy availability and ATP resynthesis equivalent between the two sets of reactions*, the combined heat (−4.4 kJ) and entropy (+62.6 kJ) exchanges of the glucose-to-pyruvate metabolic reactions can be equated to the heat (+40.0 kJ) and entropy (+18.2 kJ) exchanges of the glucose-to-lactate reactions (14) (Note that the enthalpy changes shown below are opposite those provided by Minakami and de Verdier (14) because the vantage point has changed, focusing on expenditure to the surroundings (see Table 10.2). Regardless of negative or positive internal entropy changes within a system, the overall or global entropy always increases to an equivalent extent or more):

$$\begin{aligned} \text{glucose-to-pyruvate} &= \text{glucose-to-lactate} \\ -4.4\,\text{kJ}\,\Delta\text{H} + 62.6\,\text{kJ}\,\Delta S &= +40.0\,\text{kJ}\,\Delta\text{H} + 18.2\,\text{kJ}\,\Delta S \\ 58.2\,\text{kJ} &= 58.2\,\text{kJ} \end{aligned}$$

Considering also the basic premise of Thornton's law, the 1.5-kJ difference between glucose and fat oxidation expressed as one liter of measured oxygen uptake can be presented as the glycolytic component of total glucose oxidation:

$$19.6\,\text{kJ aerobic metabolism} + 1.5\,\text{kJ anaerobic metabolism} = 21.1\,\text{kJ per liter of}\,O_2$$

When expressed as a P/O ratio, the greater mitochondrial phosphorylation value for glucose (2.7) as compared with fat (2.3) also does little to justify that some ATP is resynthesized anaerobically during complete glucose oxidation. Mitochondrial oxidative phosphorylation is no more efficient using glucose or fat as substrate; again, it is the glycolytic component of glucose degradation, not the mitochondria, that boosts the P part of the P/O ratio for glucose.

12.6 CO_2 and O_2: RER = Aerobic and Anaerobic Energy Exchange

By definition, anaerobic energy exchange does not involve oxygen, and so when included as part of an oxygen uptake measurement the conversion suggests the appearance of greater aerobic energy expenditure per liter of oxygen consumed. But it is the anaerobic component of glucose oxidation (substrate-level phosphorylation) that accounts for the additional energy expenditure. This recognition does not in any way devalue the thermal equivalent of oxygen based on RER (8, 9, 18). Energy expenditure based on the RER is simply interpreted as the anaerobic thermal component to carbohydrate oxidation based on the percentage of energy derived from glucose (Table 12.1).

There are applications for an all-aerobic energy expenditure conversion (1 L O_2 = 19.6 kJ) that does not contain a glycolytic component. As will be demonstrated in Chap. 16, an all-aerobic energy expenditure conversion that contains no anaerobic metabolic component appropriately estimates energy expenditure in the recovery from exercise, when there is little to no anaerobic glycolytic component to metabolic

Table 12.1 Respiratory exchange ratio and glucose-related heat exchange

RER	kJ	% energy from glucose
0.70	19.61	0
0.71	19.62	1.1
0.72	19.67	4.76
0.73	19.72	8.4
0.74	19.78	12.0
0.75	19.83	15.6
0.76	19.89	19.2
0.77	19.93	22.8
0.78	19.98	26.3
0.79	20.03	29.9
0.80	20.09	33.4
0.81	20.14	36.9
0.82	20.19	40.3
0.83	20.24	43.8
0.84	20.29	47.2
0.85	20.34	50.7
0.86	20.40	54.1
0.87	20.45	57.5
0.88	20.50	60.8
0.89	20.55	64.2
0.90	20.60	67.5
0.91	20.65	70.8
0.92	20.70	74.1
0.93	20.76	77.4
0.94	20.81	80.7
0.95	20.86	84.0
0.96	20.91	87.2
0.97	20.96	90.4
0.98	21.01	93.6
0.99	21.07	96.8
1.00	21.10	100.0

These data are derived from a 1901 manuscript and are as useful today as when they were first presented over 100 years ago (18). It is of interest that none of the energy exchange biochemistry behind the aerobic and anaerobic metabolic pathways was known at this time so that efficiency was explained solely from the standpoint of heat produced per volume of oxygen consumed between substrates being oxidized; that is, heat loss by the system not energy expenditure of the system.

energy exchange (also, recovery is not a physiological steady state so that the data in Table 12.1 should not be used). It will be further demonstrated that the separate use of aerobic and anaerobic estimates of energy expenditure allows researchers to measure both the anaerobic energy expenditure of exercise and the aerobic energy expenditure of recovery with no overlap. Indeed, the inclusion of anaerobic energy expenditure with an oxygen uptake measurement taken during the recovery from exercise (e.g., $1\,L\,O_2 = 21.1\,kJ$) has for years handcuffed exercise physiologists in the interpretation of exercise and recovery energy expenditure.

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Chapter 13
Anaerobic Energy Expenditure

Aerobic metabolism actually consumes oxygen so that its measurement provides a rational estimate of aerobic energy expenditure. But what is to be measured in the estimation of anaerobic energy expenditure? Scientists have not yet reached a consensus on how anaerobic energy expenditure is to be quantified. Lack of a gold standard measurement decries validation so that all current estimates of anaerobic energy expenditure are mediocre at best and just plain wrong at worst. Because of these difficulties energy expenditure tends to be quantified solely in the context of oxygen uptake. And therein lays a problem. Some scientists have grown content using a measurement of oxygen uptake to estimate the energy expenditure of all activities, including those that are fueled to a large and significant extent by anaerobic metabolism. To others (perhaps most?) this is folly (1). Concerning the latter, reasonable estimates of anaerobic energy expenditure may need to be promoted as being better than none at all (2). In one experiment involving direct analysis, for example, genetically modified yeast cells were "encouraged" to enhance anaerobic ATP resynthesis, and they did. In result, oxygen uptake decreased 36% but ATP turnover remained unchanged. It is apparent that a 36% reduction in oxygen uptake does not represent unchanged ATP turnover (3). In athletes as opposed to yeast, indirect estimates are used where it has been suggested that when an all-out sprint invokes complete fatigue in about 75 the contributions of aerobic and anaerobic energy expenditure are roughly 50% each (4), so that clearly, neither the aerobic or anaerobic contribution can be omitted.

13.1 The Oxygen Deficit

The first portrayal of oxygen uptake in the transition from rest to exercise took place in the early 1900s (5, 6). Exercise was performed on a bicycle ergometer with subjects seated quietly at rest then . . . the sudden initiation of a constant or steady-state work rate took place. What was found and is now well accepted was that, "at the transition from rest-to-work the oxygen intake does not rise instantaneously though

C. B. Scott, *A Primer for the Exercise and Nutrition Sciences*
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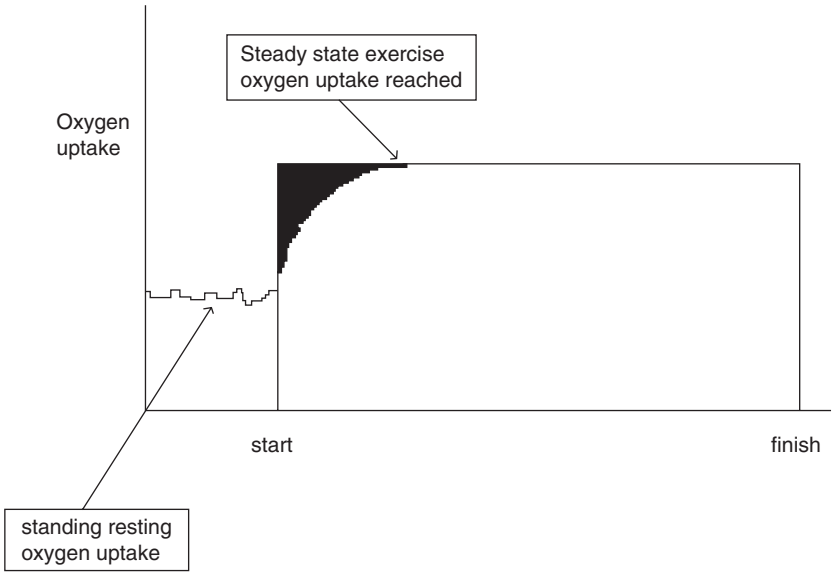

Fig. 13.1 Imagine standing over and straddling a moving treadmill belt, then suddenly stepping on and walking. The treadmill belt is moving at a steady rate and so too would you; the energy expenditure of this work rate is constant. Starting from a standing rest it takes about 2 min for oxygen uptake to rise and enter a steady state that is proportional to the energy demand of the walking speed. The area in *black* is the oxygen deficit

very rapidly to a level corresponding to the amount of work performed" (6). It was obvious to these researchers that the immediate energy demand required to perform the work not supplied by aerobic means was accounted for or supplied as anaerobic energy expenditure. The transition period that lacked oxygen consumption was termed the *oxygen deficit*. For light exercise the timely but rapid rise in oxygen uptake from rest up to a steady-state takes about 2 min so that the oxygen deficit period lasts approximately the same for easy exercise (Fig. 13.1). The rate of the rise of oxygen uptake at the start of work and during work load transitions is studied as oxygen uptake kinetics. Note that during the oxygen deficit work rates exceed the rate of oxygen update.

The oxygen deficit elegantly portrays the anaerobic energy expenditure of light to moderate exercise when energy demand and energy supply are in steady state. In Fig. 13.1, steady-state oxygen uptake is achieved at 2 min from the start of exercise. In Table 13.1 measurements are taken every 30 s within this 2-min period, but oxygen uptake within any measurement period is traditionally portrayed as a liters per-minute or rate function measurement. Thus, within a 30-s measuring period the actual amount of oxygen consumed is half that of a per-minute interval being quantified in liters of oxygen as a capacity measurement. To determine the extent of the oxygen deficit, a rate function measure of oxygen uptake (L O_2 min^{-1}) must be converted to a capacity measurement (L O_2). The oxygen deficit for 30-s measurement periods is obtained by subtracting the actual rising oxygen uptake from the

Table 13.1 Calculating the oxygen deficit; rate function and capacity measures

Time (min:s)	Rate function (O_2 equiv $L\,min^{-1}$)	Capacity (O_2 equiv L)
0:00		
0:30	0.6	0.3
1:00	1.4	0.7
1:30	1.8	0.9
2:00	2.0	1.0

eventual steady-state oxygen uptake (Table 13.2). The 2-min accumulated oxygen deficit is a summation of each 30-s measurement period (Table 13.2) (5, 7). Notice that the accumulated oxygen deficit, an estimate of anaerobic energy expenditure, is represented in units of oxygen equivalents (O_2 equiv).

The period of oxygen deficit is said to contain several anaerobic metabolic energy expenditure components: glycolysis and glycogenolysis, hydrolysis of ATP and creatine phosphate (PC) stores, and the *myokinase* reaction (also known as the *adenylate kinase* reaction; ADP + ADP → ATP + AMP). The appearance and more importantly the extent of the so-called oxygen deficit is very different with heavy or severe exercise as compared with easy exercise because intense activity often contains a significant anaerobic component (Fig. 13.2). From a retrospective (historical) standpoint, bias is indeed present in that a period of energy expenditure void of oxygen consumption and associated exclusively with anaerobic metabolism has been described using the word *oxygen*. Had intense exercise been undertaken in the first descriptions of rest-to-work transitions of oxygen uptake, with full knowledge that the rate of oxygen uptake never matched energy demand, this period of time may have gone by another name, perhaps as flippant as "anaerobic surplus" as opposed to "oxygen deficit." For years the oxygen consumed during the recovery from exercise was also thought to represent anaerobic energy expenditure as the "oxygen debt" hypothesis; another clear-cut example of the prejudice associated with oxygen-related energy expenditure.

Problems with the oxygen deficit as a measure of anaerobic energy expenditure become apparent with heavy to severe exercise, when the rate of energy demand exceeds the rate of oxygen uptake *throughout* the exercise bout (Fig. 13.2). A problem

Table 13.2 Measuring the oxygen deficit during the first 2 min of exercise

Steady-state (L O_2)	Actual O_2 uptake (L O_2)	Steady-state – actual O_2 uptake (L O_2)
1.0	0.3	0.7
1.0	0.7	0.3
1.0	0.9	0.1
1.0	1.0	0.0
		1.0 L O_2 equivalents

The accumulated oxygen deficit over the above 2-min period is presented in 30-s intervals; these are capacity measurements not rate function measurements. In the above example, anaerobic energy expenditure based on the oxygen deficit is 21.1 kJ (1.0 L O_2 = 21.1 kJ).

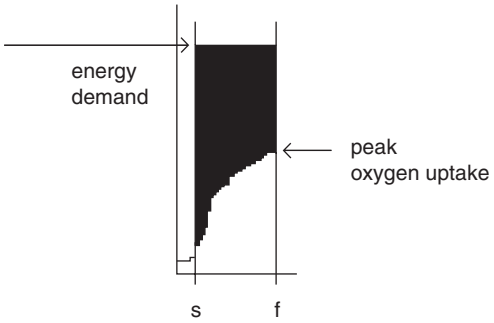

Fig. 13.2 A brief bout of heavy to severe exercise, measured in seconds, is depicted where the energy demand greatly exceeds oxygen uptake. The oxygen deficit is shown in *black*. Anaerobic metabolism makes a significant contribution to the overall energy expenditure of this exercise bout. Indeed, a measurement of oxygen uptake does not provide a valid account of the energy supply for this bout of intense exercise (s = start, f = finish)

also arises for heavy steady-state exercise as oxygen uptake becomes disproportional (nonsteady state) to unchanging power output. Likewise, the contributions of anaerobic metabolism may not remain proportional to an unchanging or steady-state power output. Because of the potential for multiple inherent errors in the estimation

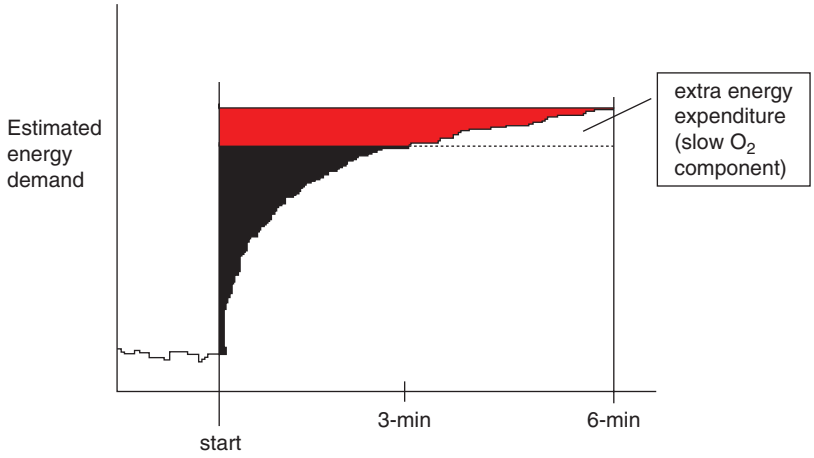

Fig. 13.3 The potential energy demand for a 6-min intense bike ride is shown (at a perceived exertion of "very hard"). The *stripped line* represents the estimated energy demand for this steady-state work rate. The oxygen deficit is shown in *black*. Unfortunately, oxygen uptake continues to climb above this line, never achieving a steady state, even though power output remains constant. The rise in oxygen uptake above the steady-state line has been termed *extra energy expenditure* (the slow oxygen component). The potential for an increase in anaerobic energy expenditure also exists (*in red*), but how much is unknown. Clearly, the presence of "extra" energy expenditure components to a steady-state unchanging power output is problematic when attempting to model energy expenditure. See also Fig. 15.5

of the energy demand for heavy to severe exercise, the size of the oxygen deficit and therefore the extent of anaerobic energy expenditure can be questioned (Fig. 13.3).

Even with shortcomings the oxygen deficit has at times proven useful in helping to model performance during heavy to severe exercise. Weyand and Bundle for example have revealed that a simplified measure of the oxygen deficit could predict performance in a large group of runners with elegant precision (8). Their simplification, a dismissal of oxygen uptake kinetics altogether, with the oxygen deficit estimated as being between VO_2max and an estimated energy demand, would be refuted by metabolic purists who discourage reasonable estimates. However, correlation between predicted and measured run times was $r = 0.97$; not bad for a supposedly invalid but not unreasonable marker of anaerobic energy expenditure.

13.2 Lactate

Exercise scientists are downright disputatious when it comes to explaining lactate ($C_3H_5O_3$) (lactic acid, $C_3H_6O_3$, is not usually produced at physiological pH, (9)). Lactate received its name because it was originally found in milk. As a product of anaerobic glycolysis, lactate is, simply, a glucose molecule that has been split in half. But while moderate levels of glucose are considered a good thing, lactate has been considered problematic, whatever its concentration (be it in muscle or blood). Lactate's reputation appears to have been sealed from the moment it was found within the muscle of a deer that had been "killed in the chase" (in 1807) (10). A connection in all likelihood was hastily convened, "exhausted deer . . . the presence of lactate." The rest as they say is history; lactate was thought to promote fatigue, exhaustion, pain, and muscle soreness. More recently lactate has been promoted in stature to that of fuel source (which it indeed is) (11). To this day, lactate's true nature continues to be debated (12). Yet regardless of personal opinion almost all agree that lactate is an active metabolite undergoing continuous production and removal within muscle and other tissues (12–15).

When the rate of pyruvate production via glycolysis and oxidative pyruvate removal via mitochondrial respiration are equivalent, energy expenditure is defined in the context of a composite of anaerobic and aerobic glucose metabolism as:

$$1\,\mathrm{L\,O_2} = 21.1\,\mathrm{kJ}$$

Lactate production proceeds when the energy (ATP) demand of a cell exceeds that of aerobic energy supply by mitochondrial ATP resynthesis; that is, (1) when pyruvate removal by mitochondria is at a maximum and/or (2) when the presence of oxygen at the electron transport chain is impaired (e.g., hypoxia). As lactate production exceeds lactate removal, an accelerated anaerobic ATP resynthesis begins to make an independent contribution to energy expenditure. Lactate production starts to exceed removal when the perceived exertion of physical work is thought to be "somewhat hard" to "hard." A popularized term for this seemingly abrupt increase in anaerobic metabolism is *anaerobic threshold*. Several descriptions of the anaerobic threshold

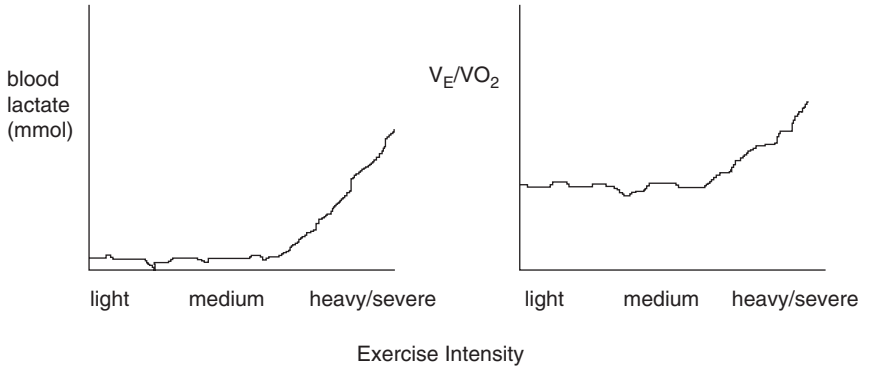

Fig. 13.4 Significant anaerobic contributions to energy expenditure are thought to begin at a perceived exertion of "somewhat hard" to "hard." On the *left*, lactate threshold; on the *right*, ventilatory threshold (V_E/VO_2): Each threshold is located at the break of the line from horizontal (the exact location can be a subjective decision). These two breakpoints may take place simultaneously but not necessarily always so

are known, being dependent on how the measurement is taken. When measured as a blood lactate concentration, a *lactate threshold* is described (some scientists describe the threshold as a 4-mmol blood lactate concentration; resting blood lactate concentrations may be 1–2 mmol) (Fig. 13.4). A threshold also is detected using ventilation measures. Normally, ventilation and oxygen uptake are proportionate during low to moderate intensity exercise (i.e., hyperpnea). As heavy to severe exercise is undertaken, hyperventilation ensues, where an abrupt increase in ventilation is seen that is disproportionate to the steady rise of measured oxygen uptake; this is termed the *ventilatory threshold* (Fig. 13.4).

A direct method of identifying anaerobic energy expenditure is to measure the heat loss of anaerobic energy exchange (recall that for anaerobic glycolysis heat loss is almost exclusively associated with the production of lactate not pyruvate (16)). Gnaiger and Kemp used direct and indirect microcalorimetry of mammalian cell cultures to reveal aerobic and anaerobic energy exchanges (17). Such a distinction can be identified by plotting the ratio of heat loss to oxygen consumed $(\mathrm{kJ/molO_2})$ with the amount of lactate produced to oxygen consumed $(\mathrm{lactate/O_2})$ (Fig. 13.5).

Based on calorimetry–respiratory (CR) data, it can be concluded that the measured heat loss of an accelerated anaerobic metabolism represents an increase in energy expenditure above that estimated by oxygen uptake. As anaerobic glycolytic energy expenditure out-accelerates aerobic energy expenditure, a measurement of oxygen uptake underreports true energy expenditure. However, anaerobic glycolytic contributions to energy expenditure appear significant only for well-defined periods of time; for example, the continuous performance of push-ups or sit-ups over a 1-min period (Fig. 13.2). As compared with glycolysis, use of the muscles' ATP and PC stores contribute more to exercise energy expenditure when intense exercise lasts seconds; for example, hurling a heavy bowling ball down a lane (18, 19). Moreover,

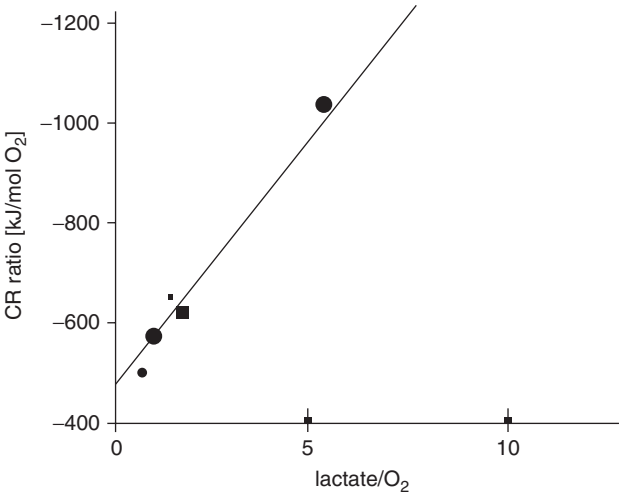

Fig. 13.5 The relationship between the measured enthalpy changes associated with lactate production and oxygen uptake for a variety of mammalian cell types is shown. The CR ratio is the calorimetry to respiratory ratio, heat to oxygen uptake. As the lactate/O2 ratio increases, so too does the CR ratio, as anaerobic glycolytic ATP resynthesis contributes to overall energy expenditure. The intercept of the line on the *Y* axis is at 470 kJ mol^{-1}, revealing complete aerobic energy transfer. Modified from Gnaiger and Kemp (17)

if the exercise intensity is low and the exercise prolonged, then the anaerobic glycolytic and ATP, PC components usually contribute insignificantly to overall energy expenditure (Fig. 13.1).

Lactate is an active metabolite, undergoing continuous production and removal, often at different rates. This fact has been used to invalidate lactate levels (in muscle or blood) as a means to quantify anaerobic energy expenditure. Should it? Although it is clear that lactate actively and continuously both enters and leaves muscle and blood at different rates, it may do so in a fairly well-depicted fashion. In 1936, the Norwegian physiologist Ole Bang revealed that by varying both the intensity and duration of *prolonged exercise*, blood lactate levels often peaked at about 10 min into exercise and then began to *decline during the exercise* period (20, 21). This finding has convinced many that lactate a priori cannot be trusted as a valid indicator of the extent of anaerobic glycolytic metabolism (i.e., anaerobic energy expenditure). For 10-min exercise period or longer, it indeed cannot (Fig. 13.6).

What apparently has been neglected are Bang's findings for *brief exercise* lasting between 1 and 10 min, where lactate always *peaks in the recovery from exercise* (not during exercise) (20, 21). Muscle and blood lactate levels are certainly not a perfect means of quantifying anaerobic glycolytic ATP resynthesis, but under specific, well-defined conditions, they have in fact proven helpful in providing a reasonable estimate of anaerobic glycolytic energy expenditure (22, 23). If this knowledge is to be usefully exploited, then a "window of opportunity" may be recognized, where lactate measurements can prove useful in the attempt to reasonably quantify anaerobic

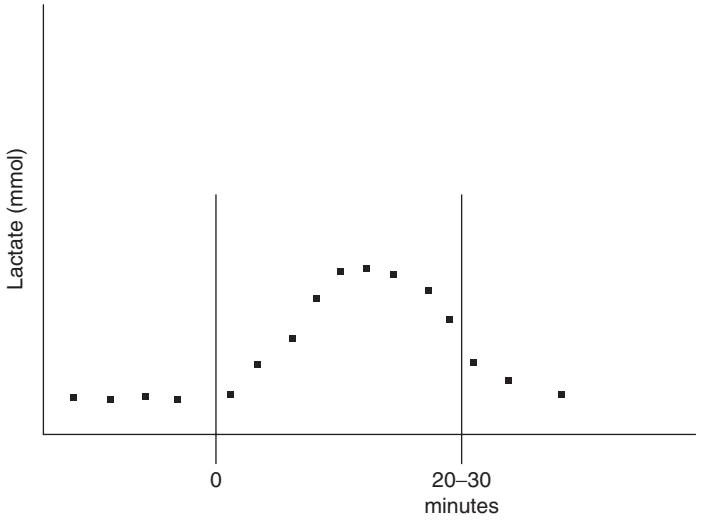

Fig. 13.6 Blood lactate before, during, and after a steady-state, 20–30 min, "hard" run on a level surface. The run begins at "0." Note that blood lactate concentration peaks mid-way through the run, and then declines. As blood lactate concentration declines, lactate removal exceeds lactate production and blood lactate cannot be used to quantify anaerobic (glycolytic) energy expenditure

glycolytic energy expenditure: for brief heavy to severe exercise only when lactate peaks in the recovery from exercise (not during exercise) (Fig. 13.7).

Again, exercise that lasts only seconds, throwing the shot put for example, contains an anaerobic energy expenditure component that consists largely of the use of the stored phosphates ATP and PC. The total energy expenditure for such activity appears to contain little glycolytic ATP resynthesis and may best be quantified as an exercise with recovery oxygen uptake measurement. In fact, resynthesis of the ATP, PC stores takes place aerobically in recovery (18). However, as seconds of heavy to severe exercise turn into half-minutes and more, both aerobic and anaerobic glycolytic energy expenditure rapidly and significantly increase. Under these conditions, the largest error incurred in the estimation of energy expenditure is made when using oxygen-only measurements that omit an estimation of anaerobic energy expenditure (18).

Under carefully defined conditions, blood lactate concentrations can reveal a linear relationship with workload. In one classic experiment, a subject sprinted up steep treadmill grades for 2–30-s duration; peak blood lactate was measured in recovery. This experiment continued over the course of several days, with the exercise duration varied each day. The blood lactate concentration of each sprint was later plotted against the duration of the exercise. The results were striking, revealing a remarkably linear relationship between blood lactate concentration and the volume of work that was completed (Fig. 13.8) (23). In a similar fashion, linear increases in blood lactate have also been shown for brief bouts of cycling and swimming (22).

The author of this text performed a similar set of experiments during weight lifting as opposed to running, cycling, and swimming. A supine bench press was

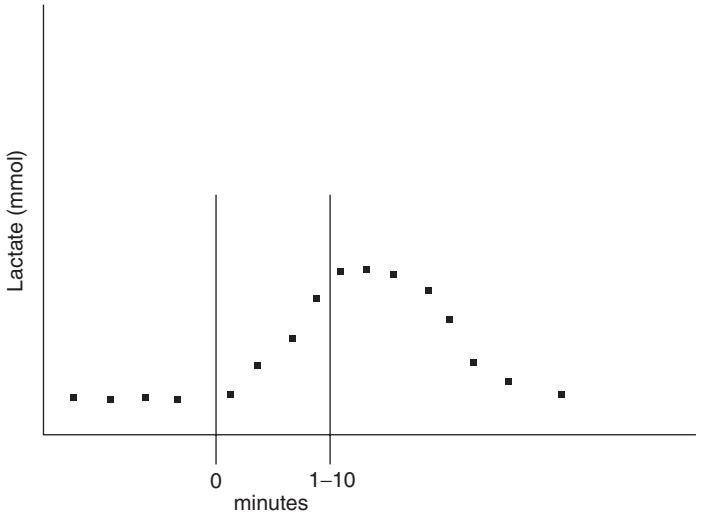

Fig. 13.7 Blood lactate before, during, and after a brief bout of heavy to severe exercise lasting between 1 and 10 min. The run begins at "0." Note that blood lactate peaks in the recovery from exercise. When lactate production exceeds lactate removal over the duration of the exercise, blood lactate concentrations have provided a reasonable estimate of anaerobic (glycolytic) energy expenditure

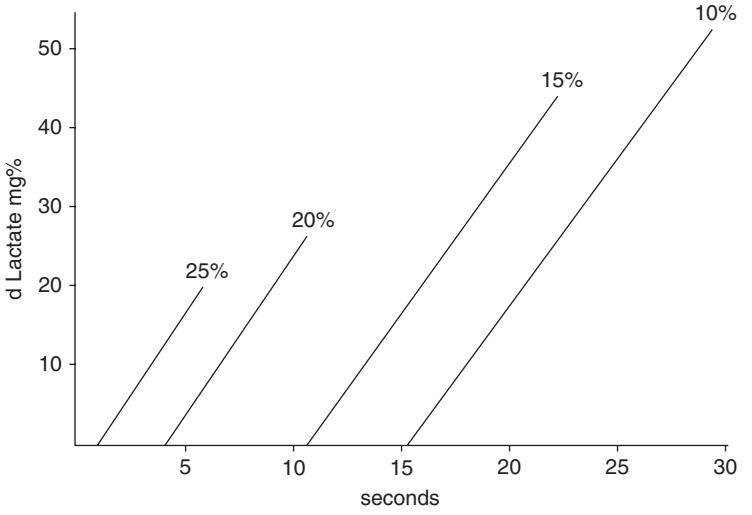

Fig. 13.8 These data are from a 1964 study that examined blood lactate concentrations after a series of brief, intense treadmill sprints lasting from 2 to 30 s. The *percentages* above each line indicate the degree of inclination (% grade) of the treadmill; speed was held constant at 11 miles h^{-1} (18 km h^{-1}) for all runs. Note both the linearity and the remarkable similarity in slope among each line. These data demonstrate the usefulness of blood lactate as a reasonable estimate of anaerobic glycolytic energy expenditure for brief and intense exercise. Modified from Margaria et al. (23)

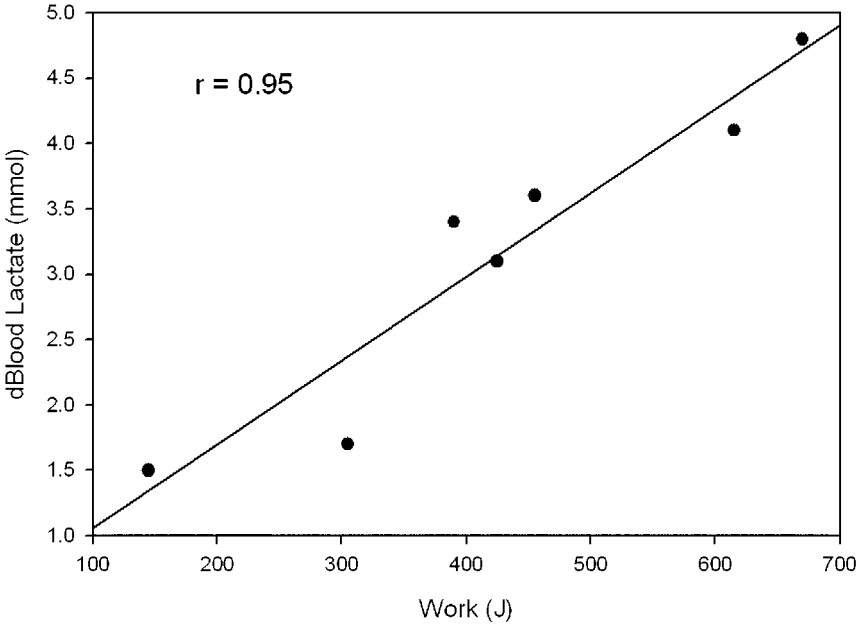

Fig. 13.9 Seven points are shown indicating seven bench press work periods. While only a case study, the correlation of blood lactate with increasing work ($r = 0.95$) demonstrates the feasibility of using peak blood lactate concentrations in the recovery from exercise to represent the anaerobic (glycolytic) energy expenditure component of a single bout of weight lifting, which is considered to be anaerobic exercise

chosen as the format of exercise, and work output was estimated with the assistance of an electronic device that measured lifting distance. Seven lifts were performed on seven different days. A Smith machine was used that allowed bar movement only in the vertical plane. A structured cadence was selected to minimize variations in power output for each repetition (although inertia was not controlled for). Blood lactate concentrations were measured 2 min into recovery. The pilot data are shown in Fig.13.9, where again, linearity was found.

Similar to the oxygen deficit, blood lactate concentrations (in mmol) are converted to energy expenditure first as an oxygen equivalent, and then as kilojoules (or kcal). The estimate requires a measure of both resting and peak blood lactate concentrations, with the difference between the two known as Δblood lactate. The conversion of blood lactate to energy expenditure is:

$$3.0\,\text{mL O}_2\,\text{kg of body weight}^{-1}\text{ per mmol of }\Delta\text{ blood lactate}$$

As an example, if a 75-kg subject had a resting blood lactate of 1.0 mmol and after sprinting uphill for 45 s blood lactate peaked in recovery at 12 mmol, then Δblood lactate would be 11 mmol. The conversion to O_2 equivalents is shown below:

$$3.0\,\text{mL O}_2 \times 75\,\text{kg} \times 11\,\text{mmol} = 2{,}475\,\text{mL O}_2 (2.475\,\text{L O}_2)$$

Like the oxygen deficit this too is a capacity measurement (not a rate) that can be converted to energy expenditure in standard format where $1\,L\ O_2 = 21.1\,kJ$:

$$2.475\,L\ O_2 \times 21.1\,kJ = 52.2\,kJ(12.5\,kcal)$$

The analysis of blood lactate is today a simple procedure. Hand-held lactate analyzers are made that are smaller then a deck of playing cards. A special strip is inserted into the analyzer and a drop of blood is placed on the strip. The analysis takes place in about 1 min. The procedure and device are very similar to how diabetics measure blood glucose.

di Prampero and colleagues have for years both demonstrated and rationalized the usefulness of blood lactate as a *reasonable estimate* of anaerobic energy expenditure, "Clearly enough, [Δblood lactate] is not the energetic equivalent of lactate formation in the working muscles and does not yield any direct information on the stoichiometric relation between lactate formation and ATP re-synthesis, It is nevertheless a very useful quantity allowing us to determine the energy release in the body whenever the blood lactate concentration increases by a given amount" (22). It must be emphasized again, however, that the term *reasonable estimate* indicates that limitations are evident; specifically the exercise must be brief and intense (when lactate peaks during recovery) (18, 19). It also is not known how well (or not) a Δblood lactate conversion describes the anaerobic glycolytic energy expenditure of intermittent or repeated bouts of exercise.

There is another positive in the use of lactate for the reasonable estimation of anaerobic glycolytic energy expenditure. Unlike the oxygen deficit that contains both anaerobic glycolysis and stored ATP, PC utilization, lactate levels represent only the former. In this regard, blood lactate measurements allow for the collection of a total energy expenditure estimate (anaerobic exercise + aerobic exercise + aerobic recovery), measurements of the oxygen deficit and recovery oxygen uptake do not (see Chap. 16) (2, 18).

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Chapter 14
Metabolic Energy Expenditure at Rest

The word metabolism represents different things to many peoples and professions. The biochemist sees metabolism as a series of enzymatic steps. A physician might define metabolism in terms of the body's response to glucose and insulin. An overweight person identifies metabolism as cursed genetics. Energy intake may be the focus of a registered dietician's concept of metabolism. Within this text, metabolism is described in the context of energy expenditure, from the body to the environment.

Whole-body energy expenditure emanates as the sum total of all biochemical reactions occurring within each and every one of your body's cells. The number of cells that comprise a human being is difficult to place into perspective, figures range from 10 to 100 trillion. Approximately 4,000 biochemical reactions have been suggested to be underway in a "typical" resting cell (1). Clearly, even under resting conditions, whole-body energy expenditure is the result of an enormity of matter and energy exchanges! Figure 14.1 abridges energy expenditure as energy demand and energy supply, the product, respectively, of ATP utilization and ATP resynthesis collectively known as ATP turnover.

While energy expenditure would be best accounted for using a direct measure of ATP turnover, current technology does not allow for the ability to tally all phosphate exchanges between those sites that utilize ATP and the metabolic pathways that resynthesize ATP. Instead, it is the direct measurement of heat production, a by-product of energy exchange, that serves to quantify energy expenditure. All other attempts to quantify energy expenditure are recognized as indirect estimations. The standard unit to express whole-body energy expenditure (anaerobic and aerobic) is the same that describes enthalpy (H), Gibbs energy (G), entropy (S), work, and thermal energy, the Joule.

14.1 Measuring Energy Expenditure: Calorimetry

Throughout the centuries, humans have made attempts at quantifying energy expenditure. Sanctorius (Santorio Santorio, 1561–1636), for example, a contemporary of

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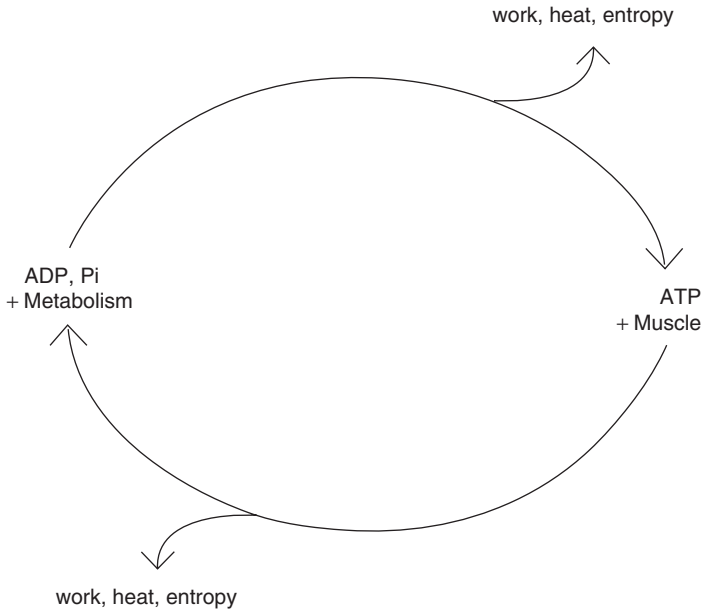

Fig. 14.1 The cycle of energy expenditure – ATP turnover – is shown as ATP utilization (energy demand) and metabolic ATP resynthesis (energy supply)

Galileo, constructed a giant scale of sorts where he took measurements before, during, and after a meal (among other things). Everything ingested and excreted was also weighed. The term *energy expenditure* was not part of Sanctorius' lexicon, nor was its measurement the working hypothesis of this man, but it nevertheless reveals an early attempt to actually quantify those exchanges that took place within and without the human body.

The first useful energy expenditure data were collected in the 1790s. Once it was recognized that life produced heat the race was on for its proper measurement. Such recognition should not be considered flippant ("Duh, of course animals produce heat"). Indeed, for perhaps thousands of years mankind held the view that life resulted from heat, not the other way around. The Greeks for example viewed the heart as a type of furnace with the lungs serving to temper the flames within; life arose and thrived as a *consequence* of that heat (2). It took more than a thousand years to disprove this belief. Throughout the nineteenth century, devices were constructed and gradually improved so that a valid means of quantifying energy expenditure was eventually created. That device is known as a calorimeter.

The caloric value of the food we eat is directly measured via combustion as bomb calorimetry (3). The device entails a stainless steel bomb (actually a shot glass-sized container) as part of an enclosed system. A sample of dried food is placed within the bomb; the bomb's interior is filled with a pressurized all-oxygen atmosphere, sealed, and is then placed within the calorimeter. The calorimeter chamber is filled with a known volume of water. The water provides the surroundings to the bomb's internal system. The calorimeter walls are heavily insulated to prevent heat leakage

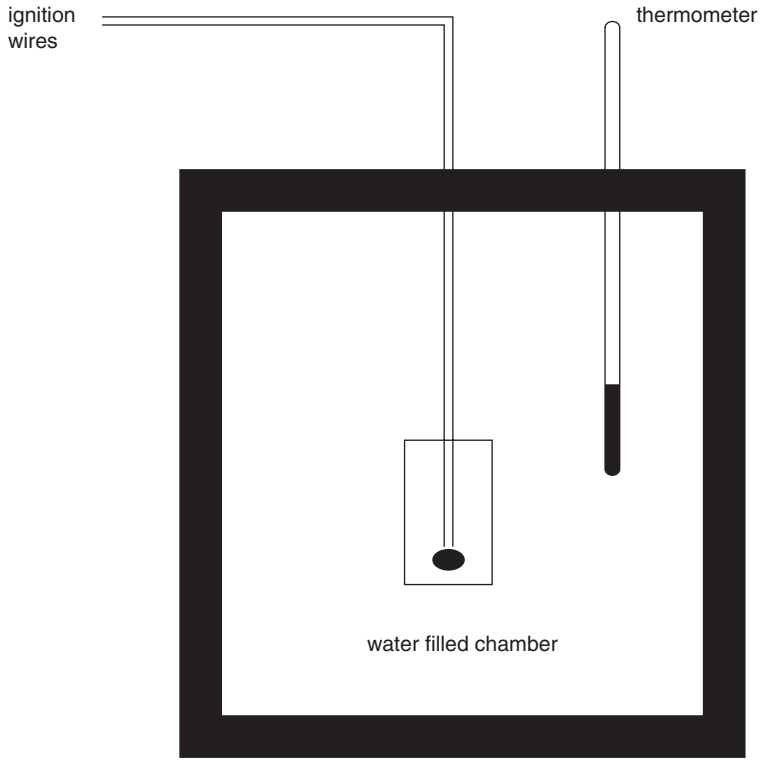

Fig. 14.2 The simplified schematic of a bomb calorimeter is shown. The bomb is shown as the rectangle located inside the heavily insulated water-filled calorimeter chamber. A spark created by the ignition wires triggers the combustion of the foodstuff (*the black oval*) inside the bombs pressurized oxygen-filled interior

to the outside environment. The bomb itself however is constructed so that most if not all heat generated within passes to the water. Ignition wires fed through the calorimeter and bomb create a spark that ignites the foodstuff inside. Heat produced by the burnt food inside the bomb is "captured" by the water and the temperature change is measured by a thermometer (from Chap. 4, the product of the volume of water and temperature change indicates the amount of heat expended from the reaction) (Fig. 14.2).

Direct calorimetry is the process whereby the heat loss of living creatures is quantified (no bombs are involved!). In humans, ~80% of heat loss is radiative and convective, the remaining 20% is evaporative (conductive heat loss is negligible). Calorimeters have been drastically improved because of technological innovations, but the overall designs of many of these devices have actually not changed all that much since they were first developed (Fig. 14.3). Of primary concern is the leaking of heat from the calorimeter to the environment. To measure the thermal output of a cell, animal or human, heat needs to be contained while measurements are carefully recorded. Thermal barriers are thus of primary concern. Engineering and construction skills must be at a premium. Larger animals necessitate larger

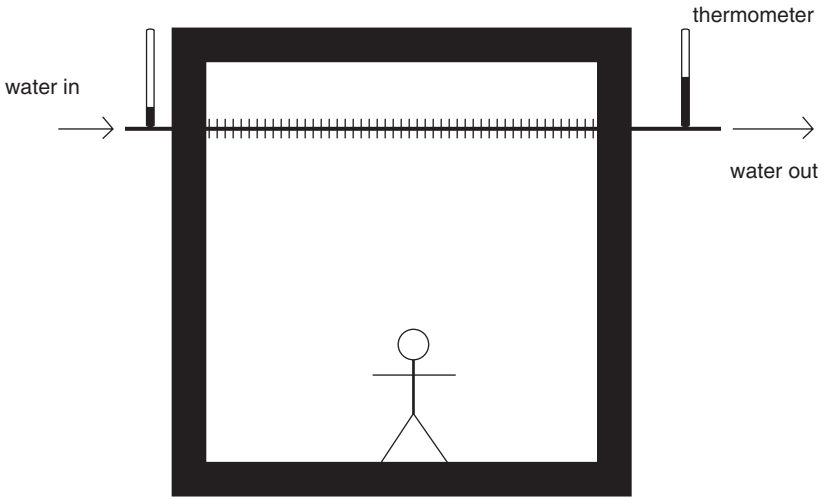

Fig. 14.3 A simplified schematic of direct calorimetry is shown (there are many types). Heat from the subject rises and is captured by the heat-sink device at the top of the calorimeter that in turn warms the water traveling through it. By measuring the volume of water passing through the calorimeter and its change in temperature, a measure of metabolic energy expenditure is obtained

equipment, increasing the difficulty of construction and the operational procedures involved. Talented technicians are required. Given the variability in energy expenditure throughout a given day, lengthy measurement periods are essential, often taking days (your body also tends to store heat throughout the day, releasing heat at night). During a steady state the animal or human must be somewhat immobile during the measurement period (ask yourself, how long can you stay relatively immobile in a chamber the size of a large closet?). Because of these difficulties and challenges, whole-body direct calorimeters are rare devices, yet their contributions to science have been rather formidable (3).

Well into the 1800s it was thought that life held a "vitalism" and was subject to rules that were different from other phenomena on planet Earth (e.g., weather and life were controlled differently; the former is applicable to physics, the latter not). Moreover, it was thought that human beings held a special superiority and so did not adhere to those principles that governed animal life. Succinctly put, the calorimeter provided the disproof for the aforementioned rationales (3, 4). Over time more complete measurements were made. Calorimeters were modified and other recordings were developed; all of life's intakes and excretions in solid, liquid, and gaseous forms were eventually accounted for (5).

When gas exchanges are measured as opposed to measurements of heat loss in the quantification of energy expenditure, the process is known as indirect calorimetry. Respiratory gas exchange is measured as oxygen uptake, carbon dioxide production, and ventilation. In turn, these measurements are used to *estimate* metabolic heat loss (put another way, gas exchange measurements can be converted to Joules):

$$O_2 \text{ uptake and } CO_2 \text{ production} \approx \text{Joules (or kJ) of energy expenditure}$$

Indirect calorimetry is perhaps the most recognized form of energy expenditure measurement (6, 7). Devices known as metabolic carts are nowadays connected to a personal computer for analyses of gas concentration. Over the years metabolic carts have evolved, steadily increasing the speed of gas analysis while decreasing in size, from racks of equipment, to desktop units, to portable masks with telemetry systems. Energy expenditure is, however, first and foremost the result of ATP turnover, and currently we are unable to directly measure this. It needs to be kept soundly in mind that heat is a direct by-product of ATP turnover (among other things) so that direct measurements of heat loss help describe energy exchange. All other measurements – oxygen uptake, carbon dioxide production, doubly-labeled water, heart rate, podometers, physical activity recall questionnaires – provide an *indirect estimate* of energy expenditure. Entropy also needs to be accounted for if *everything* imported from the surroundings to the system and expended from the system to the surroundings is to be considered, a valid accountability of an open system is that demanding.

14.2 The Energy Expenditure of Rest

Life costs. Far-and-away the most expensive part of a day resides in those maintenance activities that are performed by all cells, tissues, and organs. The lowest metabolic rate reached in a given day occurs while sleeping. Sleeping 8 h a day on average represents one-third of daily energy expenditure. Once awake and without any movement, energy expenditure rises about 10% from sleeping values so that in a sedentary person wakefulness accounts for 60–75% of daily energy expenditure (8). The energy expenditure of wakefulness is influenced by a myriad of factors ranging from anxiety to environmental temperature. Because of this the measurement of energy expenditure during rest requires strict and standardized methodology. Standard conditions entail: supine rest, no stress or anxiety, a temperate, darkened and quiet environment, a 12-h fast and a period of measurement acclimation (9). Under standard conditions the maintenance period of wakefulness has been termed basal metabolic rate (BMR) or standard metabolic rate (SMR). The term resting metabolic rate (RMR) implies that strict conditions were not met. For example, many measurements of "resting metabolism" are obtained from people who wake-up from their own bed, dress, brush teeth, drive a car to a testing facility, and then attempt to return to a standardized condition. A BMR or SMR measurement indicates that the test subject was never removed from standard conditions. Scientists who estimate exercise energy expenditure usually subtract from this a person's resting energy expenditure (REE). This procedure is used to account for the cost of the exercise itself, not the cost of the exercise plus the underlying (resting) metabolic rate of living. Under these conditions, REE can be defined as a standing rest (e.g., before upright running) or a seated rest (e.g., before seated cycling).

Researchers who obtain a resting measure of metabolism also need to strictly describe the devices utilized to collect the expired air sample because these too can affect the measurement. Whole-room indirect calorimeters are popular in some

research laboratories where a person's exhaled air is collected as part of room air. Yet such a "room" is actually an expensive suite of sorts. Other labs and clinical practices measure gas exchange collected through a special mouthpiece that is attached to a length of hose (perhaps 6–9 feet in length) that in turn is connected to a metabolic cart for analyses of the expired air. Mouthpieces and masks can however temporarily result in slight hyperventilation, affecting the RMR measurement; a period of practice usually alleviates concern (10, 11). Ventilated hoods also are popular, where a clear plastic canopy is placed over the head and shoulders of a supine subject. A pump is used to continually draw air through the hood and this air is analyzed for its oxygen and carbon-dioxide content. When using less-expensive methods of gas collection, studies have shown that the hood method is preferable to a mouthpiece or face-mask because it interferes minimally with the subject being tested (11).

What are the major contributions to RMR? This question can be answered at the cellular, tissue, organ, and whole-body level with most estimations based on oxygen consumed (not heat and entropy exchanges). Within a given "resting" cell, the leading demands for energy include (but are certainly not limited to) (12, 13):

1. *Na^+-K^+ATPase:* With death residing at equilibrium, life requires a constant maintenance of its gradients to continue the displacement of equilibrium. Gradient maintenance occurs through the use of pumps known as ATPases. One of the better known gradients in biology is seen as sodium (Na^+)- and potassium (K^+)-ion concentrations that are located within and without a cell's outer membrane. Cell membranes are leaky, and because of their respective gradients, Na^+ spontaneously traverses cell membranes from outside to inside; the spontaneous K^+ gradient is just the opposite, from inside to outside (see Fig. 8.2). ATP is the fuel that ATPase pumps use to move ions back "upstream," rebuilding their respective gradients.
2. *Ca^{2+}-ATPase:* Calcium (Ca^{2+}) is an intracellular signaling ion. The release of Ca^{2+} concentrations from storage within a membrane-derived intracellular vesicle usually triggers a cellular response of some kind. After the response is triggered, that calcium must be pumped back into its storage vesicle, recreating the gradient. ATP fuels this process. The Ca^{2+}-ATPase pump may also be found on the outer membrane of certain cells.
3. *Mitochondrial proton leak:* Because biological membranes are not perfect boundaries, not all oxygen consumed by mitochondria goes toward ATP resynthesis. Protons continuously leak through the inner mitochondrial membrane. These protons are not associated with energy supply, being instead a contributor to energy demand. It costs to reconcentrate protons to one side of a membrane, to rebuild the gradient. It is thought that mitochondrial proton leaks may be part of a "planned" heat loss by cells (see point 4).
4. *Cell membrane make-up:* Cell and mitochondrial membranes are comprised of fatty acids, both saturated and unsaturated (mono- and polyunsaturated too). The degree of unsaturation seems to contribute to the leaking of ions through biological membranes. In turn the H^+, Na^+, K^+, and Ca^{2+} pumps expend energy in an attempt to maintain their respective ionic gradients, serving perhaps as a leading

candidate in the origin of a living cell's RMR. Hulbert and Else have proposed that the amount and composition of the lipid component of the membrane bilayer may act as a natural RMR pacemaker (13). The lipid content and composition of a membrane may be altered somewhat by diet but appears predominantly determined by genetic factors.

5. *Substrate (futile) cycling:* A given enzyme-controlled biochemical reaction or series of reactions can at times appear "wasteful." For example, reactants A + B may be converted to products C + D; then, just as quickly, products C + D are immediately re-converted back to A + B by the same or another enzyme; little appears to have been accomplished by this procedure; a futile cycle is the apparent result. On a larger scale, a futile cycle is found as fat stores (triacylglycerols) are broken down during intense exercise, not used for fuel and thus loading the blood stream with more fatty acids than are utilized. When the exercise ends, some fat is used to fuel recovery, yet many of these fatty acids undergo conversion straight back to their original form as stored fat (i.e., a futile cycle). Whether at the level of the cell or the whole body, a cost may be required to promote either the forward or backward rate of the futile cycle (or perhaps both). Why engage a metabolic futile cycle? If the exchanges taking place throughout, the biochemical pathways were being regulated by so-called futile cycles, they may not be regarded as futile (14).
6. *Protein turnover:* Wear and tear creates the ongoing need for new protein to replace old. Whether considered separately or together, protein breakdown accompanied by protein synthesis are thought to be rather expensive processes.

Cells form tissues and tissues form organs. It is recognized that some tissue types consume more energy than others not only because they are more active but because they represent a larger part of the body's overall mass. As a part of whole-body oxygen consumption for example, the liver is rather active, consuming about 17% of the body's oxygen uptake but representing only about 2% of total body mass (12). Skeletal muscle represents about 42% of body mass and consumes about 20% of the body's oxygen (12). Oxygen use by the gastrointestinal tract is thought to be 10%, kidney 6%, lung 4%, and heart 11% (12). The reader should understand these values are highly variable whether comparisons are made between gender, age groups, conditions of health and disease, and among animal species. Regarding differences among animal species it may be comforting to know that a rat's brain utilizes 3% of that animal's RMR, the figure is 20% for humans (12).

The calculations of Flatt are instructional in that they consider aerobic energy expenditure in terms of ATP amounts: if the enthalpy of ATP was 75 kJ mol^{-1} and the daily energy expenditure of a human subject was 10,042 kJ (2,400 kcal), then

Table 14.1 Estimated resting daily energy expenditure

Subject	Kcal day^{-1}	L O_2 day^{-1}	kgATP day^{-1}	Hamburgers day^{-1}	Apples day^{-1}
Woman	~1,300	~260	~60	5.2	18.6
Man	~1,700	~350	~75	6.8	24.3

Table 14.2 Resting metabolic rate (RMR = kcal/24 h) based on height (cm), weight (kg) and/or age (yrs)

Subjects	Equation	reference
Animal kingdom	$RMR = 70 \times kg^{0.75}$	(16)
Women athlete	RMR = 50.4 + 21.1 (kg)	(17)
Women nonathlete	RMR = 795 + 7.18 (kg)	(17)
College-aged women	RMR = 736 + 8.63 (kg)	(18)
Dieting women	RMR = 688 + 6.5 (kg) − 2.9 (age)	(19)
Women	RMR = 667.051 + 1.729 (cm) + 9.74 (kg) − 4.737 (age)	(20)
Men	RMR = 77.607 + 4.923 (cm) + 13.702 (kg) − 6.673 (age)	(20)
Men	RMR = 879 + 10.2 (kg)	(21)

roughly 134 mol of ATP are required throughout a 24-h period, equivalent to one's body weight (34). Under these conditions the body's ATP pool turns over once every minute. A user-friendly portrayal of daily energy needs or demands is provided in Table 14.1, where units are described and compared using calories, oxygen uptake, "small" hamburgers (at 250 kcal each), apples (at 70 kcal each), and kilograms of ATP (the intake of hamburgers and apples are to be considered separately).

Over the years, a variety of studies that attempt to model human RMR have been conducted. Naturally, the methodologies used to create these models can differ, as do the populations that were sampled, as such variance is evident (see (15)). In Table 14.2 several published equations that estimate the RMR for a given human subject are provided. As humans age declines are evident in almost all those factors that contribute to RMR (13). Once the age of 50 is reached, humans can expect about a 4% reduction in RMR per decade (22, 23).

14.3 Eating and Energy Expenditure

After eating, energy expenditure rises, representing the costs of digesting and assimilating nutrients. This physiological response – termed the thermic effect of feeding (TEF), dietary-induced thermogenesis (DIT), or specific dynamic activity (SDA) – is closely related to the amount of food energy ingested and its composition (34). In addition to muscular motility and peristalsis of the stomach and intestinal tract, the TEF is heavily affected by the amounts and costs of the take-up and distribution of foodstuff within the body's cells: cellular transportation, breakdown, assimilation, activation, storage and/or oxidation for energy. Carbohydrates, proteins, and fat can all undergo oxidation to resynthesize ATP (energy supply) but the incorporation of these macronutrients into body tissue or storage requires ATP (energy demand). When referring to the three macronutrients, the SDA of protein is highest, increasing the underlying metabolic rate up to 25%; carbohydrate and fat increase energy expenditure from 2 to 5%. When also considering the amount of protein, fat, and glucose in three "typical" meals overall, 24-h energy expenditure increases by about

10%. As a result of breakfast, lunch, and dinner, single meals become daily meals, so that regular meals appear to maintain the highest natural RMR.

Without food cells become starved and their underlying metabolic rate initiates a slow-down, reducing whole-body RMR by about 1% a day (34). With this potential decrease in mind, regular eating and drinking actually keeps the body's metabolism operating at about 25% higher than during a period of starvation (i.e., starvation may decrease RMR by up to 25%) (34). Carefully designed exercise programs involving weight training for example, can serve to preserve more active body mass (i.e., lean body mass), thus helping to maintain whole-body RMR during extreme dieting (24).

14.4 Pregnancy and Energy Expenditure

Women when pregnant are eating for two (or more). Naturally, this assumes an increase in energy intake and energy expenditure over the course of a pregnancy. Recommendations by health authorities propose increasing caloric intake by 1,046–1,255 kJ day^{-1} (250–300 kcal day^{-1}) for pregnant mothers (25). However, information from dietary surveys are not in accordance with these recommendations, sometimes revealing little to no increase in energy intake over the course of a pregnancy (26). Moreover, correlation between energy intake and gestational weight gain in pregnant mothers is typically poor ($r = 0.2$–0.3) (26). Based on these data, it has been suggested that pregnant women might be best off to "eat in accordance with appetite" (27).

The existing scientific literature appears to shed little light on overall recommendations of weight gain and energy intake to pregnant mothers. But what about recommendations based on energy expenditure measurements? Can measurements of REE during pregnancy help set nutritional guidelines? Surprisingly, the answer to this question appears to be a negative one. Koop-Hoolihan et al. performed what was considered to be a model study of metabolic research and concluded that "the use of a single recommendation for increased energy intake in all pregnant women is not justified" (28). The following was written in an accompanying editorial, "The findings related to the energy cost of pregnancy were – in a word – variable. The degree of variation from subject to subject was astonishing. Although RMR increased consistently with advancing gestation, the degree of increase differed among individual subjects by a factor of 8" (26). Astonishing indeed!

Recognizing such extreme variability, the author of this text, while the director of a metabolism and exercise testing laboratory, was afforded a rare opportunity for a case study when a colleague became pregnant. Many studies have measured energy expenditure only periodically throughout gestation, perhaps every month or once every 3 months (to represent all three terms). Because of the proximity of this subject to the testing facility, weekly measurements could be taken. The question was asked, is the between-subject variability seen in the literature also evident within a single subject?

The subject was 25 years of age, 172 cm in height, and 82.8 kg in weight at 7 months prior to conception. It was at this time that the subject consented to routine

REE measurements for dietary advice and guidelines. A 7-month pre-gestation REE measurement served as a baseline measure. At 5 weeks of gestation, this woman became aware of her pregnancy, she weighed 83.9 kg; this was the start of 34 regular scheduled REE measurements. All gas exchange measurements were collected by the author every 6.8 ± 2.5 days at 08:00–09:00 am, 12-h postprandial, supine, in a darkened 24°C room via a mouthpiece with pneumotach, noseclip, and metabolic cart (MedGraphics, Minneapolis, MN). Manual calibrations of the metabolic cart were performed twice immediately before each measurement. The subject underwent a brief practice procedure prior to each measurement that consisted of 5 min of apparatus use followed by 20 min of undisturbed rest (no apparatus) and a subsequent 10-min REE measurement (10). REE data were averaged over the 10-min testing period. Baseline REE was $6,515\,\mathrm{kJ\,day^{-1}}$ $(1,555\,\mathrm{kcal\,day^{-1}})$ and at delivery (week 39) was $8,236\,\mathrm{kJ\,day^{-1}}$ $(1,968\,\mathrm{kcal\,day^{1}})$. Gestational weight gain is highly individualistic and for this subject was large at 31.1 kg. Labor was induced at week 39 and was followed by the unremarkable delivery of a healthy 3.6-kg girl. The mother chose to nurse. REE fell to baseline within three weeks of delivery.

The data reveal a trend toward an increase in energy needs during the second and third trimesters. Moreover, within-subject variability was readily apparent (Fig. 14.4). Such high weekly variance in REE indeed questions the strict setting of dietary guidelines for a given woman throughout the course of pregnancy.

Can the observed variance in REE measurements be reduced? On the one hand, energy expenditure variance throughout pregnancy may be very real as the oxygen

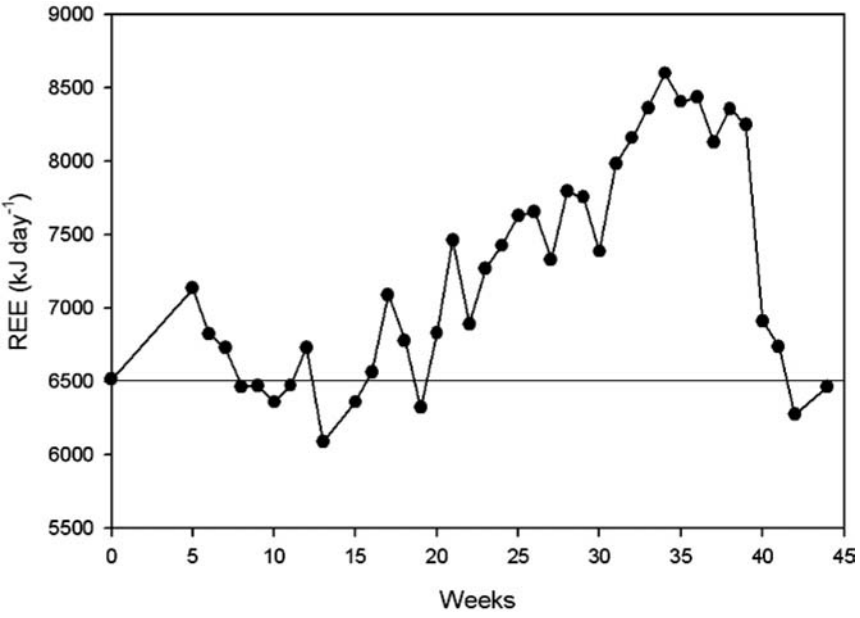

Fig. 14.4 Note the week-by-week fluctuations in REE during the first 21 weeks of pregnancy. From 21 weeks onwards an upward trend is observed, yet weekly variability is still evident. Pregnancy ended at week 39, dropping below baseline 3 weeks later

uptake measurements in Fig. 14.4 reveal. If during fetal and maternal development oxygen is involved in biochemical reactions outside of energy expenditure, then this would confound the REE estimate. On the other hand, better measurement methodology may be needed. The use of ingested doubly-labeled water is popular because of its ability to estimate the energy expenditure of daily activity without the restrictions of enclosing a subject in a sealed room or attaching them to a hose with mouthpiece. Such freedom from physical limitations is a distinct methodological advantage. However the ingestion of doubly-labeled water entails the measurement of carbon-dioxide production, not oxygen uptake, so that energy expenditure is actually being estimated as carbon dioxide. Metabolic heat loss is estimated at $\pm 10\%$ accuracy with carbon-dioxide measurements, $\pm 1.5\%$ accuracy when analyzing oxygen uptake (this is the reason why energy expenditure conversion often focuses on oxygen uptake) (3).

Measurements of anaerobic energy expenditure in pregnant women under normal conditions are difficult to find in the literature, and so it is unknown, for example, if anaerobic metabolism (i.e, anaerobic glycolysis) is fluctuating in a reciprocal up and down fashion when compared with oxygen uptake, creating less overall fluctuation in energy expenditure (i.e., as one goes up the other goes down, so that overall energy expenditure remains relatively constant). In one study involving pregnant rodents, accumulation of liver lactate was found throughout gestation, suggesting a possible anaerobic component (29).

As revealed earlier with glycolytic pyruvate vs. lactate production, entropy changes resulting from energy exchanges might also need to be taken into consideration during growth and development (of the fetus and pregnant mother). Such changes have been modeled but only for rather simple open systems such as single-cell organisms and insects (30–32). But that is likely to change. Zotin and Zotin suggest, "The notion of negative entropy characterizes a system organization" (33); a statement that provides a rather succinct description of the dramatic organization – energy consumption (ΔH) and energy transfer (ΔS) required of fetal (and maternal) development (see Chap. 9, Sect. 9.2). Viewed in the context of an open system then, gestation appears to represent an ideal period for measuring, estimating and/or calculating aerobic energy expenditure, anaerobic energy expenditure, heat production, enthalpy (ΔH), Gibbs energy (ΔG), and entropy (ΔS) – that is, *all* system and surroundings exchanges – to determine how or if each fluctuates during fetal development. Only then may strict dietary guidelines obtain validity.

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Chapter 15
Metabolic Energy Expenditure of Activity (Work and Exercise)

Muscle is well recognized as an energy-conversion device because of its ability to convert energy from one form to another. Yet as demonstrated in previous chapters, energy demands also are imposed by the orderly transfer of energy and materials along an operating metabolic pathway. The energy-exchange devices of muscular contraction and metabolism are coupled: (1) chemo-chemical energy conversion and transfer via the metabolic pathways – from the chemical bonds of the food we eat to the chemical bonds of ATP and (2) chemo-mechanical energy conversion and transfer via muscle displacement – from the chemical bonds of ATP to physical force. In addition to contraction, there are other expenditures – ion pumps and protein turnover too – but here, primary focus is on the collective result of muscle contraction and the estimate of whole-body energy expenditure.

15.1 Rate vs. Capacity vs. METs

Energy expenditure is represented in a variety of formats that include measurements of rate, capacity, and metabolic equivalents (METs).

Rate measurements are ideally suited for aerobic energy expenditure because a volume (V) of oxygen uptake can be recorded per minute $(\mathrm{VO_2\,min^{-1}})$ and subsequently so too can energy expenditure $(\mathrm{kJ\,min^{-1}})$. For example, if oxygen is consumed at a steady rate of $1\,\mathrm{L\,min^{-1}}$ at an RER of 0.70, then energy expenditure is estimated as:

$$1\,\mathrm{L\ VO_2\,min^{-1}} = 19.6\,\mathrm{kJ\,min^{-1}} (4.7\,\mathrm{kcal\,min^{-1}})$$

At rest or with steady-state light to moderate exercise, a measurement of steady-state oxygen uptake provides a *valid* means of estimating energy expenditure (Fig. 15.1). Anaerobic energy expenditure is, unfortunately, difficult to quantify as a

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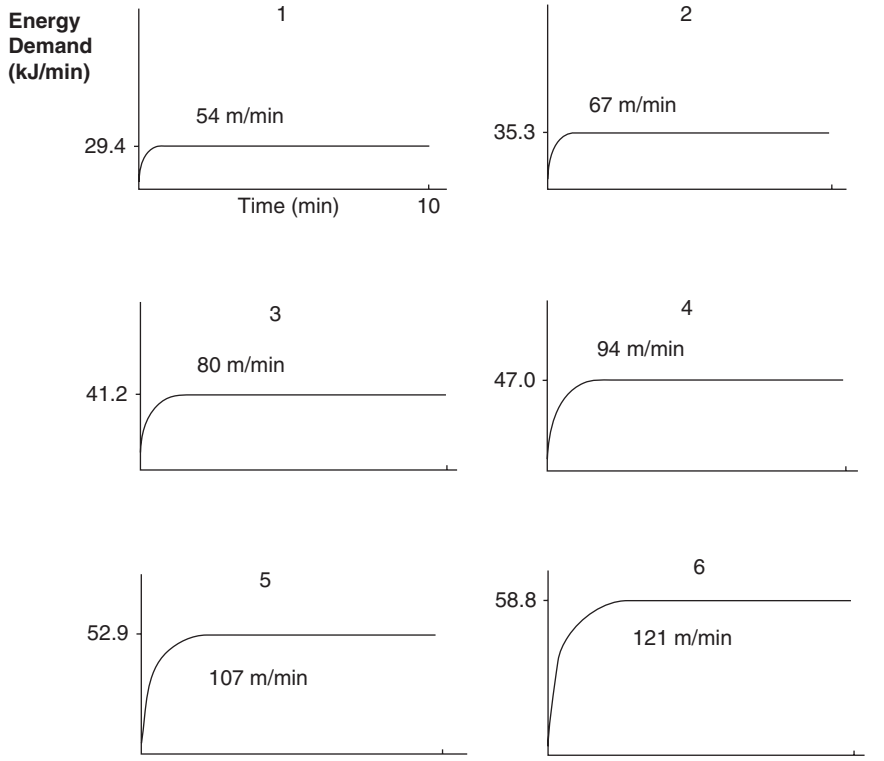

Fig. 15.1 Energy demand ($kJ\,min^{-1}$) and treadmill speed ($m\,min^{-1}$) are shown for six separate 10-min exercise periods. A single individual performed all six exercise trials. The grade of the treadmill was 10% for all six trials. Notice that steady-state oxygen uptake was achieved for all workloads signifying easy to moderate intensity exercise

rate function measure. Anaerobic activities are known to be brief and intense, conditions that preclude the ability to obtain a steady-state estimate of energy expenditure. This is certainly a limitation.

Anaerobic energy expenditure, in fact all energy expenditure, can be estimated in the context of a capacity. A capacity measurement portrays an aliquot of energy expenditure for a complete time period; that is, a single bout of exercise, from start to finish. Based on the physiology of longer, slower, distance-type exercise for example, walking at a pace where oxygen is consumed for 30 min and at a rate of $1\,L\,min^{-1}$ (RER = 0.70), the total amount of energy expended is estimated at:

$$30\,min \times 19.6\,kJ\,min^{-1} = 588\,kJ(141\,kcal)$$

Figure 15.2 demonstrates the hypothetical relationship between work performed during three separate bouts of brief, intense, resistance-type training (e.g., push-ups)

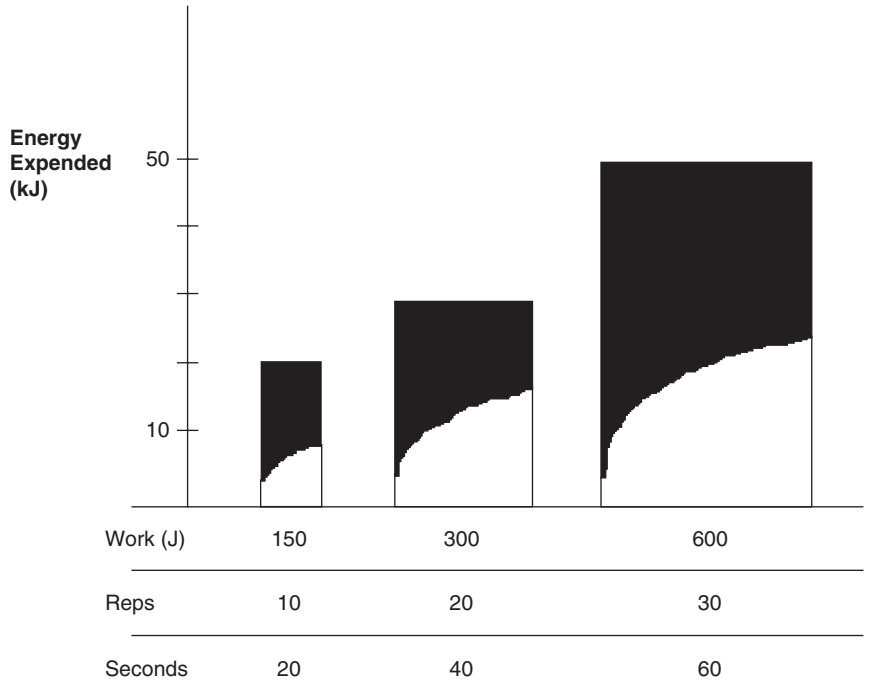

Fig. 15.2 Hypothetical energy expenditure and work load are shown for three separate bouts of the push-up exercise. Each bout contains an anaerobic (*in black*) and an aerobic (*in white*) energy-expenditure component

and the estimated anaerobic and aerobic energy expenditure throughout each bout. In this example a steady rate of Oxygen update is never achieved (an oxygen deficit is apparent). These data are also reported in a capacity format.

METs are strictly a representation of aerobic energy expenditure where 1 MET represents the oxygen uptake of a "typical" person resting in a reclining position; the value associated with this is:

$$3.5\ \text{mL}\ O_2\ \text{min}^{-1} = 1\ \text{MET}$$

This universally accepted MET value was obtained decades ago by testing a single subject ($N = 1$). Nowadays, such a case study (data from a single person) would never be accepted as representing the energy expenditure of an entire population. Yet with decades of human bias behind this MET equivalent, the number is here to stay. Data obtained from a much larger population ($N = 769$) revealed resting oxygen uptake to be about 30% lower than $3.5\,\text{mL}\ O_2\,\text{min}^{-1}$ (at $2.6 \pm 0.4\,\text{mL}\ O_2\,\text{min}^{-1}$) (1).

Table 15.1 METs for a few selected activities

Activity	METs
Guitar playing (rock & roll)	3.0
Weight training (light)	3.0
Calisthenics (no weight)	4.0
Gymnastics	4.0
Golf (no cart)	4.3
Outside painting	5.0
Walking (4 mph)	5.0

MET values provide a reasonable estimate of aerobic energy expenditure. Upon closer examination of the above data, however, is it to be believed that playing a guitar is energetically equivalent to a light-weight training work-out? Does painting outside really expend more energy than calisthenics (push-ups, sit-ups, and the like)? Does golfing "burn more calories" than gymnastics (floor exercise, high bar, rings, balance beam, etc.) or are semantics to be blamed? For aerobic activity the table appears fine, for anaerobic activity it does not. If Table 15.1 also were to include a reasonable estimate of anaerobic exercise energy expenditure, then the MET values would most likely be higher for heavy to severe exercise and activity that contains an anaerobic component (i.e., weight training, calisthenics, gymnastics). Information from (2)

METs also describe exercise energy expenditure as multiples of resting metabolic rate, being especially used in clinical rehabilitation programs: 1 MET is resting energy expenditure, 2 METs is 2× resting energy expenditure, 3 METs is 3× resting energy expenditure, and so on. It also has been suggested that the numerical MET value can be extended to caloric expenditure as:

$$1\,\mathrm{kcal\,kg^{-1}\,h^{-1}}$$

Thus, a 70-kg person working at 3 METs for 2 h expends 420 kcal (1,758 kJ) (1):

$$70\,\mathrm{kg} \times 3\mathrm{METs} \times 2\,\mathrm{h} = 420\,\mathrm{kcal}(1,758\,\mathrm{kJ})$$

It is important to recognize that MET values do not contain an anaerobic energy-expenditure component and this can be problematic when estimating the energy demands of heavy to severe but not light to moderate exercise and activity (Table 15.1).

Imagine the physical intensity of pushing a broken down car to the side of a road, a tug-of-war contest or shoveling wet, heavy snow. Powerful isotonic and isometric muscle contractions often constrict blood vessels, reducing blood flow or stopping it altogether. Under these conditions, anaerobic metabolism rather than aerobic metabolism may contribute most to a muscles' energy expenditure. The muscles' use of oxygen is usually not at a physiological maximum (i.e., VO_2 max) during brief intense activity but it may certainly reach a peak value. Figure 15.3 demonstrates how the use of both anaerobic and aerobic components may more reasonably portray energy expenditure as METs for brief periods of heavy to severe exercise, work, and activity.

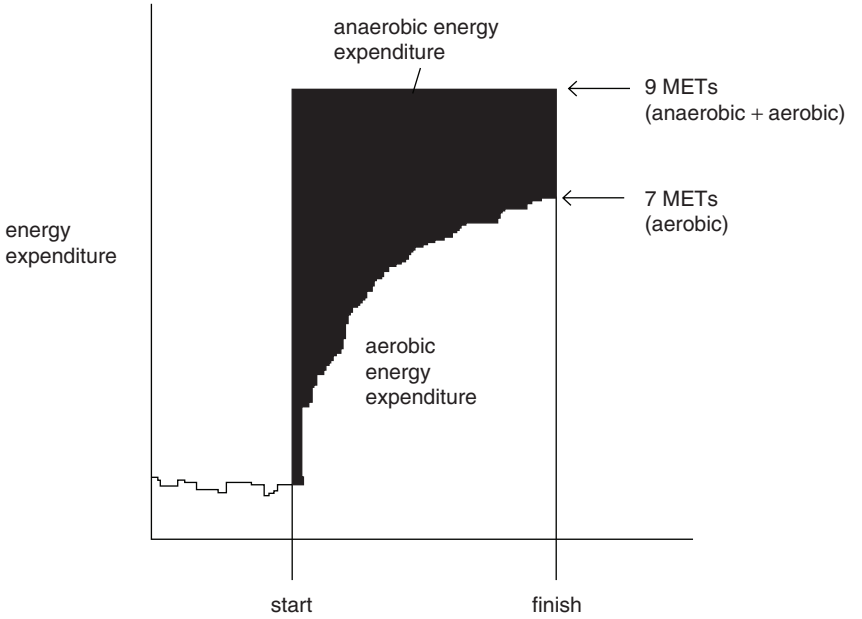

Fig. 15.3 MET tables typically profile exercise and activity in terms of multiples of resting oxygen uptake (i.e., aerobic energy expenditure). To the contrary, this figure reveals METs as comprised of aerobic (*white*) and anaerobic (*black*) energy expenditure. A peak in VO_2 is found at 7× resting oxygen uptake (7 METs). But in terms of both aerobic and anaerobic energy expenditure the metabolic rate is actually 9 METs

15.2 Muscle

Muscle is a chemo-mechanical converter, the energy within ATP being converted into mechanical force. Contraction proceeds when the energy of ATP hydrolysis is large enough to promote movement within muscles molecules.

The molecular aspects of muscle contraction occur at the level of the actin–myosin protein interface. The spread of calcium (Ca^{2+}) throughout the muscles' many sarcomeres initiates muscle contraction (Fig. 15.4).

The actin–myosin motor has been described as both a catalyst and a mechanical ratchet (3). Myosin is in fact an ATPase, catalyzing ATP hydrolysis. In the resting state, myosin and actin are unattached with myosin, tightly binding the products of ATP hydrolysis, ADP, and Pi (until the ADP and Pi are allowed to disperse (repulse) no conversion of chemical to mechanical energy takes place). When muscle is stimulated to contract myosin and actin bind, then the Pi and ADP are released (in that order). Myosin attaches to actin perpendicularly, but upon the release of Pi and ADP, the head of the myosin protein tilts at a sharper angle; this is the power stroke, contraction – the mechanical part of chemo-mechanical conversion.

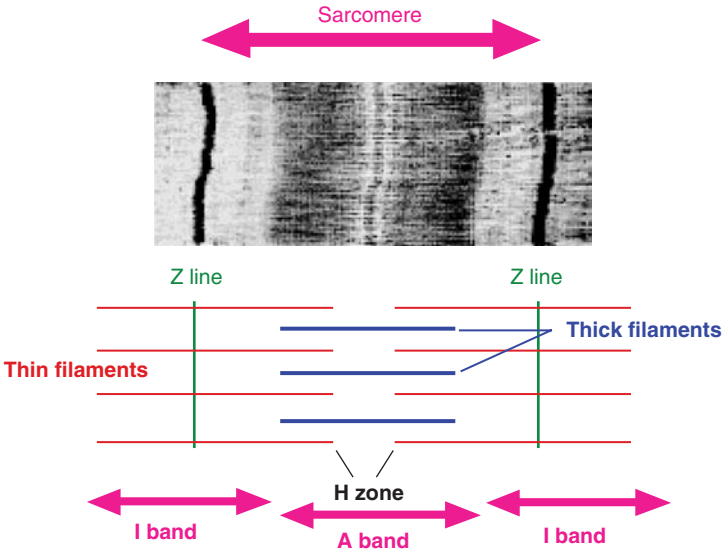

Fig. 15.4 A muscle sarcomere, the contractile component of muscle. A single muscle cell may contain several thousand sarcomeres. The molecules of contraction are shown as actin (*thin filaments in red*) and myosin (*thick filaments in blue*) (from http://commons.wikimedia.org/wiki/Image:Sarcomere.gif)

The conformational change in the head of the myosin molecule represents a lower energy state (upon death and the absence of energy supply, rigor mortis sets in, the state of uninterrupted contraction). The subsequent binding of ATP by myosin causes dissociation of the actin–myosin interface (the so-called resting state). ATP subsequently undergoes hydrolysis to form ADP and Pi and the Gibbs energy change of this reaction is stored within the myosin protein molecule; the myosin head resumes its higher energy state "resting" position, being prepared for the next cycle of binding-and-dissociation with actin. The complete cycle is known as the power stroke.

Under high loads it appears that one ATP molecule is responsible for one power stroke (supplied by the actin–myosin interface) (3, 4). At lighter and perhaps moderate workloads, the energy of one ATP molecule may promote several power strokes at an efficiency of 40% or more (4). The power stroke however represents only one aspect of muscular ATP utilization. ATP is also required to maintain the resting electro-chemical potential of the sarcomere membrane (via the $Na^{+}-K^{+}$ ATPase) and the Ca^{2+} storage facilities (via the Ca^{2+}-ATPase). The energy expended by muscle contraction is considered primarily the result of chemo-mechanical conversion by actomyosin, the orderly movement of energy and materials along the metabolic pathways, and the supporting ion movement within and without the muscle cell.

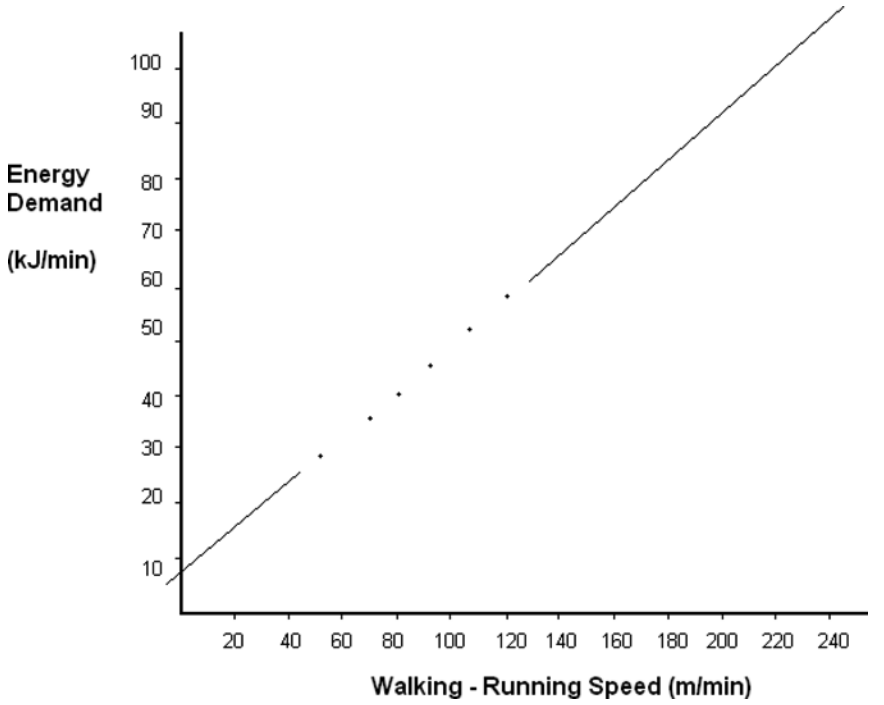

Fig. 15.5 The energy demand and treadmill speed for the six exercise trials in Fig. 15.1 are portrayed here by six dots. Note the linear extrapolations that can be made above and below this power output-to-energy-expenditure relationship. These data have limitations in that they only represent the energy expenditure of longer duration, easy to moderately easy, steady-state exercise. Energy demand can however be *predicted* for treadmill speeds where subjects never achieve a steady rate of oxygen uptake.

15.3 Work and Energy Expenditure Relationships

At steady-state power outputs, a steady rate of oxygen uptake provides an estimate of energy expenditure for that particular workload. In Fig. 15.1, the energy demand, based on oxygen uptake for a single individual, is recorded for six 10-min bouts of treadmill exercise at six different treadmill speeds. The treadmill grade was held at 10% for all six exercise periods.

If the energy demand of the six exercise periods in Fig. 15.1 were plotted on a single graph, a rather remarkable relationship with work is demonstrated. As can be seen in Fig. 15.5, energy demand has a linear relationship with steady-state power output during easy to moderately-easy longer duration exercise. Thus, the modeling of energy expenditure is rather simple for long, slow distance-related exercise; there is a direct correlation between the rate of work and the rate of energy expenditure.

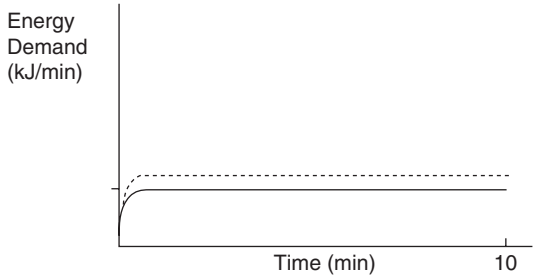

Fig. 15.6 Two identical twins of equal body mass and composition take a leisurely stroll at $54\,m\,min^{-1}$ (2.0 mph). The *bottom solid line* reveals lower energy expenditure at this work load, indicating a better exercise economy for one of the twins, the *dotted line* reveals greater energy expenditure and thus a worse economy. Economical athletes are often at a distinct advantage during competition because they expend less energy at a given race pace

Based on steady-state linear relationships between less-intense exercise and its associated energy expenditure, the energy demand for brief, and/or intense, heavy to severe exercise may also be predicted. But there are shortcomings here. In fact, when work rates take place well above measured rates of oxygen uptake (i.e., above VO_2 max, VO_2 peak or during an oxygen deficit phase at the start of exercise), the relationship between work and energy expenditure may not be linear at all. Moreover, the energy expenditure of a single work rate often varies among people, for a variety of reasons.

Estimates of aerobic energy expenditure for a given individual are ideal for that specific person but may only portray a rough approximation of energy expenditure for another person (or peoples). For example, as a "rule of thumb," a $100\,kcal\,(418\,kJ)\,mile^{-1}$ estimate of energy expenditure has been used for walking, running, or jogging. Yet some people require more then 100 kcal, some less during a 1-mile jog; body weight and power output figure heavily into this (heavier people and faster running speeds increase energy demands). Under recognized limitations, however, a *reasonable estimate* of energy expenditure – a $100\,kcal\,mile^{-1}$ approximation – can be useful, as depicted by the electronic display on exercise equipment for example. At other times greater accuracy is required; for example, as part of the detailed training and eating regimen of an elite athlete. Likewise the precise knowledge of an athlete's energy expenditure at a given workload, such as at racing pace, can provide valuable performance-related information.

The relationship between energy expenditure and workload among individuals is known as exercise economy and it is almost always expressed as a measure of oxygen uptake (Fig. 15.6). Using 25 tests per subject to model the energy demand-power output relationship for each, Medbo et al found a 16% range in oxygen uptake among treadmill runners working at identical power outputs (5). A measure or estimate of economy can serve as a useful tool to help predict performance outcomes because economical athletes utilize less energy to perform a given amount of work, placing themselves at a distinct advantage during competition (6, 7) (it can only be wondered as to how anaerobic energy expenditure would fit into the description

Fig. 15.7 The two lines provide a dramatic demonstration of differences in economy for two subjects during participation of an identical ramp-type work test lasting 20 min or more (11). As heavy exercise is approached and fatigue ensues, additional muscle is recruited and energy demand does not remain linear for the subject whose data is shown in the *top line*. A departure from linearity makes predicting the energy expenditure of heavy to severe exercise problematic because most models of energy expenditure are based on linear not curvilinear relationships. See also Fig. 13.4

of exercise economy when extreme energy demands are greatly supplemented with anaerobic energy exchange).

During heavy to severe exercise the workload–energy-expenditure relationship may not remain linear (see Figs. 13.4 and 15.7). In accordance with traditional oxygen-only views of energy expenditure, increases in energy expenditure that creep above linearity have only been identified using oxygen-uptake measurements. These increases have been termed "extra energy expenditure" (8). Again, following traditional oxygen-only descriptions of energy expenditure, the "extra" demand for energy expenditure during heavy to severe exercise is termed the *slow component of* O_2 *uptake* (8). However, heavy to severe work rates likely invokes an anaerobic component to this so-called "extra" energy expenditure (9). "Extra" nonlinear energy demands are found during both steady-state power output (10) (Fig. 13.4) and ramp-type work where power output steadily increases (11) (Fig. 15.7). Evidence suggests that the potential for "extra" energy expenditure results from the additional recruitment of muscle as intense work progresses and fatigue sets in (10). The presence of nonlinearity in energy expenditure during heavy to severe exercise represents a real problem for the reasonable estimation (extrapolation) of both aerobic and anaerobic energy expenditure. But all is not lost; reasonable estimates of energy expenditure, while controversial, are available (Figure 15.3). The issue of what is and is not a reasonable estimate continues to be debated in the scientific literature (12–14).

15.4 Glycolytic vs. Respiratory Efficiency

In a world that often focuses on aerobic metabolism (i.e., oxygen uptake), inefficient is the usual description of anaerobic metabolism. To the contrary aerobic

Table 15.2 In-series energy-exchange efficiency

Krebs cycle						
84%						
Krebs cycle		Electron transfer		Efficiency		
84%	×	97%	=	81%		
Krebs cycle		Electron transfer		H^+ gradient		Efficiency
84%	×	97%	×	80%	=	65%
Aerobic metabolism		Chemo-mechanical conversion		Efficiency		
65%	×	45%	=	29%		
Anaerobic metabolism		Chemo-mechanical conversion		Efficiency		
65%	×	45%	=	29%		

The three independent energy-exchange gradients are shown for aerobic metabolism: Krebs cycle, electron transfer, H^+ gradient. In going from top to bottom, notice the more exchange devices placed in-series, the lower the overall efficiency. The coupling of aerobic or anaerobic energy exchange (65%) to muscle contraction (45% efficiency) suggests a whole-body efficiency of running or cycling at 29%. These numbers are hypothetical (demonstration purposes only)

metabolism is thought to be a rather efficient process. Are these statements true? Only 2 ATPs are resynthesized during net anaerobic glycolysis (3 ATPs if glycogen is the starting point). Compared with aerobic (mitochondrial) metabolism, where ~32 ATPs are resynthesized from a molecule of glucose, it indeed looks as if glycolysis is woefully inefficient in terms of the *amount* of ATP resynthesized. Because there is no evidence to suggest that the ATP resynthesized from anaerobic metabolism is of lower quality (less $-\Delta G$) than that of aerobically resynthesized ATP, an interesting question arises: Why do cells retain glycolysis as a limited anaerobic energy-exchange device?

There are several ways to compare and thus interpret aerobic and anaerobic efficiency (although efficiency is defined strictly as the ratio of output to input). To begin, anaerobic glycolysis *is* inefficient in terms of the amount of ATP resynthesized per glucose moiety; 2 ATPs as compared with the 32 additonal ATPs involving mitochondrial respiration. Moreover, a good deal of available energy is still contained within lactate, an end product of glycolysis.

Another method of interpretation is to examine the overall efficiency of coupled energy-exchange devices. As an in-series compilation of efficiency, the metabolic and work-related devices of energy exchange are suggested in Table 15.2. As a generalization, the more exchange devices placed in-series, the lower the overall efficiency. In Table 15.2 the two metabolic pathways are comparable in efficiency (even though aerobic respiration involves additional in-series energy-exchange devices as compared with anaerobic metabolism; krebs cycle × electron transfer × H^+ gradient versus substrate level phosphorylation.).

Another way to compare aerobic vs. anaerobic efficiency is to rationalize both phosphorylation potential (i.e., efficiency of the actual process of ATP resynthesis) and the energy content of the substrate being utilized during metabolism (15, 16). With this interpretation there is evidence to suggest that anaerobic substrate-level (glycolytic) phosphorylation is as much or more an efficient energy-exchange device than is aerobic respiratory (mitochondrial) phosphorylation (17, 18). Per unit,

fat also contains much more energy than does glucose. Using the parameters of phosphorylation potential and substrate energy content, the greater amount of energy contained within fat may be purposely coupled to a less-efficient aerobic means of ATP resynthesis. On the other hand, a molecule or mole of glucose contains less energy than fat, but at heavy to severe work rates, working muscle may switch to a greater rate of anaerobic glycolysis for its "as much or more" efficiency of ATP resynthesis (15, 16).

Efficiency can be further viewed as a lower heat loss during the conversion of energy to work output. Heat-only measurements of muscle contraction (i.e., complete ATP turnover) suggest that anaerobic glycolytic metabolism may be more efficient as compared with aerobic metabolism (17). A thermal rationale also can be applied to the use of the ATP, PC stores during intense exercise, representing only one-half of ATP turnover and thus "incomplete" heat loss interpreted as "improved" efficiency during contraction; the metabolic resynthesis of these stores, the other-half of ATP turnover and its associated aerobic heat production, takes place in recovery (18) (it must be kept in mind however that heat production, not ATP resynthesis, can be a metabolic goal (19, 20); also heat and entropy are both expenditures, but only the former is actually measured in the consideration of efficiency (21) (see Fig. 9.3).

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Chapter 16
Total Energy Expenditure of Exercise and Recovery

The differences between closed and open systems are very real and must be accounted for; survival comes at a continual cost. Life's expenditures have been flippantly described as:

> You can not win,
> You can not break even,
> You can not get out of the game. (Anonymous)

"Playing life's games" requires the use of body's musculature. Movement in all forms – exercise, physical activity, work, training, competing, fleeing – acutely increases energy expenditure (perhaps chronically too in the well trained (1)). Feats of speed, strength, and power also require energy to be expended during a recovery period. Exercise and the recovery energy expenditure that results are combined in an estimate of total energy expenditure requiring three independent measures (Fig. 16.1):

Aerobic exercise energy expenditure
Anaerobic exercise energy expenditure
Aerobic recovery energy expenditure

16.1 Aerobic Exercise Energy Expenditure

Energy is expended during the exchange of chemical energy to mechanical force; work, heat, entropy, carbon dioxide, and water are put-out to the environment as oxygen is consumed. Using twenty-first century technology, the measurement of oxygen uptake for the estimation of aerobic energy expenditure is a rather simple task. In addition to individual differences in oxygen uptake economy during exercise, researchers further understand that a given amount of biological and measurement variability is always evident (the shortest sampling periods lasting seconds (e.g., breath-by-breath) have the largest variance as compared with measurements that average oxygen uptake over a 1-min period (or longer) (2)).

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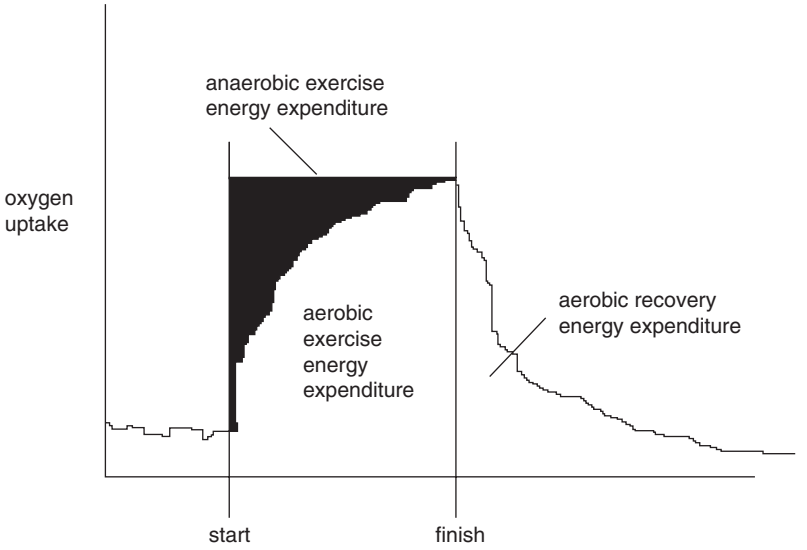

Fig. 16.1 The three components of total energy expenditure during and after a brief bout of heavy exercise

Lower intensity, steady-state, longer duration exercise is supported in full by aerobic metabolism so that a measurement of oxygen uptake adequately estimates the energy expenditure associated with oxygen-related ATP turnover (Fig. 16.2). Depending on the type or mixture of substrates consumed by working muscle during steady-state exercise, energy expenditure per liter of oxygen consumed ranges from 19.6 kJ (all fat) to 21.1 kJ (all carbohydrate) (see Table 12.1).

Muscle contraction may be fueled largely by anaerobic metabolism during heavy to severe exercise. To obtain a more complete estimate of the energy expenditure for intense exercise, anaerobic energy exchange warrants consideration.

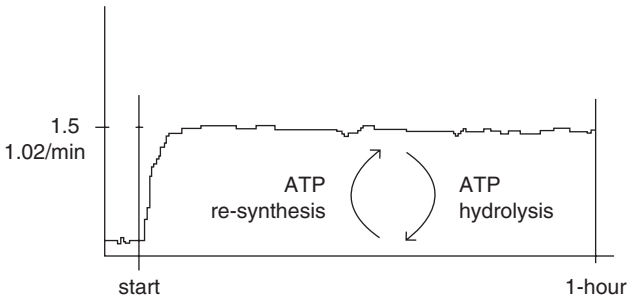

Fig. 16.2 Moderate intensity steady state exercise is depicted above lasting 1 h in length. A measurement of oxygen uptake (at 1.5 L of O_2 min^{-1}) provides an estimate of the energy expended during ATP hydrolysis (energy demand) and ATP resynthesis (energy supply) for this period of exercise

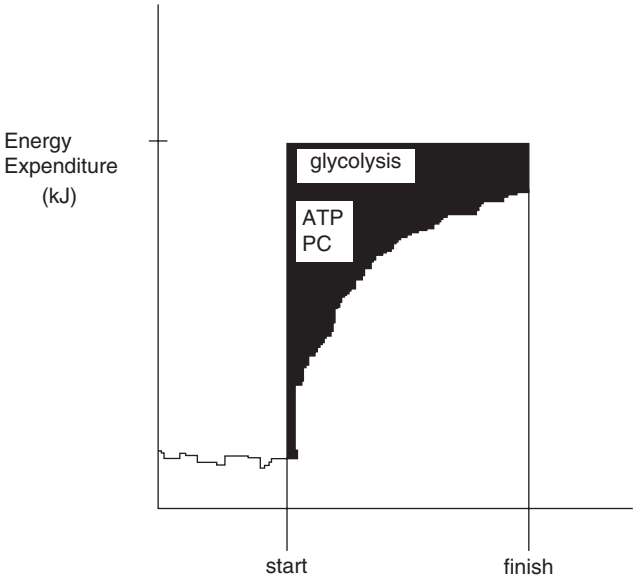

Fig. 16.3 The anaerobic energy expenditure components are shown for a brief bout of heavy to severe exercise

16.2 Anaerobic Exercise Energy Expenditure

The two predominate sources of anaerobic energy expenditure are (Fig. 16.3):

1. rapid anaerobic glycolysis (substrate-level phosphorylation)
2. stored "high energy" phosphates (ATP, PC)

Both sources of anaerobic energy exchange need to be accounted for when attempting to estimate anaerobic energy expenditure (3). Muscle biopsies appear to provide the most insightful reflection of anaerobic energy exchange. The biopsy procedure is, however, invasive and a minuscule sample of muscle only hints at the metabolic events, aerobic and anaerobic, within entire muscle beds made-up perhaps of thousands of muscle fibers composed of several fiber types (ranging from fast-twitch glycolytic fibers to slow-twitch oxidative fibers). As described earlier, the two non-invasive methods of estimating anaerobic energy expenditure require a measurement of blood lactate or the oxygen deficit; both provide an indirect accounting (or estimate) of anaerobic energy exchange.

In real time, the oxygen-deficit period contains anaerobic glycolysis along with the use of the ATP, PC stores. A measurement of lactate concentration provides only an estimate of the anaerobic glycolytic contribution to exercise energy expenditure. Contributions by the two anaerobic components can vary dramatically depending on the duration, intensity, and type of exercise. For example, short bouts of strength-type, heavy-resistance, weight training involving

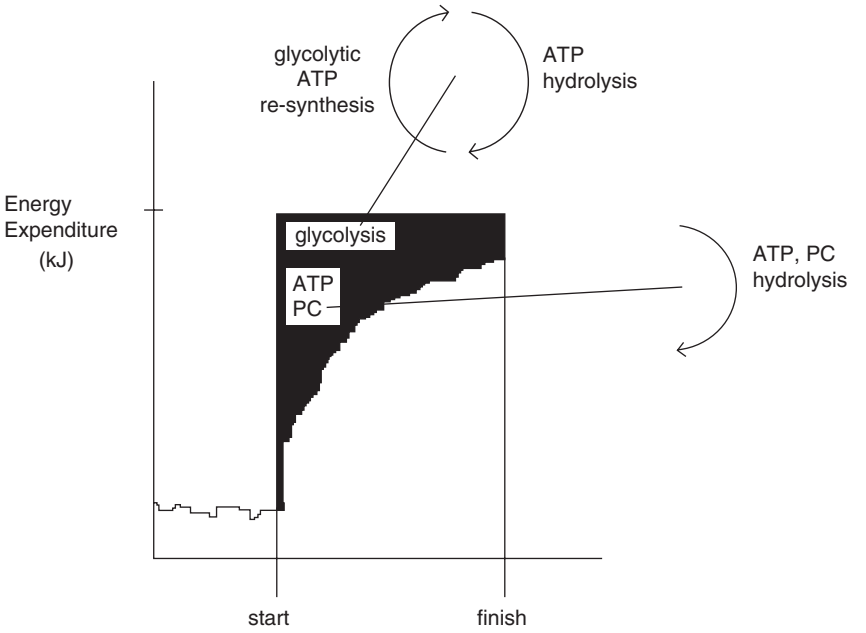

Fig. 16.4 Two components of anaerobic exercise energy expenditure as part of the oxygen deficit (in black) are shown in *real time* for a brief bout of heavy to severe exercise. Note that glycolysis is associated with complete ATP turnover. ATP and PC hydrolysis represents only a half-cycle of ATP turnover

limited repetitions may be fueled largely by the ATP, PC stores. To the contrary, longer lasting, moderate resistance, muscular endurance-type resistance training may contain a larger anaerobic glycolytic component with limited ATP, PC contributions (4).

Recall that a measure of oxygen uptake to estimate energy expenditure (kJ) represents a complete cycle of ATP turnover. Lactate measurements in turn are converted into oxygen equivalent units (then into kJ) so that they too represent a complete cycle of ATP turnover (5, 6). A measure of the oxygen deficit likewise is portrayed by oxygen equivalent units, also representing complete ATP turnover. In *real time*, however, the oxygen deficit contains ATP and PC usage to support muscle contraction but not the metabolic resynthesis needed for restoration (Fig. 16.4) (7, 8).

In real time, resynthesis of the ATP, PC stores actually takes place after exercise, during recovery (9–11). Thus, when expressed in oxygen equivalent units, a measure of the oxygen deficit cannot be included along with a recovery oxygen uptake measurement because when doing so the ATP, PC turnover component is accounted for twice. A measurement of the oxygen deficit in the portrayal of anaerobic energy expenditure is an acceptable practice only when estimating aerobic and anaerobic exercise energy expenditure (Fig. 16.5), not exercise and recovery energy expenditure.

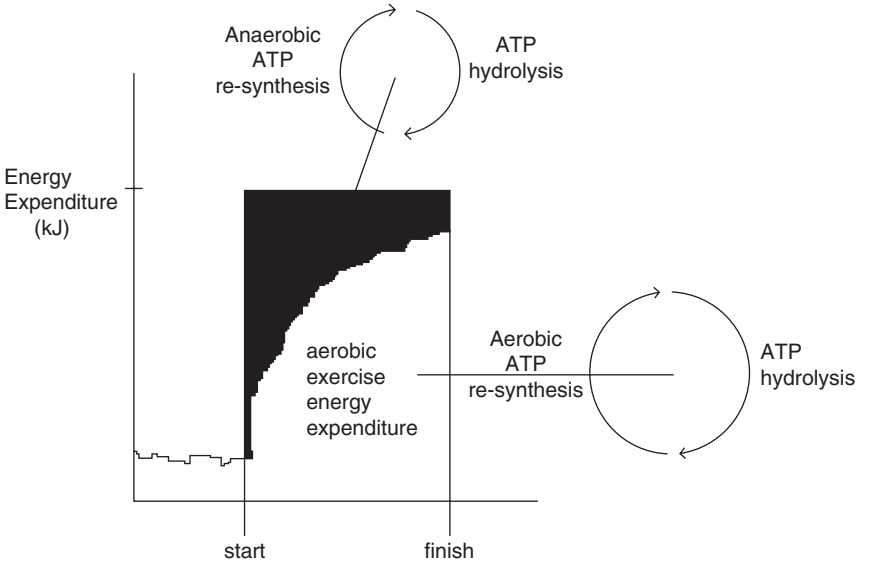

Fig. 16.5 The oxygen deficit (in black) does not partition anaerobic exercise energy expenditure into anaerobic glycolytic and ATP, PC components. When measured respectively as oxygen uptake and oxygen equivalent units, aerobic (in white) and anaerobic (in black) energy expenditures are expressed as a complete cycle of ATP turnover. Recovery energy expenditure is absent from the above diagram

16.3 Aerobic Recovery Energy Expenditure

Whole-body energy demands elevated throughout exercise gradually diminish to resting levels during recovery and the pattern of oxygen uptake follows suit (see Figs. 16.6 and 16.7). Depending on exercise intensity and duration, recovery oxygen uptake can remain elevated for minutes to hours (perhaps even days after extreme sporting events) (10). Over the years the oxygen consumed in recovery has been described using terminology that both offers and dismisses explanations of how anaerobic exercise and aerobic recovery energy expenditure are to be interpreted. Respectively, the oxygen debt and excess postexercise oxygen consumption (EPOC) are two prominent examples of such terminology. In a straight-forward manner the energy expenditure of recovery here will be termed *aerobic recovery energy expenditure*. Skeletal muscle is not contracting during an inactive recovery but energy exchange is essential to reacquire a resting homeostasis, in muscle cells and throughout the body. Some of the demands for aerobic energy exchange during recovery are provided in Table 16.1 (from (10)).

Research has shown that the recovery from exercise appears to be solely aerobic; there is little to no rapid anaerobic glycolytic component to recovery energy expenditure (9, 11). Oxygen uptake measurements are therefore extremely useful in the estimation of recovery energy expenditure, again representing a complete cycle

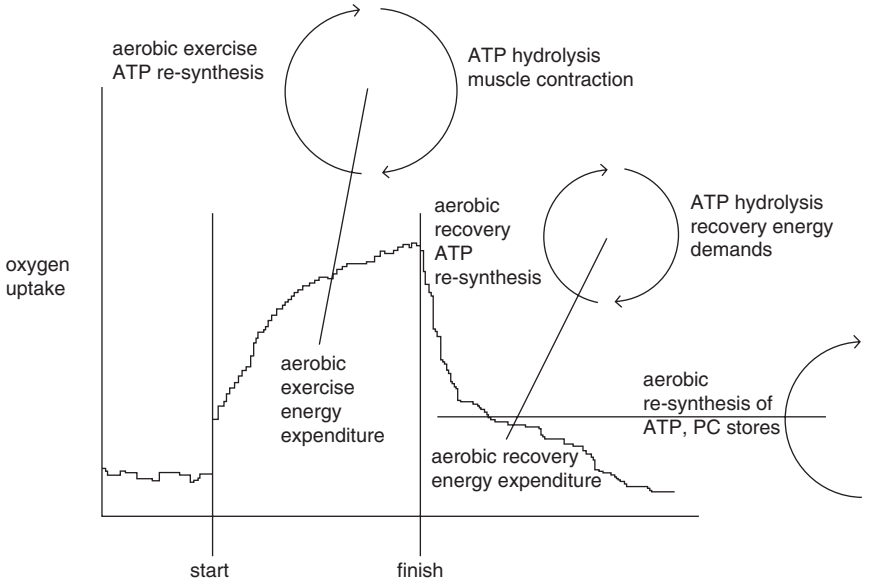

Fig. 16.6 Aerobic energy expenditure for exercise and recovery is depicted in *real time*; anaerobic exercise energy expenditure is not shown. Complete ATP turnover is accounted for by exercise related oxygen uptake. Recovery related oxygen uptake also is associated with complete ATP turnover in the reattainment of cellular and whole-body homeostasis. However, resynthesis of the ATP, PC stores represents an aerobic ATP half-cycle and, in *real time*, is not associated with ATP, PC hydrolysis during exercise

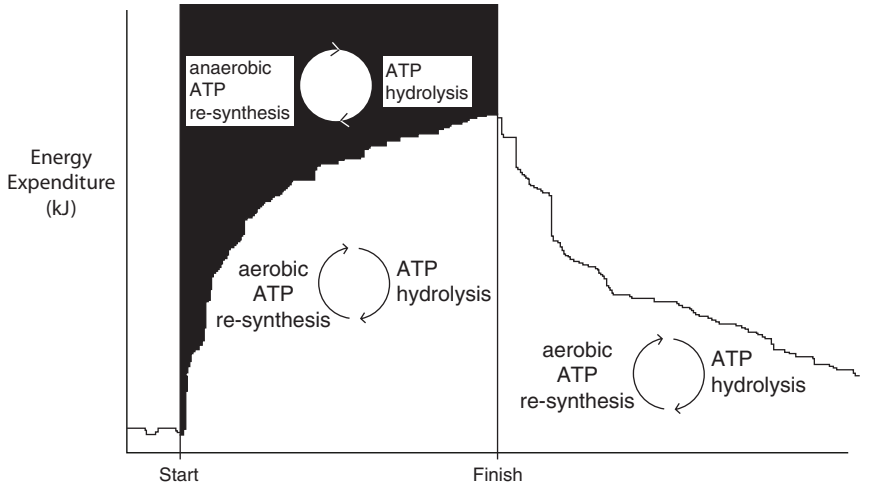

Fig. 16.7 The above diagram portrays an all-out 2-min sprint up a steep hill: start to finish along with recovery. Anaerobic glycolytic exercise energy expenditure is shown in black as measured by Δ blood lactate. Aerobic exercise and recovery energy expenditure also are displayed. This figure demonstrates each of three complete estimations of complete ATP turnover that comprise total energy expenditure

Table 16.1 ATP demands during the recovery from exercise

Resaturation of hemoglobin and myoglobin (this is an O_2 demand not an ATP demand)
Cost of ATP, PC resynthesis
Cost of increased circulation (e.g., heart) and ventilation (e.g., diaphragm)
Cost of glycogen resynthesis from lactate
Triglyceride-free fatty acid cycling
Protein turnover
Hormonal effects on energy expenditure (e.g., epinephrine, growth hormone/factors)

of ATP hydrolysis to fuel recovery energy demands and the mitochondrial resynthesis of that ATP. But again care must be taken when considering restoration of the ATP, PC stores. In real time, resynthesis of the ATP, PC stores in recovery (but used during exercise) represents only a half-cycle of ATP turnover (Fig. 16.6). Yet recovery energy expenditure accounted for by oxygen uptake represents complete ATP turnover (Fig. 16.7).

The conundrum created by an indirect estimate of ATP, PC usage and resynthesis has straight-jacketed exercise physiologists for years. The same is true for anaerobic glycolysis as described in the next section (the oxygen debt hypothesis). As a result many exercise scientists have resorted to measuring only one or two of the three components of total energy expenditure in the avoidance of redundancy issues:

1. *Aerobic exercise energy expenditure* (lacking anaerobic exercise and aerobic recovery measurements). This is extremely useful for estimating the energy expenditure of low-to-moderate intensity steady-state exercise (Fig. 16.2) (Table 12.1). It is unacceptable when estimating energy expenditure for anaerobic exercise.
2. *Aerobic and anaerobic exercise energy expenditure* (lacking an aerobic recovery measurement). This is ideal for those who desire only to consider the cost of a bout of exercise (Fig. 16.5).
3. *Aerobic exercise and aerobic recovery energy expenditure* (lacking an anaerobic exercise measurement). Acceptable only for low to moderate intensity exercise and its recovery; these components have perhaps been the most problematic in allowing (or rather not allowing) for a reasonable estimate of anaerobic energy expenditure (Fig. 16.6). These two measurements do not properly account for anaerobic exercise that contains a significant glycolytic component (i.e., a large lactate concentration after exercise is complete).

16.4 Dismissing the Oxygen Debt Hypothesis

It has been hypothesized since the 1920s that aerobic recovery oxygen uptake represented anaerobic exercise energy expenditure in addition to aerobic recovery energy expenditure. This idea was known as the oxygen debt hypothesis and its lasting

influence has perhaps been influenced by the fact that it characterizes a half-truth: the "debt" of ATP, PC resynthesis created during exercise *is* repaid in recovery.

Supporters of the oxygen debt hypothesis went too far, however, in suggesting that recovery oxygen uptake not only represented use and resynthesis of the ATP, PC stores, but also the ATP utilized and resynthesized as rapid anaerobic glycolysis with lactate production. Much of the hypothesis was based on knowing how much lactate was formed and how much was later oxidized in recovery. A valid determination of either complete lactate production or complete removal would seemingly allow for a reasonable estimate of anaerobic glycolytic energy expenditure. Disproof of the oxygen debt hypothesis was demonstrated by the ubiquity of lactate removal (12). Lactate can be converted into glucose, glycogen, amino acids, and protein. It also is found in sweat, urine, and saliva. With so many avenues of disappearance, it is not possible to obtain a valid account of lactate removal. Yet as interesting as the ubiquity of lactate removal is, this information does little to quantify anaerobic glycolytic and recovery energy expenditure. Indeed, information concerning lactate removal has instead been used to inform scientists how not to obtain an estimate of anaerobic energy expenditure! So how can a concurrent estimate of anaerobic exercise and aerobic recovery energy expenditure be obtained?

Recall that the breakdown of glucose-to-pyruvate evolves less heat than does the breakdown of glucose-to-lactate; the reduction of pyruvate to form lactate is the largest source of heat production during glycolysis, from the metabolic system to the surroundings. Based on the *reversible* thermodynamics of a closed system as the oxygen debt hypothesis apparently was, a reversal in heat transfer – from the surroundings to the system – during the removal or reconversion of lactate-to-pyruvate would promote the concept that oxygen uptake can account for an accelerated pyruvate-to-lactate energy exchange. However, within the context of an open *irreversible* system, it is difficult to conceive of how the heat expended from glycolytically (anaerobic) supported muscle contraction could be represented by a measurement of mitochondrial oxygen uptake during recovery as the oxygen debt hypothesis proposed. Anaerobic metabolic glucose degradation as a part of aerobic energy exchange (at $1.5\,\text{kJ}\,\text{LO}_2{}^{-1}$) can only be represented by oxygen uptake when the rate of glycolysis matches that of mitochondrial respiration (i.e., when anaerobic pyruvate production matches aerobic pyruvate removal, where $1\,\text{LO}_2\,\text{min}^{-1} = 21.1\,\text{kJ}\,\text{min}^{-1}$). When rapid anaerobic glycolytic energy exchange proceeds at a rate that exceeds that of mitochondrial respiration, anaerobic energy expenditure is not accounted for by a measure of recovery oxygen uptake (13).

As an open system, muscle contraction fueled by rapid anaerobic glycolysis irreversibly increases heat and entropy in the surroundings; they are not later removed from the surroundings by mitochondria during the oxidation of lactate (14). Table 16.2 reveals that in respiring cells and tissues that were separately "fed" pyruvate and lactate, similar amounts of heat were produced per volume of oxygen consumed. This experiment demonstrates that when lactate is reconverted back into pyruvate for complete oxidation by mitochondria, heat is not consumed (reversed) as part of the reaction. Lactate production and lactate oxidation involve independent

Table 16.2 Respiratory heat production (ΔH) for pyruvate and lactate oxidation

	$\Delta H\,(kJ\,mol\,O_2{}^{-1})$		
	Pyruvate	Lactate	*p*
Hybrid cells	−517	−516	0.97
Cardiac muscle fibers	−506	−502	0.92

energy-exchange devices, each representing separate and additive components to the measurement of total energy expenditure for exercise and recovery (14).

Recovery energy expenditure can be described in the context of an oxygen debt for ATP, PC restoration. Aerobic recovery energy expenditure also has traditionally and incorrectly been used to estimate rapid anaerobic glycolytic ATP resynthesis as part of oxygen uptake during the recovery from exercise as, 1 L of O_2 uptake = 21.1 kJ. This conversion contains an anaerobic glycolytic energy expenditure component (1.5 kJ) that should not be accounted for twice, once as a Δblood lactate or oxygen deficit estimate of anaerobic energy expenditure (in O_2 equivalents) and again as part of recovery oxygen uptake. Instead, the energy expenditure of recovery should be free of the anaerobic glycolytic component, being based entirely on aerobic (mitochondrial) respiration. How is this accomplished? The all-aerobic conversion demonstrated earlier as Thornton's law, where 1 L of O_2 uptake = 19.6 kJ, void of the anaerobic glycolytic component, eliminates the false rationale of rapid anaerobic glycolysis during exercise being portrayed by a measurement of recovery oxygen uptake (14–19).

16.5 Total Energy Expenditure

Three measurements are available to provide a reasonable estimation of total energy expenditure for both exercise and recovery (with limitations):

1. anaerobic (glycolytic) exercise energy expenditure,
2. aerobic exercise energy expenditure (oxidizing fats and/or carbohydrates),
3. aerobic (nonglycolytic) recovery energy expenditure.

Within the strict limitations of brief and intense exercise, when peaking in recovery (not during the exercise), lactate concentrations can provide a reasonable estimate of *anaerobic (glycolytic) exercise energy expenditure* (3–6, 19, 20).

$$\Delta\text{blood lactate} \times 3\,\text{mL}\,O_2 \times \text{weight (kg)} = \text{mL } O_2 \text{ equivalents}$$

then 1 L O_2 = 21.1 kJ (assuming equivalent aerobic and anaerobic efficiency)

The estimation of *aerobic exercise energy expenditure* is straight-forward, using a measurement of oxygen uptake during exercise (dependent on substrate utilization, see Table 12.1):

$$1\,\text{L of exercise } O_2 \text{ uptake} = 19.6 - 21.1\,\text{kJ}$$

Aerobic (nonglycolytic) recovery energy expenditure representing: (1) fat and lactate oxidation (10), (2) use and resynthesis of the ATP, PC stores, and (3) the energy demands of recovery:

$$1\,\text{L of recovery } O_2 \text{ uptake} = 19.6\,\text{kJ}$$

ATP turnover for each of the three components of total energy expenditure is detailed in Fig. 16.7.

16.6 Weight Loss: Low vs. High Intensity Activity

It is acknowledged that, (1) "physical activity affects body composition and weight favorably, by promoting fat loss, while preserving lean mass" and, (2) "the rate of weight loss is positively related to the frequency and duration of the exercise program, thereby suggesting a dose-response relationship" (21). Exercise prescriptions that focus on dose–response relationships also include exercise intensity as a key variable. How does exercise intensity affect the rate and amount of body weight and/or fat mass loss? The answer is complex and seemingly dependent on how one examines this issue.

Part of the complexity resides in the variable being studied. For example, is it body weight or body fat losses that are of utmost concern? Other issues are at play here in that energy intake may not be taken into account and this confounds the problem when comparisons are made – people may eat more after exercising at higher exercise intensities and not lose weight. Higher intensity activity may conserve or build lean body tissue (fat-free mass) (22, 23). Lower intensity activity has the potential advantage of reducing injury in overweight exercisers, a legitimate concern.

Reciprocal arguments have been created to support both low and high intensity programs in the reduction of body fat. Exercise programs have focused on substrate utilization during activity, glucose (and glycogen) vs. fat "burning" for example. As an example, exercise programs designed for fat loss traditionally focus on fat "burning" at lower exercise intensities coupled with longer durations. From this perspective long slow distance training has been advocated as the best way to reduce the body's fat stores. While it is true that higher exercise intensities are associated with muscle glycogen utilization, it is apparent that a significant amount of fat is also broken down and subsequently dumped into the blood stream during intense exercise, even though that fat may not be consumed during exercise. This fat (triacylglycerides) appears to be ready as a fuel for recovery (24). Scientists have shown that a period of initial exercise followed by passive recovery can subsequently affect substrate oxidation during additional exercise bouts with greater fat and less carbohydrate utilization (25, 26). In this context exercise programs designed for fat oxidation should be intermittent in nature.

Several studies have in fact revealed greater body fat losses with higher intensity exercise (27–32). If high-intensity exercise "burns calories" at a greater rate

than lower intensity exercise, should the exercise program focus more on how much energy is expended as compared to what type of fuel is utilized? Statistical comparisons of groups exercising at low and high intensities are limited because the amount of energy expended is often different between groups exercising at differing intensities; for example, 30-minutes of heavy exertion "burns more calories" than 30-minutes of low exertion activity. A better study design would involve identical energy expenditure between exercising groups to provide a clear example of the effects of intensity alone on fat loss. When overall energy expenditure is taken into consideration, being identical for low- and high-intensity exercise, higher exercise intensities are generally not associated with greater body weight or fat loss (22, 33, 34). As pointed out in the beginning of this section, it may be that body fat losses associated with higher intensity exercise are simply a result of energy expenditure in a dose–response manner, the greater the total energy expenditure for both exercise and recovery the greater the chance for body fat loss (23). In practice then, the best exercise programs for body weight or fat loss would involve intermittent heavy to severe work bouts utilizing large muscle groups followed by an active recovery. Sprinting a given distance or over a given time "burns more calories" than walking; walking or jogging during the recovery from that sprint continues to elevate "calorie burning" above resting levels, and consumes fat to do so. It all adds up (Fig. 16.8).

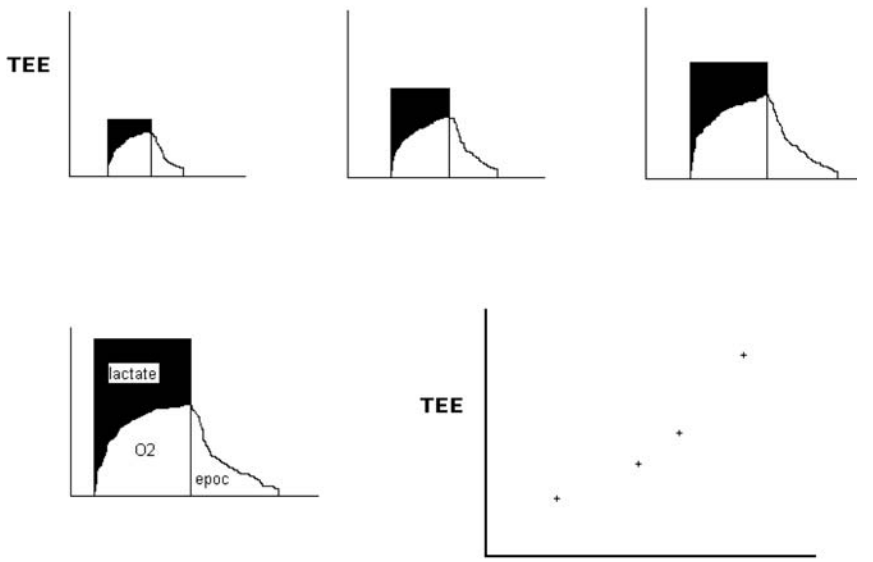

Fig. 16.8 Total energy expenditure (TEE) is shown for 4 intense workloads. Each of these is plotted in the bottom right to reveal a true curvilinear relationship as opposed to predicted and false linear relationship

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