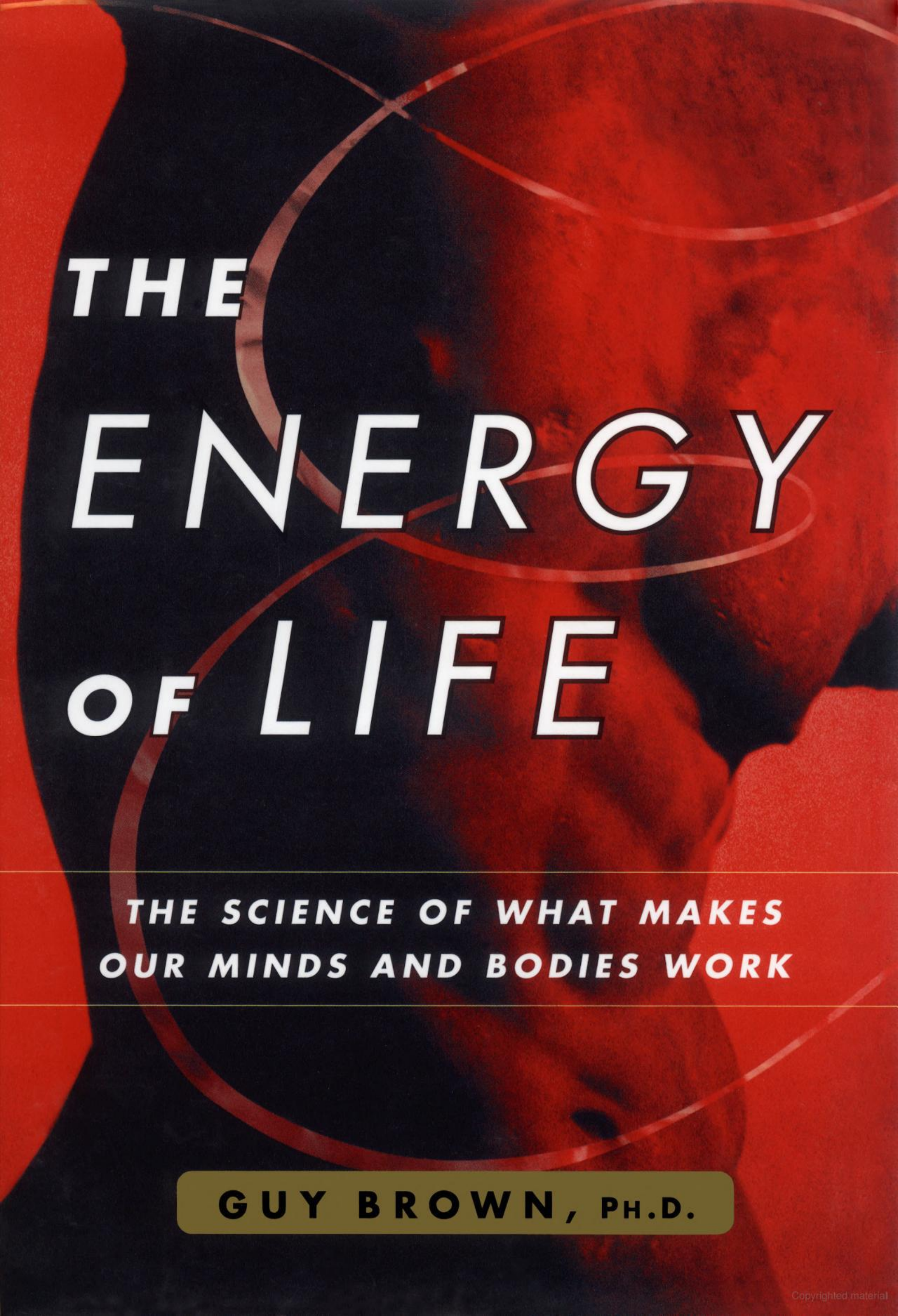

THE ENERGY OF LIFE

THE SCIENCE OF WHAT MAKES OUR MINDS AND BODIES WORK

GUY BROWN, PH.D.

The Energy of Life

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Introduction

Every morning of our lives we wake up and reach out from unconsciousness to consciousness, from nothingness to being, from dream to reality. And when the full force of reality hits us like a sledgehammer, we must choose between sinking back into nothingness or grabbing hold of reality. To wake up and get on with life we need energy—body energy and mind energy. We need body energy to get out of bed, make the coffee, run for the bus, beat our competitors, and drag ourselves home again. We need mind energy to arouse and motivate us to want to get out of bed and do something. This book is about energy: what it is, how we get it, and how we lose it again. But in discussing these practical things, we will unavoidably be touching on more fundamental issues. What is life? How does it work? And why do we bother getting out of bed in the morning at all?

You are awake now, and although you are doing nothing more than reading this book, every one of the hundred thousand billion cells in your body is consuming energy—lots of energy. A quarter of it is being used to process bits of information like this book, another quarter is being used to replace worn-out bits of your body, and much of the rest is wasted as heat to keep you warm. Your brain is hungry for energy too. It is consuming energy at ten times the rate of rest of the body, and the brain is very particular about what type of energy it will use—but you had better give it what it wants, because if the brain is deprived of energy for more than ten minutes, it will be irreversibly damaged. Perhaps you had better replenish your energy stores by breathing in some of that fresh air and having something to eat.

What is this thing—energy—that divides the strong from the weak, the young from the old, the living from the dead? How does energy animate the body and mind? How does it enable a body to grow, a finger to move, a mind to think? Energy is the basic constituent of the universe—even more fundamental than matter. Energy is the origin of all change. Every single event in the universe, from the collision of atoms to the explosion of stars, uses energy. And our own bodies, even in dreamless sleep, require large amounts of it. To be alive is to be a continuous transformer of energy, a machine that transmutes the food we eat and the air we breathe into a dancer's dance and a poet's dream.

There is abundant evidence that how energetic we feel is a major component of how happy, healthy, productive, and creative we are. It may be more important for our overall well-being to track the influences that boost or drain our energy than it is to follow our calorie intake or bank accounts. Energy is a central aspect of our lives. Without it, our personal world shrinks to a small number of essential tasks, people, and places; we have no energy to face anything except the essential minimum. With an abundant supply of body and mind energy, our world opens up as we expand our interactions with people, projects, and places to occupy all the available time of life.

Vitality, passion, dynamism, confidence, the ability to concentrate and work without rest, to think fast and coherently, to resist fatigue and exhaustion—in short, energy—are the essential qualities, above everything else, required to succeed in life. Number one on the *Harvard Business Review*'s list of essential qualities for business success is "a high level of drive and energy." Everybody is looking for that sparkle in friends and lovers to make things happen. Most of all, everybody is looking for that energy within themselves—the motivation, drive, and oomph to get off our backsides and do something; the endurance, stamina, and resolve to carry through what we are already doing and need to do; and courage and will to break out of the old routines when necessary and change direction. We may know how to do something, but without the will and creative energy, and more. In physical science, the meaning of "energy" is more restricted and concrete (as with most other scientific terms), which makes it more useful for some purposes but less useful for others. However, the popular concept of energy captures something crucial to all of us in our everyday lives.

The Energy of Life takes the popular and ancient concept of biological energy and looks at it from the point of view of the latest science. In doing so, we cover a lot of territory, from physics and energetics to psychology, through the evolution of life to the origins of cell death. We look at how and why energy was discovered, how the infinitely delicate machinery of our cells makes the miracles of motion and thought possible, and how that same magnificent machinery creates fatigue, obesity, disease, aging, and death. We also examine how energy is related to the perception of time, why we sleep and dream, and the connection between energy and sex. Then at the end of our journey, we can come back to the more practical question of why we as individuals sometimes lack energy and what we can do to get more.

A history of how our ideas of energy and life evolved appears in the appendix. If you find any of the book heavy going, you might find it enlightening to turn to this story of living energy, which introduces the background ideas of bioenergetics in a more leisurely pace and fashion.

The
Energy
of
Life

1

Energy Itself

I taught the science of body energy, or bioenergetics, at Cambridge University for many years before I realized that I did not understand what energy was. Tutorials (or supervisions, as they are called in Cambridge) are meant to be cozy but fiercely intellectual chats between a teacher and one or two students over tea and scones. However, teachers (called fellows in Cambridge) often rattle on without knowing what the hell they are talking about. And one fine day I discovered that was true of me and energy. Part of the problem with energy is that it is rather an abstract idea, so one answer to the question, "What is energy?" is, "A concept in the scientist's head." A more subtle problem is how the concept of energy has evolved historically, so that many layers of meaning, which are not always consistent, have been superimposed on the words and symbols. So take heart; if you do not at first understand the meaning of energy, it will not necessarily disqualify you from doing scientific research or teaching bioenergetics at Cambridge. In science as in life, you do not necessarily have to understand a concept in order to be able to use it.

According to current scientific ideas, energy is *not* an invisible force field coursing through the body, moving arms and legs here and cooking up great thoughts in the brain, like some benign ghost dashing around pulling the levers of the body and mind. The modern idea of energy is the world. Energy is the one thing that remains constant (is conserved) through all change. Everything can be created from or dissolved into energy, including matter itself, as demonstrated by the explosion of an atom bomb and Albert Einstein's famous equation, $E = mc^2$. According to this rather abstract scheme of things, then, energy is the ultimate substance and fabric of the world, from which all else evolves and into which all else ultimately dissolves.

But energy itself does not produce movement or change. So what does? According to Sir Isaac Newton (1642–1727), all movement or change is brought about by a force. In our everyday lives, we experience only two types of force: gravitational force and contact forces. The gravitational force pulls things toward the center of the earth and causes all heavenly (and not so heavenly) bodies to attract each other. Contact forces occur when we push or pull something—when I lift a chair, when a car hits a lamppost, or when a volcano explodes. The gravitational force occurs because every bit of matter is attracted to every other bit, causing them to accelerate toward each other. All the contact forces are actually different manifestations of one immensely powerful force: the electric force. The electric force is the force of attraction or repulsion between all charged bits of matter. The gravitational force and the electric force account for virtually all movement and change in our universe. There are two other forces known: the strong nuclear force and the weak nuclear force, but their range of action is so small that they can be observed only by breaking open the nucleus inside an atom. Thus, these nuclear forces have no apparent effect on biology or our everyday lives.

Although the gravitational force is important for large objects like us, it is not significant for small objects like a cell. The electric force is roughly one thousand million million million million million million times stronger than the gravitational force, and at the level of molecules and cells, it is the only force that matters. The gravitational force causes attraction—that is, two bits of matter will accelerate toward each other. But the electric force causes either repulsion or attraction depending on whether the bits of matter carry the same or different charges: opposites attract; likes repel. The electron carries a negative charge; the proton carries a positive charge. All things, including our bodies, can be considered to be made up of different arrangements of protons and electrons.

There are also neutrons, but they have no charge and behave a bit like an electron and a proton stuck tightly together. All bits of matter are made up of roughly equal numbers of electrons and protons. If this were not so, there would be an excess of positive or negative charge, and this would create a huge force pushing the excess charge out, leaving a roughly neutral group of electrons and protons. The power of the electric force is truly immense. If two people, standing an arm's length apart, were each to have 1 percent more electrons than protons in their bodies, they would be blown apart by an electric force sufficient to move the weight of the entire earth.

The power of the electric force is not always evident at the everyday level because most things contain almost exactly the same number of protons and electrons, so there is no net force between objects. Still, we notice this force when things get up close, so that the electrons actually get to feel each other. When we push a cup with our finger, this is the electrons on the surface of our finger repelling the electrons in the cup. Similarly, all contact forces (that is, whenever something touches, pushes, or crushes something else) are due to electron repulsion. If you want to experience directly what electrons feel like, just touch somebody's body with your hands, all that you can feel is electrons.

Essentially everything that happens in the body is due to these electrons' and protons' bumping into each other and rearranging themselves. Some arrangements of protons and electrons are more stable than others; they last longer. We call these stable arrangements *molecules.* As molecules collide, they may break up and rearrange, forming new molecules. Different molecular arrangements have different energies associated with them. This is due to the different arrangement of protons and electrons within them. For example, a molecule might contain a number of electrons packed close together, and producing such an arrangement would require lots of energy, because the electrons would have to be pushed together against the strong repulsion of their negative charges. But if that part of the molecule is broken apart and rearranged, then a lot of this energy will be released as the different electrons and associated molecules fly apart. Turning one arrangement or molecule into another either requires energy or releases energy, depending on whether the new arrangement has more or less energy than the old.

The essential task of animal life is to take molecules (food and oxygen) from the environment and rearrange the protons and electrons so that there is less repulsion between the electrons in the molecules produced (that is, carbon dioxide and water). This process releases energy, just as burning the food would do. However, the body cannot afford to release the energy as heat, because living organisms cannot use heat as a source of energy. Energy on its own is not enough to power life. There is something even more fundamental that drives all living processes. Erwin Schrödinger, the great Austrian physicist and creator of quantum mechanics, called it negative entropy (or negentropy). In order to understand it, we need to traverse the infamous second law of thermodynamics.

The Second Law and the Secret of Life

It is tempting to pass discreetly over the second law, to ignore it and hope nobody notices, because it is a notoriously slippery idea. However, up close, it can be awe inspiring and beautiful. Some of the most creative scientific minds have described it as one of the greatest creations of human culture. C. P. Snow in his lecture and book *The Two Cultures* compared the cultural value of the second law to Shakespeare's plays and suggested that for those who aspired to be called "cultured," an ignorance of the second law was on a par with an ignorance of Shakespeare's plays. The target of Snow's comments was intellectuals, and particularly Oxbridge ones, who decried the apparent ignorance of scientists in classical cultural matters and did not realize there was an alternative culture at least as deep as theirs. Whether we aspire to be "cultured" in this sense, it remains true that the second law is central to a real understanding of change, just as Darwin's theory of natural selection is central to an understanding of evolution. But the second law is slippery; there are almost as many interpretations of it as there are people interpreting.

The second law arises from the general principle that if something is randomly perturbed (jiggled around), the components of that something will become more randomly distributed. If we put some children's plastic bricks in a tin box and shake the box, the bricks will become more randomly distributed. If the bricks were initially stacked on top of each other, or in one corner of the box, or separated into their different colors, then after the shaking, they will be more randomly distributed. The bricks will become unstacked, they will spread around the box, and the colors will be mixed up. Notice that the opposite does not happen. If the bricks are initially randomly distributed in the box and we shake it up, they will not arrange themselves into a more ordered pattern. This follows a general principle that a system undergoing random perturbations will become more randomly distributed with time, not more ordered. Why? Because a random distribution is much simpler to obtain than an ordered distribution. A random distribution isn't a *particular* distribution; it is lots and lots of different distributions that have in common only the fact that they are not ordered, whereas an ordered distribution, such as the different colored bricks separated into piles, is a very particular distribution that can be brought about only in a small number of ways. Thus, if components like bricks are subjected to a random perturbation—say, the bricks are randomly jumping between piles—then it is much more likely that each perturbation will result in a more random distribution. One of the many blue bricks in the blue pile will more probably jump into the red pile than the only red brick in the blue pile jump into the red pile. Ordered distributions are less probable than random distributions. That is the essence of the second law.

The same principle may be illustrated with a pack of cards. If we start with the cards in order, arranged in suits from ace to deuce, and we then shuffle them extensively (random jiggling), we end up with a disordered arrangement of cards. But the opposite does not usually happen unless you are a card shark. There are only a few different arrangements that are considered ordered, whereas there are millions of different arrangements that are thought of as disordered. When we shuffle, the pack jumps from one arrangement to another randomly selected arrangement. If there are one ordered arrangement and a million disordered arrangements, then a randomly selected arrangement produced by shuffling has a one in a million chance of turning up the ordered selection, and a near certainty of producing another disordered arrangement.

The kind of system the Second Law deals with is usually a whole bunch of molecules bumping into each other, such as a lump of wood, or an animal, or the sun, or a cell, or the universe. The random perturbation is provided by the heat in the system—that is, anything that is hotter than absolute zero consists of molecules jiggling around in a random fashion. The heat simply is the jiggling of the molecules, and jiggling is random in the sense that the different molecules are banging into each other in random directions at a range of different speeds and at different times. This jiggling causes the matter and energy of the system to redistribute, and because the jiggling is random, the new distribution of matter and energy will be more random than before. For example, if a bunch of molecules are initially in one corner of a box, the thermal jiggling will eventually redistribute them all over the box. If some of the molecules in the box are initially moving much faster than the others, then the random collisions will redistribute the energy more evenly. If there are initially different types of molecules in different parts of the box, then the random jiggling will mix them all together. If two liquids, say, orange juice and black currant juice, are layered on top of each other (according to the strict instructions of my four-year-old son), then they will eventually mix together, because this is a more random distribution of the molecules. If the temperature is high enough that the atoms start redistributing between molecules (that is, get torn off some and stuck onto others), then we are going to end up with a more random distribution of atoms between molecules. Thus, if two molecules *can* chemically react, eventually they *will* react.

The extent to which the matter and energy of a system are randomly distributed can be measured and is called *entropy.* High entropy means a random system; low entropy means an ordered system. The second law can therefore be stated in this way: During any natural change, entropy always increases. The wonderfully useful concept of entropy was invented by the German physicist Rudolf Clausius in 1850, but its real meaning in terms of atoms and molecules was discovered by the Austrian physicist Ludwig Boltzmann at the end of the nineteenth century. Unfortunately for Boltzmann, atoms were not then yet in vogue, and his explanation of change in terms of the purposeless movement of atoms was thought to undermine purpose in the universe, in a similar way to Darwin's recent undermining of purpose in biology. Boltzmann, although recognized as one of the greatest physicists of his day, suffered other spontaneous process that *increases* entropy, so that there is a net increase in entropy. For example, the cell manages to concentrate inside itself molecules that are rare outside, thus decreasing entropy, by coupling this concentrating process with the transport of sodium inside, which increases entropy because there is much more sodium outside the cell than inside it. The coupling is simply done by a molecular machine, located in the cell membrane (the thin wall that surrounds the cell), which allows sodium into the cell only when it is accompanied by another molecule that the cell wants to accumulate. The molecular machine acts as a gatekeeper that couples the transport of sodium to the transport of other wanted molecules, so that the entry (or exit) of one cannot occur without the entry (or exit) of the other.

Similarly, the cell manages to make DNA by coupling this ordering-inducing process to a disordering process, the splitting of ATP (adenosine triphosphate). ATP is a general-purpose energy source within the cell, and its breakdown or disordering can be coupled by many different cellular machines to essential ordering processes, such as the synthesis of DNA. However, this cannot go on forever; in a few seconds, all the ATP in the cell will be broken down, and the cell will be full of sodium. The ATP must be remade and the sodium pumped out of the cell again. But these processes *decrease* entropy, so they have to be coupled to some other entropy-increasing processes. Thus, the cell requires a chain of coupling processes, which is eventually connected to the burning of food, continuously maintaining the import of food and oxygen from the environment and the export of carbon dioxide and heat. This is the key trick of life: the coupling of processes that you want but are impossible, to processes that are possible and can be continuously replenished.

The chain of energy that links every molecular event in our body does not end in the environment outside our body. The food and oxygen on which we feed to power our bodies must be replenished somewhere in the environment; otherwise, it would rapidly be depleted. Animals must feed on other animals or plants as a source of energy, which are thus linked in a food chain or web of energy. Ultimately, the plants of the world produce both the food energy and the oxygen that power us and the other animals of the world. Almost all energy on earth comes from the sun. Perhaps the ancients were right to think of the sun as a god, source of all things in the world. The sun is spewing out stupendous quantities of energy as light into empty space. A tiny fraction of that light is caught by the plants on earth and used to power the conversion of water and carbon dioxide into the complex molecules of the plant (which become food for animals) and into oxygen (which is released into the air). In terms of the second law, the conversion of earth and air into all the improbable forms of life is made possible by coupling it to the conversion of pure starlight into random heat energy.

Now that you know the secret of life and the second law, you are entitled to call yourself a "cultured" person according to C. P. Snow. However, before you rush off to that cocktail party, you had better brush up on Shakespeare's plays.

2

The Life Machine

Our body is a machine for living. It is organized for that, that is its nature.

—Napoleon speaking in Leo Tolstoy's *War and Peace*

Is man a machine? It is an old question, slowly changing its shape as concepts of ourselves and machines evolve. In this new era of genetic engineering, cloning, smart computers, and the Internet, our concept of a machine may have to be extended beyond simply a mechanical device made of metal, to include such entities as virtual machines made of software and even living organisms redesigned to perform specific functions. It is necessary to examine the composition of humans in more detail to see whether our components are in fact machine-like, so we can begin to unravel the mystery of the energy of life. We are entering the realm of modern cell and molecular biology, currently the most successful of all the sciences and perhaps the most successful cultural activity within society today. We shall see that modern biology describes the body as made up of a vast quantity and variety of tiny molecular machines, coded for by our genes, and designed by evolution, perhaps with the goal of ensuring the survival of those genes.

Since World War II there has been steadily mounting excitement among biologists as the phantasmagoric goings on within the cell have slowly come into focus. Some things, such as cars or cups, appear less and less interesting as you look at them in more detail or a smaller scale. But the opposite has happened with biology. It has proved to be like a set of Russian dolls that become more and more intricate as you open them. Or the secret tomb of an Egyptian pharaoh, which reveals more and more astounding treasures as you penetrate closer to the mummy. On the surface, a human looks quite a simple kind of thing: a few limbs for manipulating the world and a few orifices for getting things in and out of the body. But go down to a million-fold smaller scale, to the realm of a single cell and its machinery, and we enter a different world of almost unimaginable complexity. Hundreds of thousands of different entities are doing tens of thousands of different sorts of things, at an invisibly frantic pace, within a stupendously complex and dynamic structure. And this complexity is not a result of chaos or random forces; everything is designed, manufactured, and controlled within the cell, or so it seems.

The cell is a vast, teeming metropolis, the life of which cannot be captured by a single image, scheme, or science. This metropolis rather gradually came into focus as the tools of molecular and cell biology developed over the past few decades. Luckily, the increase in complexity with smaller scales is not a bottomless pit; otherwise, biologists would have been left dangling in a hopeless morass, and it must have felt that way much of the time. As we penetrate down to a scale one-billion-fold smaller than the human body, suddenly we discover a layer of relative simplicity and familiarity once again. We are in the realm of atoms, protons, and electrons—a region already thoroughly explored by chemists and physicists, a sphere of reassuringly fixed, rigid, and simple laws. But this reassuring simplicity and familiarity should not distract us from the fact that this is the realm of quantum mechanics, the very edge of the knowable whose delicate frontier can be touched only with mathematics. This, then, is a world that is literally unimaginable; no image or metaphor can truly depict the behavior of electrons, protons, and photons. Electrons and photons have no structure or image; they are the theoretical entities by which structure and image are explained. Biochemistry sits uneasily between the familiar world of everyday objects and the unimaginable world of quantum mechanics. And biochemists tend to be somewhat schizophrenic in their treatment of molecules; we use images and metaphors from the familiar world to depict entities that have one foot in an entirely different world.

A cell is a bag full of water, with lots of different molecules floating around in the water. The wall of the bag is called the cell membrane and completely surrounds the cell, controlling what molecules get in and out of the cell. Inside the cell are lots of other membranes, which enclose separate compartments. So we have a bag full of water (and other molecules), containing lots of smaller bags of different sizes and shapes, which also contain water (and other molecules). It does not sound much like an efficient machine so far—more like a soggy paper bag or used condom—but we need to swap our light microscope for an electron microscope and penetrate to a smaller scale to see the machine-like nature of the cell.

A cell is very small, and of variable size and shape—an average human cell might be 20 microns (0.02 millimeters) across—but it is very large compared to the size of the molecules it contains. If we increased the scale of everything 100 million times, then we could see an atom; it would be 1 centimeter across—about the size of a pea. Small molecules like sugars, amino acids, and ATP would be 5 to 10 centimeters—the size of apples and light bulbs. And proteins would be 20 centimeters to 1 meter—the size of children or televisions. On this scale, an average cell would be 2 kilometers across—a vast, spherical, space-age metropolis. There is effectively no gravity within a cell, so this metropolis is located out in space, with its inhabitants floating around inside. The cell is bounded by a cell membrane and divided up into many compartments by internal membranes, each 0.5 meter thick on our expanded scale. The compartments include a maze of tunnels—the width of a small road on our expanded scale—connecting different parts of the cell. Attached to these tunnels and floating throughout the cell are a huge number of ribosomes, the factories that make proteins, which would be 3 meters across—the size of a car. And the cell is also crisscrossed by a vast number of filaments—1 meter across on the enlarged scale, like steel girders or pylons—which act as the skeleton of the cell, and to which the proteins may attach. Mitochondria, the power stations different loads. Their motoring is again powered by the ubiquitous ATP. (A similar type of machinery is used to power muscle contraction itself.) The ATP that provides the energy for these machines is itself made by a huge electrically driven rotating motor. The energy input allows protein machines to have dynamic functions, such as clocks, motors, switches, assembly factors, and information processors. Even more complex machines are used to make DNA, copy genes, make proteins, destroy proteins, and transfer information across the cell membrane. Each of these processes requires the coordinated activities of ten or more proteins, acting together as an integrated machine, so that each activity can be performed before moving onto the next activity. In principle, all these processes could go backwards but this would prove disastrous for the cell, so the machines use ATP to drive the tasks they perform in one direction only.

The manufacture of proteins is the most energy-expensive process going on within the body. When you are resting, about one-fifth of your energy is being expended on protein synthesis, even though all that protein is continuously broken down again. During growth, protein synthesis consumes even more energy—about half of the very high energy production of babies is used for protein synthesis. It is a very expensive business, but we have seen that proteins are the most important elements of the cell. The proteins are the machines that do everything: the muscle contraction, the transport, the regulation, and the synthesis and breakdown of all molecules (including other proteins). They make energy, contract muscles, and process information. They are also hormones, antibodies, receptors, and structural components of the cell. All of the active processes of the cell are done by proteins, while the DNA simply acts as a passive store of information about protein structure. Fats are used either as an energy fuel or to make the membranes of the cell. Most of a cell's volume is water—roughly 70 percent—but of the remaining space, 40 to 80 percent is protein, so a cell really is packed with protein. This is not homogeneous protein; a cell has 10,000 to 20,000 different types of protein, each doing a different job.

We hear so much about DNA and genes that many people assume that DNA is the most important part of the cell. However, in terms of the day-to-day business of the cell, the DNA is relatively unimportant. In fact, some cells, such as our red blood cells, get rid of their DNA altogether and survive quite happily, until they need to make more proteins. It is the proteins that do virtually everything in the cell, including manufacturing and regulating the DNA. The DNA is a static form of information, like a library, providing a blueprint for the proteins—the actual machinery of the cell. Each gene (that is, a unit of DNA) codes for a single, particular type of protein in the cell. So the 100,000 genes in the human genome (all of the DNA in a cell) provide all the necessary information to produce the 100,000 different types of protein that make up a human.

Sequencing all the DNA in the human genome (that is, the total set of genes) is an extremely expensive and time-consuming project, but it is nothing compared to the next task of working out what the 100,000 different proteins coded for by the 100,000 genes actually do. We know what only 1 percent of these proteins do in sufficient detail, and that has taken us about one-hundred years to find out. Proteins were first described by Justus von Liebig in 1824 and identified with enzymes at the end of the nineteenth century. Their structure was slowly elucidated during the twentieth century. First, it was worked out that proteins consist of a long string of amino acids, that is, a sequence of small molecules of which there are about twenty different types. Then the British scientist Fred Sanger devised an ingenious method for working out the sequence in which these amino acids were strung together. He received the Nobel Prize in 1958 for sequencing insulin, the protein hormone that is deficient in diabetics, and he subsequently received a second Nobel Prize in 1980 for devising a method to sequence DNA, essentially the same method that is now being used to sequence the human genome. The string of amino acids that makes up a protein folds up into a distinctive three-dimensional shape, which is different for different proteins. And it was this three-dimensional structure that was so difficult to work out, and yet so important for understanding how proteins actually worked as machines.

Max Perutz solved this crucial problem of determining the three-dimensional structure of proteins. Perutz was born in Vienna in 1914 and moved to Britain after the rise of nazism. However, he ended up being interned in Canada as an enemy alien during World War II. After the war, he returned to the Cavendish Laboratory in Cambridge to study how x-rays might be used to determine the structure of biological molecules. Francis Crick and James Watson joined the same laboratory in 1949 and 1951 and had worked out the structure of DNA by 1953. Perutz's job was more difficult; it took him from 1937 until 1960 to finally determine the structure of a single protein, hemoglobin. He went on to demonstrate how hemoglobin acts as a mechanical machine for the uptake, transport, regulation, and release of oxygen in the blood. He showed how the structure of hemoglobin moves or "breathes" during its function of transporting the molecule of life. And it was Max Perutz who set up the Medical Research Council unit for molecular biology in Cambridge that has claimed so many Nobel prizes, including Perutz's own in 1962, Fred Sanger's for sequencing DNA, Aaron Klug's for determining how proteins assemble together, Caesar Milstein's for working out how to make the immune system proteins known as monoclonal antibodies, and John Walker's for finding the genes and determining the structure of the motor protein that makes ATP. Also at this unit were Sidney Brenner, who discovered messenger RNA and helped determine the genetic code, and Hugh Huxley, who determined the mechanism and structure of muscle. Thus the science of molecular biology has dominated the end of the twentieth century. And the twenty-first century looks set to be dominated by the application of that knowledge in fields as diverse as genetic engineering, agriculture, medicine, electronics, pharmaceuticals, and fields yet to be dreamed of. Much of biology is now concerned with proteins in one way or another, and the sequencing of the human genome will provide an even greater stimulus to working out what these protein machines do, how they do it, and how that can be changed.

The Freeways of the Cell Metropolis

A series of enzymes converting a molecule from one form to another via intermediates is known as a *metabolic pathway.* A molecule may follow this pathway within the cell, being converted from one form (the substrate of the pathway) to another (the product of the pathway) via a number of intermediate forms. Many different metabolic pathways in a cell link many different molecules, and many of these pathways are connected, so that the product of one pathway may be the substrate or an intermediate of another pathway. A huge web is formed within the cell. Molecules enter the cell from the blood, via the transporters, and then follow one or more of these pathways, until they are converted into end products (such as carbon dioxide and water), which then leave the cell and are taken away by the blood. Transporters are an integral part of these pathways, as substrates must be transported into the cell, intermediates may need to be transported across different membranes within the cell, and the end products may need to be transported out of the cell.

There are actually three different types of pathway in the cell that transfer three different sorts of things:

1. Mass transfer (or metabolic) pathways, which transfer bits of molecules
2. Energy transfer pathways, which transfer energy
3. Signal transfer pathways, which transfer information

The history of biochemistry in this century has been mostly concerned with trying to trace these pathways through the huge web of interactions that occur within cells. The metabolic pathways were mostly mapped in the first half of this century, the energy transfer pathways from the 1940s to 1960s, and the signal transfer pathways from the 1960s on into the future. Signal transfer pathways lead from hormones or other signaling molecules outside cells, through receptors that span the cell membranes, to "second messenger" pathways inside cells, and through specialized enzymes that convert other enzymes in a cascade, which finally end at a particular protein machine's switch turned off or on. Alternatively, the signal pathways may lead to the DNA of the cell, controlling whether particular genes are turned off or on, and thus whether particular proteins are made or not. These pathways transfer and process information from the cell's environment and from other cells in the body in order to help determine which enzymes, transporters, and genes the cell should be using and at what rate they should be working. Most routes of signal transfer are probably still unmapped.

Maps of metabolic, energy, and signaling pathways adorned the walls of biochemical laboratories everywhere until recently, although they are considered somewhat dated now as molecular biology has pushed metabolism out of fashion. These maps served a similar function to geographical maps of little known territory. They help to orientate the explorer and act as a psychological prop for the cell explorer wading through a more or less impenetrable jungle of cellular interactions. If we tried to draw a realistic map of all these pathways with all the information now available, we would produce a vast mess, with thousands of molecules connected by thousands of different pathways. And we would end up lost in our own map. However, mapping the cell and its machinery will provide work for biologists for some time to come.

The Human Machine

On the scale of molecules, the cell can be seen today as a vast metropolis, inhabited by billions of throbbing machines, interacting with trillions of other molecules in an apparently frenetically chaotic fashion. There is no overall director of this activity. Only if we have a map or plan can we discern that this apparently chaotic activity is producing coherent, meaningful behavior on a larger scale: the import and distribution of food, energy and information, necessary for the maintenance, function, and reproduction of the cell—or metropolis.

Can we say now whether a cell is in fact a machine? Part of the motive for calling something a machine is that we understand all its parts, how they interact, and what function they perform. If we do not know what something is made up of, how it works, and what it is for, then we are unlikely to think of it as a machine. On these criteria, cells are slowly becoming machines. However, what we regard as a machine also depends on current fashion and technology. What about our original question: Is man a machine? For man to be a machine, he would need to have been designed for some purpose. A few hundred years ago, religion could have supplied the designer and purpose. Today evolutionary biologists would say that evolution by natural selection provides the designer, and survival and reproduction of the genes provide the purpose. There remains the question of free will and subjectivity. The reluctance charged molecule trying to cross the membrane against the huge electrical force. The inside of the body is wet, soft, and gooey, being 70 percent water. This seems unpromising territory for electricity, as we have been taught that electricity is carried in hard metal wires surrounded by plastic insulation, and causes trouble if mixed with water. However, the reason that water and electricity should not be mixed is that water is a reasonably good conductor of electricity, although the electricity is not carried by electrons (as in wires) but rather by protons and salt (sodium chloride) within the water. If my four year old stuck live electric wires into the bath, he could electrocute the cat, and the current could be increased by adding salt to the bathwater. Similarly, within cells, most of the electric currents are carried by protons and salt moving within the water of the cell.

Electricity seems mysterious. It creeps under our floors and through our walls, silently energizing our homes and cities. It streaks across the sky as lightning, the weapon of gods. Now it seems that our own spirits and souls are powered by it. What is this stuff? Electricity is the flow of charge—just as a stream is a flow of water. Water flows wherever it can from high ground to low ground under the force of gravity. Electrical charge flows by whatever route it can from areas of high charge to areas of low charge driven by the electrical force. All matter is made up of a mixture of electrons (which are negatively charged), protons (which are positively charged), and neutrons (which are neutral, with no net charge). Most bits of matter have exactly equal numbers of electrons and protons, so the matter has no net charge. But if there is an excess of electrons, then the matter is negatively charged, or if there is an excess of protons, then the matter is positively charged. Within a wire, the flow of charge is due to the flow of electrons, which because of their infinitesimal size and loose binding to the metal of the wire can pass through the metal. But electricity does not have to be carried by electrons; any mobile charge will do. Within the cells of our body, electricity is carried by electrons, protons, phosphate, or sodium ions. Sodium is an element making up half of common salt (sodium chloride), and when salt dissolves in water, the sodium floats free of the chloride; but the chloride takes an electron from the sodium, so that the sodium has one excess positive charge. An "ion" just means an atom or molecule with a charge, so the sodium ion is just the sodium atom with its positive charge. Phosphate is a small molecule, the stuff that gardeners fertilize their plants with, and when it is dissolved in water, it has a negative charge. Protons and electrons are fundamental particles, the proton being positively charged and electrons negatively charged. A proton stuck together with an electron makes a neutral hydrogen atom. Just as water flowing down a stream can do work by pushing a mill wheel, so electrical charge flowing in a wire can do work by pushing the charges within an electrical motor. However, the electrical force is much greater than the gravitational force and can do correspondingly more work.

The ancient Greeks were aware of some of the strange properties of electricity. Thales, the sixth century B.C. founder of philosophy and science, knew that rubbing amber caused it to attract other objects. Hippocrates, the fifth century B.C. founder of medicine, knew that the electric torpedo fish gave a shock, which was later used to treat headaches. But the first scientific studies were performed by the English doctor William Gilbert, who distinguished between electric and magnetic forces and coined the term *electric* (from the Greek *elektron,* for amber). Many other scientists contributed to the elucidation of the properties of electricity in the seventeenth and eighteenth centuries, including Benjamin Franklin and Joseph Priestley, and some identified it with the vital force or spirit. This was apparently confirmed by Galvani's dramatic discovery in the 1770s of "animal electricity." Luigi Galvani (1737–1798) was a physician in Bologna, Italy, and when dismembering a frog he found by chance that an electric spark passed from the scalpel to the leg nerve, causing contraction of the frog's leg. This discovery led to a number of ghoulish experiments, including one stormy night cutting a frog in half and connecting its leg nerves to a wire pointing into the sky. Remarkably, the legs contracted in time with the thunder and lightning, and the myth of Frankenstein's monster and the electric life force was born. Count Alessandro Volta (1745–1827), an Italian physicist, used these insights to show that electricity was the force behind nerve transmission and muscle contraction. Thus, for a while, electricity was regarded as intimately connected with the vital force; and, indeed, inasmuch as anything deserves to be called the vital force, electricity is it.

So where does the electricity that drives us come from? It comes from the food we eat and the air we breathe. Within our cells, electrons are ripped off the food and fed to the oxygen. In going from the food to the oxygen, the electrons pass down an electron transport chain, consisting of a little wire of copper and iron atoms located within proteins in a membrane. Electrons are fed into the wire from food molecules at high energy, and electrons are pulled out of the other end of the wire to oxygen at low energy. Thus, an electric current flows along the wire and can be used to do work as the wire passes through various protein machines within the membrane. This is a bit like water flowing in a pipe or river: water can be pushed in at one end and pulled out at the other, and wheels can be pushed by the flow of water to do work. Thus a mill wheel is pushed around by water passing from a high energy level (above the wheel) to a low energy level (in the stream below). In a similar way, a stream of electrons passing down the electron transport chain, from a high energy level to a low energy level, drives various machines (the "proton pumps"). However, the streaming of electrons down the electron transport chain is not continuous but rather a stop-and-go affair; the electrons have to stop and be carried between various molecules within the chain. It is a bit like a canal with locks, mills, and millponds.

The Electron Transport Chain

The concept of the electron stream passing down an electron transport chain was developed as a synthesis of the opposing views of Heinrich Wieland (1877–1957) and Otto Warburg (1883–1970). These two great German biochemists spent much of their illustrious careers at war with each other, although they called a truce during World War I, when Warburg served with the cavalry on the Eastern Front and Wieland directed research on chemical warfare. Wieland seems like the archetype of the coldly analytic, evil scientist, dissecting out the heart of nature. He determined the structure of many deadly toadstool poisons and he worked on the chemical composition of the pigments that give the color to butterflies' wings. He was awarded the Nobel Prize in 1927 for determining the chemical structure of steroids—though this structure later turned out to be wrong. Warburg meanwhile had to wait until 1931 to get his

Nobel Prize, which caused him some angst. He had a reputation as an arrogant and petty man but undoubtedly a brilliant scientist. Warburg was director of the Max Planck Institute of Cell Physiology in Berlin, until removed from this position in 1941 by the Nazis because be was part Jewish. But such was his international prestige that he was soon reinstated, and in 1944 he was nominated for a second Nobel Prize, although Nazi rules prevented him from accepting it.

Eighteenth- and nineteenth-century scientists had shown that food digested by the gut was burned using oxygen from the air we breathe within every cell of our body: the processes of cellular respiration. The problem that bioenergeticists faced at the beginning of the twentieth century was how the electrons get from the food to the oxygen. This is not a trivial problem because electrons cannot easily travel by themselves (unless transported by a metal, such as iron or copper); that is why most things cannot conduct electricity. However, electrons can be transferred from molecule to molecule if packaged together with protons as hydrogen atoms (remember that one electron plus one proton makes a hydrogen atom, with the symbol H). Wieland proposed that molecular machines (enzymes) within the cells ripped hydrogen off the food and this "activated hydrogen" somehow reacted with oxygen (O_2) to produce water (H_2O). Wieland's proposal was based on the findings by many other biochemists between 1900 and 1920 that there were indeed molecular machines in tissue that could rip hydrogen off food and other organic molecules. These machines were named dehydrogenases, meaning a molecular machine that removes hydrogen from things, and the theory was called the dehydrogenase theory of respiration.

Otto Warburg strongly disagreed. His theory was that respiration occurs because there is an iron-containing machine within cells that binds oxygen; oxygen takes electrons from the iron, and the iron then takes electrons from food. Warburg believed that there was a single machine (the "respiratory enzyme"), which was an oxidase—a machine that used oxygen and took electrons from other molecules, and was responsible for consuming all the oxygen that the body breathes in and uses. Warburg came to this conclusion after his discovery in 1913 that very small amounts of cyanide completely inhibit the oxygen consumption of cells and tissues. Cyanide and oxygen were known to bind to iron, and Warburg believed that the cyanide was binding to the iron within his respiratory enzyme, and thus prevented oxygen from binding the same iron, resulting in the inhibition of respiration and consequently death.

Neither Wieland nor Warburg emerged victorious. In fact, both were right and wrong; both were looking at the opposite ends of the same chain of machines: the electron transport chain. At the top end of that chain were the dehydrogenases, which ripped electrons off the food, and at the bottom end of the chain was an oxidase, which contained iron and fed electrons to oxygen. Wieland and Warburg had been examining opposite ends of a great elephant. Wieland had the trunk where the electrons went in and stated firmly that this was all there was to the elephant; while Warburg had the tail where the electrons came out and thought this was the essence of the elephant. Their apparent blindness is not surprising considering the methods available to them. They ground up body tissue and looked for various activities of the tiny machines within, but they did not know at that time that there were in fact about fifty thousand different machines with different activities within the tissue—which was probably a good thing, since had they known, they might never have tried.

The opposing views of Wieland and Warburg were eventually reconciled when the link between them was discovered by a Polish-born Jew working in England as a parasitolist, David Keilin. In between the head and backside of the elephant was a chain of cytochromes—molecular machines that took electrons from the dehydrogenases and passed them on to the oxidase. *Cytochrome* means "cell color," and the cytochromes are indeed the constituents of cells that give them color. In fact, they change color when they gain or lose electrons, and this was how Keilin discovered them and their role in respiration. Keilin was working on the pigments and colors of insects, and used a hand-held prism that split the light from tissue into its rainbow spectrum, so that he could directly see which colors were changing within the tissue. He came across some moths that had no hemoglobin, which made it much easier to see the non-hemoglobin pigments of the body (that is, the cytochromes). He glued a moth by its back to a slide, and noticed that when it beat its wings frantically in a futile attempt to escape, its flight muscles changed color, and changed back again when they stopped beat-