THE BIOLOGY OF BELIEF

Unleashing the Power of Consciousness, Matter & Miracles

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When the "cultured cells" are ailing, look first to the cell's environment, not to the cells themselves.

CHAPTER 2

IT'S THE ENVIRONMENT, STUPID

I will never forget a piece of wisdom I received in 1967, on the first day I learned to clone stem cells in graduate school. It took me decades to realize how profound this seemingly simple piece of wisdom was for my work and my life. My professor, mentor, and consummate scientist Irv Konigsberg was one of the first cell biologists to master the art of cloning stem cells. He told me that when the cultured cells you are studying are ailing, you look first to the cell's environment, not to the cell itself, for the cause.

My professor wasn't as blunt as Bill Clinton's campaign manager, James Carville, who decreed, "It's the economy, stupid," to be the mantra for the 1992 presidential election. But cell biologists would have done well to post, "It's the environment, stupid," over our desks, just as the "It's the economy, stupid" sign was posted at Clinton headquarters. Though it wasn't apparent at the time, I eventually realized that this advice was a key insight into understanding the nature of life. Over and over I learned the wisdom of Irv's advice. When I provided a healthy environment for my cells, they thrived; when the environment was less than optimal, the cells faltered. When I adjusted the environment, these "sick" cells revitalized.

But most cell biologists knew nothing of this wisdom of tissue culture techniques. And scientists moved sharply away from considering environmental influences after Watson and Crick's revelation of DNA's genetic code. Even Charles Darwin conceded, near

the end of his life, that his evolutionary theory had shortchanged the role of the environment. In an 1876 letter to Moritz Wagner he wrote: "In my opinion, the greatest error which I have committed has been not allowing sufficient weight to the direct action of the environments, i.e., food, climate, etc., independently of natural selection . . . When I wrote the *Origin*, and for some years afterwards, I could find little good evidence of the direct action of the environment; now there is a large body of evidence." (Darwin, F 1888)

Unfortunately, Darwin's followers perceived that his return to Lamarckian "thinking" was a sign of Darwin's aging and now addled mind. Rather than following their master's revised vision, Darwinian evolutionists chose to remain more Darwinian than Darwin! The problem with the Darwinian underemphasis on the environment is that it led to an overemphasis on "nature" in the form of genetic determinism—the belief that genes "control" biology. This belief has not only led to a misallocation of research dollars, as I will argue in a later chapter, but, more importantly, it has changed the way we think about our lives. When you are convinced that genes control your life and you know that you had no say in which genes you were saddled with at conception, you have a good excuse to consider yourself a victim of heredity. "Don't blame me for my work habits—it's not my fault that I've been procrastinating on my deadline . . . It's genetic!"

Since the dawning of the Age of Genetics, we have been programmed to accept that we are subservient to the power of our genes. The world is filled with people who live in constant fear that, on some unsuspecting day, their genes are going to turn on them. Consider the masses of people who think they are ticking time bombs; they wait for cancer to explode in their lives as it exploded in the life of their mother or brother or sister or aunt or uncle. Millions of others attribute their failing health not to a combination of mental, physical, emotional, and spiritual causes but simply to the inadequacies of their body's biochemical mechanics. Are your kids unruly? Increasingly the first choice is to medicate these children to correct their "chemical imbalances" rather than fully grappling with what is going on in their bodies, minds, and spirits.

confusion of correlation and causation

Of course there is no doubt that some diseases, like Huntington's chorea, beta thalassemia, and cystic fibrosis, can be blamed entirely on one faulty gene. But single-gene disorders affect less than two percent of the population; the vast majority of people come into this world with genes that should enable them to live a happy and healthy life. The diseases that are today's scourges—diabetes, heart disease, and cancer—short circuit a happy and healthy life. These diseases, however, are not the result of a single gene, but of complex interactions among multiple genes and environmental factors.

What about all those headlines trumpeting the discovery of a gene for everything from depression to schizophrenia? Read those articles closely and you'll see that behind the breathless headline is a more sober truth. Scientists have linked lots of genes to lots of different diseases and traits, but scientists have rarely found that *one* gene causes a trait or a disease. In the realm of human diseases, defective genes acting alone only account for about 2% of our total disease load. (Strohman 2003)

The confusion occurs when the media repeatedly distort the meaning of two words: correlation and causation. It's one thing to be linked to a disease; it's quite another to cause a disease, which implies a directing, controlling action. If I show you my keys and say that a particular key "controls" my car, you at first might think that makes sense because you know you need that key to turn on the ignition. But does the key actually "control" the car? If it did, you couldn't leave the key in the car alone because it might just borrow your car for a joy ride when you are not paying attention. In truth, the key is "correlated" with the control of the car; the person who turns the key actually controls the car. Specific genes are correlated with an organism's behavior and characteristics. But these genes are not activated until something triggers them.

What activates genes? The answer was elegantly spelled out in 1990 in a paper entitled *Metaphors and the Role of Genes and Development* by H. F. Nijhout. (Nijhout 1990) Nijhout presents evidence that the notion that genes control biology has been so frequently repeated for such a long period of time that scientists have forgotten it is a hypothesis, not a truth. In reality, the idea that genes control biology is a supposition, which has never been

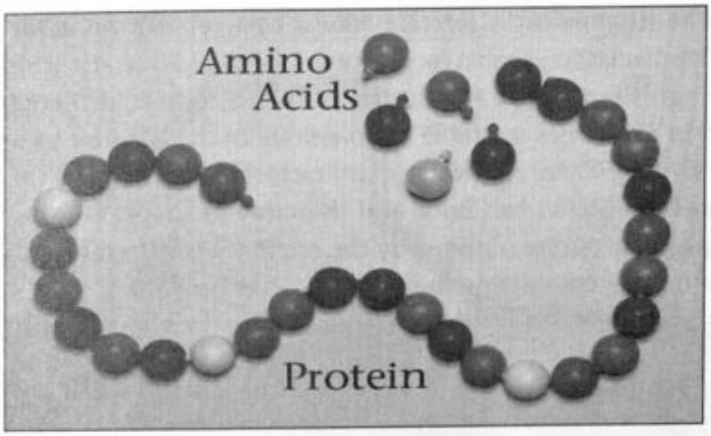
proven and, in fact, has been undermined by the latest scientific research. Genetic control, argues Nijhout, has become a metaphor in our society. We want to believe that genetic engineers are the new medical magicians who can cure diseases and while they're at it create more Einsteins and Mozarts as well. But metaphor does not equate with scientific truth. Nijhout summarizes the truth: "When a gene product is needed, a signal from its environment, not an emergent property of the gene itself, activates expression of that gene." In other words, when it comes to genetic control, "It's the environment, stupid."

Protein: The Stuff of Life

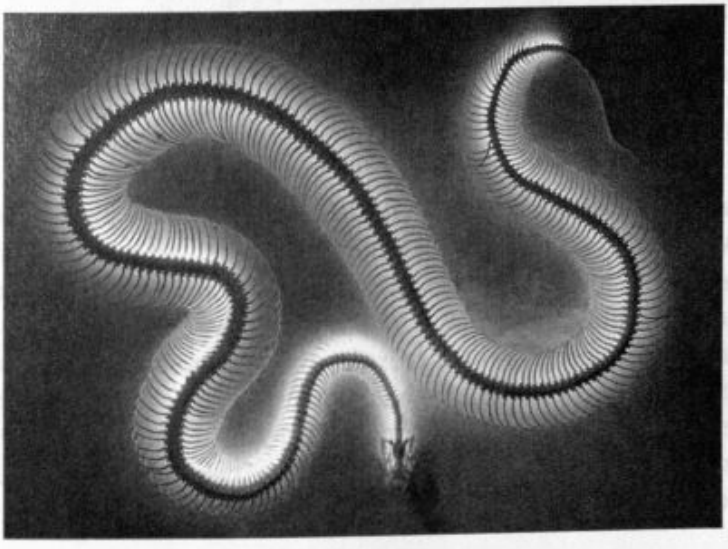
It is easy to understand how genetic control became a metaphor as scientists with ever-greater excitement zeroed in on the mechanisms of DNA. Organic chemists discovered that cells are made up of four types of very large molecules: polysaccharides (complex sugars), lipids (fats), nucleic acids (DNA/RNA), and proteins. Though the cell requires each of the four molecular types, proteins are the most important single component for living organisms. Our cells are, in the main, an assembly of protein-building blocks. So one way of looking at our trillion-celled bodies is that they are protein machines, although, as you know, I think we are more than machines! It sounds simple, but it isn't. For one thing, it takes over 100,000 different types of proteins to run our bodies.

Let's take a closer look at how our cells' 100,000 plus proteins are assembled. Each protein is a linear string of linked amino acid molecules, comparable to a child's pop bead necklace, as illustrated at the top of the following page.

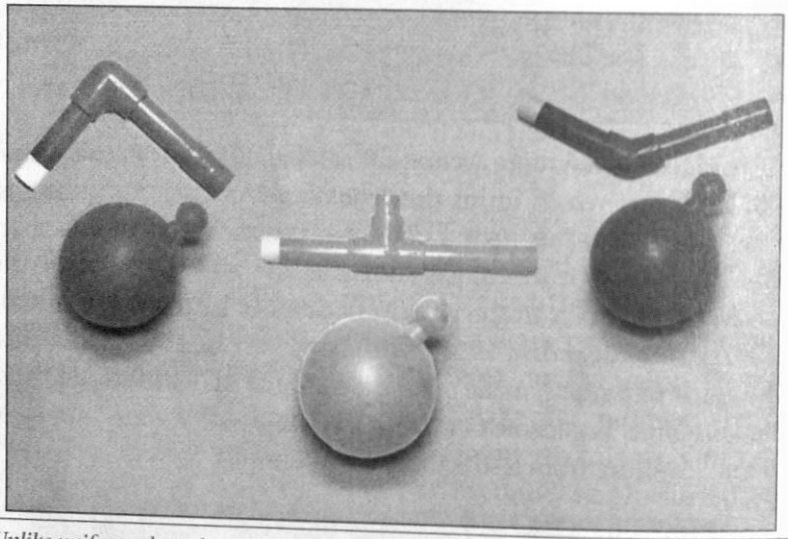
Each bead represents one of the twenty amino acid molecules used by cells. Though I like the pop bead analogy because everyone is familiar with it, it is not an exact one because each amino acid has a slightly different shape. So to be completely accurate, you should think of a pop bead necklace that got mangled a bit in the factory.



And to be even more accurate, you should know that the amino acid necklace, which forms the "backbone" of the cells' proteins, is far more malleable than a pop bead necklace, which falls apart when you bend it too much.The structure and behavior of the linked amino acids in the protein backbones better resemble that of a snake's backbone, as shown below. (©Warren Jacobi/Corbis) The spine of a snake, made up of a large number of linked subunits, the vertebrae, is capable of coiling the snake into a wide variety of shapes, ranging from a straight rod to a knotted "ball."

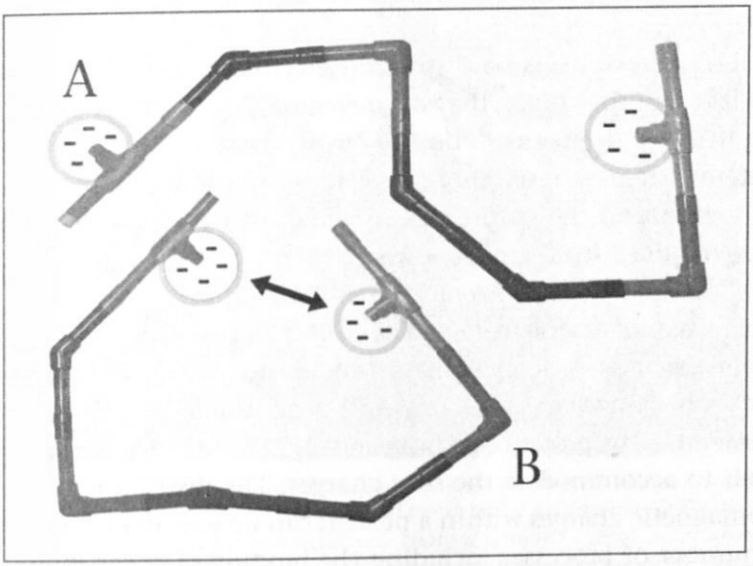


The flexible links *(peptide bonds)* between amino acids in a protein backbone enable each protein to adopt a variety of shapes. Through the rotation and flexion of their amino acid "vertebrae," protein molecules resemble nano-snakes in their ability to writhe and squirm. There are two primary factors that determine the contour of a protein's backbone and therefore its shape. One factor is the physical pattern defined by the sequence of differently shaped amino acids comprising the pop bead–like backbone.



Unlike uniform-shaped pop beads, each of the twenty amino acids comprising protein backbones has a unique shape (conformation). Consider the differences between the character of a "backbone" made from identically shaped pop beads and one assembled from the differently shaped pipe fittings illustrated above.

The second factor concerns the interaction of electromagnetic charges among the linked amino acids. Most amino acids have positive or negative charges, which act like magnets: *like* charges cause the molecules to repel one another, while *opposite* charges cause the molecules to attract each other. As shown on the following page, a protein's flexible backbone spontaneously folds into a preferred shape when its amino acid subunits rotate and flex their bonds to balance the forces generated by their positive and negative charges.



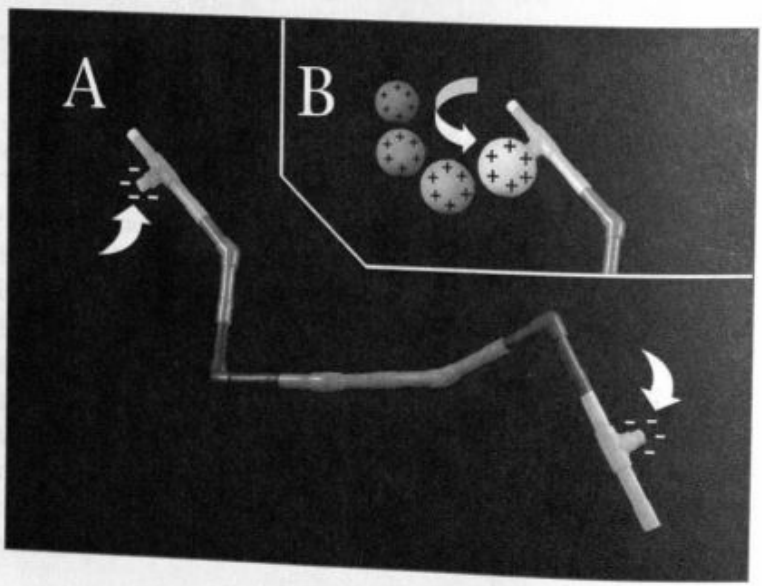
The protein backbones shown in A and B have the exact same amino acid (pipe fitting) sequence but reveal radically different conformations. Variations in the backbone's shape result from differential rotations at the junctions between adjacent pipe fittings. Like the pipe fittings illustrated above, the protein's differently shaped amino acids also rotate around their junctions (peptide bonds), allowing the backbone to wriggle like a snake. Proteins shape-shift though they will generally prefer two or three specific conformations. Which of the two conformations, A or B, would our hypothetical protein prefer? The answer is related to the fact that the two terminal amino acids (pipe fittings) have regions of negative charges. Since like charges repel each other, the farther apart they are, the more stable the conformation. Conformation A would be preferred because the negative charges are farther apart than they are in B.

The backbones of some protein molecules are so long that they require the assistance of special "helper" proteins called chaperones to aid in the folding process. Improperly folded proteins, like people with spinal defects, are unable to function optimally. Such aberrant proteins are marked for destruction by the cell; their backbone amino acids are disassembled and recycled in the synthesis of new proteins.

How Proteins Create Life

Living organisms are distinguished from nonliving entities by the fact that they move; they are *animated*. Cells harness the energy of protein movements to do the "work" that characterizes living systems, such as respiration, digestion, and muscle contraction. To understand the nature of life one must first understand how protein "machines" are empowered to move.

The final shape, or *conformation* (the technical term used by biologists), of a protein molecule reflects a balanced state among the electromagnetic charges of the amino acids comprising the backbone. However, if the protein's positive and negative charges are altered, the protein backbone will dynamically twist and adjust itself to accommodate the new charges. The distribution of electromagnetic charges within a protein can be selectively altered by a number of processes including the binding of other molecules or chemical groups such as hormones, the enzymatic removal or addition of charged atoms (ions) in the backbone's amino acids, or interference from electromagnetic fields such as those emanating from cell phones. (Tsong 1989)



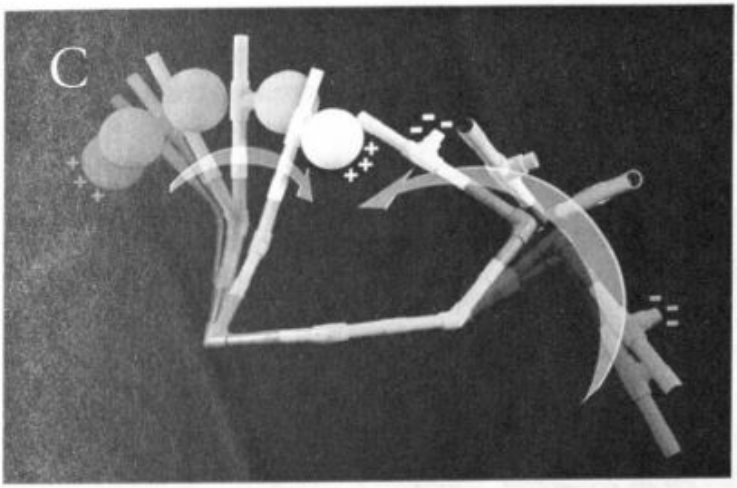
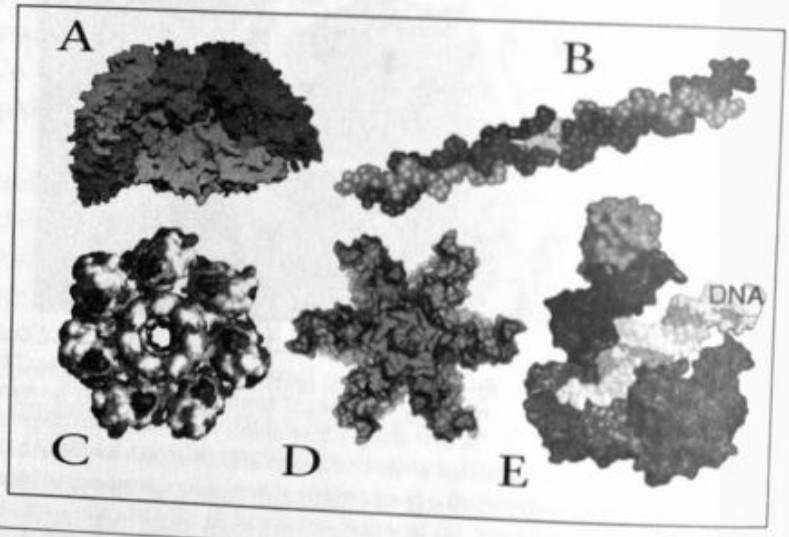


Figure A shows the preferred conformation of our hypothetical protein backbone. The repelling forces between the two negatively charged terminal amino acids (arrows) causes the backbone to extend so that the negative amino acids are as far apart as possible. Figure B shows a close-up of an end amino acid. A signal, in this case a molecule with a very positive electric charge (white sphere), is attracted to and binds with the negative site on the protein's terminal amino acid. In our particular scenario, the signal is more positive in charge than the amino acid is negative in charge. After the signal couples with the protein, there is now an excess positive charge at this end of the backbone. Since positive and negative charges attract one another, the backbone's amino acids will rotate around their bonds so that positive and negative terminals will come closer together. Figure C shows the protein changing from conformation A to conformation B. Changing conformations generates movement and the movement is harnessed to do work, providing for such functions as digestion, respiration, and muscle contraction. When the signal molecule detaches, the protein returns to its preferred extended conformation. This is how signal-generated protein movements provide for life.

The shape-shifting proteins exemplify an even more impressive engineering feat because their precise, three-dimensional shapes also give them the ability to link up with other proteins. When a protein encounters a molecule that is a physical and energetic complement, the two bind together like human-made products with interlocking gears, say an eggbeater or an old-fashioned watch.

Examine the following two illustrations. The first shows five uniquely shaped proteins, examples of the molecular "gears" found

in cells. These organic "gears" have softer edges than machine-shop-manufactured gears, but you can see that their precise, three-dimensional shapes would enable them to securely engage with other complementary proteins.

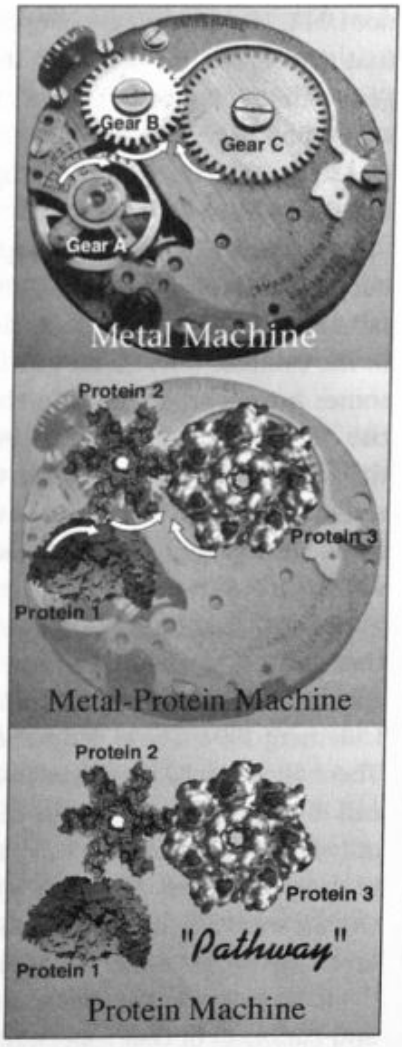


Protein Menagerie. Illustrated above are five different examples of protein molecules. Each protein possesses a precise three-dimensional conformation that is the same for each copy of itself in every cell. A) Enzyme that digests hydrogen atoms; B) Woven filament of collagen protein; C) Channel, a membrane-bound protein with hollow central pore; D) Protein subunit of "capsule" that encloses a virus; E) DNA-synthesizing enzyme with attached helical DNA molecule

In the second illustration (p. 29), I chose a wind-up watch to represent the workings of the cell. The first picture shows a metal machine, revealing the gears, springs, jewels, and case of the watch model. When Gear A turns it causes Gear B to turn. When B moves it causes Gear C to turn, etc. In the next image, I overlay the human-made machine gears with softer-edged organic proteins (magnified millions of times in proportion to the watch) so that it becomes visually conceivable that proteins could be like the watch's mechanism. In this metal-protein "machine," one can imagine Protein A rotating and causing Protein B to revolve, which in turn causes Protein C to move. Once you see that possibility, you can look to the third figure in which the human-made parts are removed. Voilà! We are left

with a protein "machine," one of the thousands of similar protein assemblies that collectively comprise the cell!

Cytoplasmic proteins that cooperate in creating specific physiologic functions are grouped into specific assemblies known as *pathways*. These assemblies are identified by the functions they perform, such as respiration pathways, digestion pathways, muscle contraction pathways, and the infamous, energy-generating Krebs cycle, the bane of many a science student who has to memorize every one of its protein components and complex chemical reactions.



Can you imagine how excited cell biologists were when they figured out how the protein machines work? Cells exploit the movements of these protein assembly machines to empower specific metabolic and behavioral functions. The constant, shape-shifting movements of proteins—which can occur thousands of times in a single second—are the movements that propel life.

The Primacy of DNA

You'll notice that, in the above section, I didn't discuss DNA at all. That's because it is the changing of the proteins' electromagnetic charges that is responsible for their behavior-generating movement,

not DNA. How did we get to the widespread and often-cited notion that genes "control" biology? In the *Origin of Species,* Darwin suggested that "hereditary" factors were passed on from generation to generation, controlling the traits of the offspring. Darwin's influence was so great that scientists myopically focused on identifying that hereditary material which, they thought, controlled life.

In 1910, intensive microscopic analyses revealed that the hereditary information passed on generation after generation was contained in chromosomes, thread-like structures that become visible in the cell just before it divides into two "daughter" cells. Chromosomes are incorporated into the daughter cell's largest organelle, the nucleus. When scientists isolated the nucleus, they dissected the chromosomes and found that the hereditary elements were essentially comprised of only two kinds of molecules, protein and DNA. Somehow the protein machinery of life was entangled in the structure and function of these chromosome molecules.

The understanding of the chromosome's functions was further refined in 1944 when scientists determined that it was DNA that actually contained hereditary information. (Avery, et al, 1944; Lederberg 1994) The experiments that singled out DNA were elegant. These scientists isolated pure DNA from one species of bacteria—let's call it Species A—and added the pure DNA to cultures containing only Species B bacteria. Within a short time, Species B bacteria began to show hereditary traits that were formerly seen only in Species A. Once it was known that you needed nothing other than DNA to pass on traits, the DNA molecule became a scientific superstar.

It was now left to Watson and Crick to unravel the structure and function of that superstar molecule. DNA molecules are long and threadlike. They are made from four nitrogen-containing chemicals called bases (adenine, thymine, cytosine, and guanine, abbreviated as A, T, C, and G). Watson and Crick's discovery of DNA's structure led to the fact that the sequence of the A, T, C, and G bases in DNA spells out the sequence of amino acids along a protein's backbone (Watson and Crick 1953). Those long strings of DNA molecules can be subdivided into single genes, segments that provide the blueprint for specific protein backbones. The code for recreating the protein machinery of the cell had been cracked!

Watson and Crick also explained why DNA is the perfect hereditary molecule. Each DNA strand is normally intertwined with a second strand of DNA, a loosely wrapped configuration known as the "double helix." The genius of this system is that the sequences of DNA bases on both strands are mirror images of each other. When the two strands of DNA unwind, each single strand contains the information to make an exact, complementary copy of itself. So through a process of separating the strands of a double helix, DNA molecules become self-replicating. This observation led to the assumption that DNA "controlled" its own replication . . . it was its own "boss."

The "suggestion" that DNA controlled its own replication *and* served as the blueprint for the body's proteins led Francis Crick to create biology's Central Dogma, the belief that DNA rules. The dogma was so fundamental to modern biology it was essentially written in stone, the equivalent of science's Ten Commandments. The dogma, also referred to as "the Primacy of DNA," is a fixture of almost every scientific text.

In the dogma's scheme of how life unfolds, DNA perches loftily on top, followed by RNA. RNA is the short-lived Xerox copy of the DNA. As such, it is the physical template encoding the amino acid sequence that makes up a protein's backbone. The Primacy of DNA diagram provides the logic for the Age of Genetic Determinism. Because the character of a living organism is defined by the nature of its proteins and its proteins are encoded in the DNA, then by logic, DNA would represent the "first cause," or primary determinant of an organism's traits.

The Central Dogma's assumption of a one-way flow of information from DNA to RNA to protein is profoundly important. Since proteins represent the physical body, the dogma implies that your physical body, and your life experiences cannot send information back and alter the DNA. According to the Dogma, DNA controls your life and you cannot influence your DNA!

The Human Genome Project

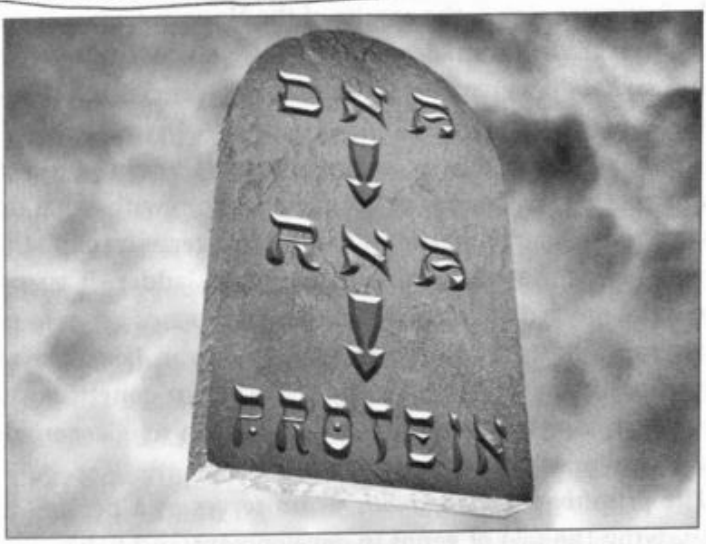
After DNA achieved superstar status, the remaining challenge was to create a catalog of all the genetic stars in the human firmament. Enter the Human Genome Project, a global, scientific effort begun in the late 1980s to create a catalog of all the genes present in humans.

From the outset, the Human Genome Project was a massively ambitious one. Conventional thought held that the body needed one gene to provide the blueprint for each of the 100,000 plus different proteins that make up our bodies. Add to that at least 20,000 regulatory genes, which orchestrate the activity of the protein-encoding genes. Scientists concluded that the human genome would contain a minimum of 120,000 genes located within the twenty-three pairs of human chromosomes.

But that wasn't the whole story. A cosmic joke was unfolding, one of those jokes that periodically unsettle scientists convinced they have discovered the secrets of the universe. Consider the impact of Nicolaus Copernicus' discovery published in 1543 that the Earth was not the center of the universe, as was thought by the scientist-theologians of the day. The fact that the Earth actually revolved around the sun and that the sun itself was not the center of the universe undermined the teachings of the Church. Copernicus' paradigm-busting discoveries launched the modern, scientific revolution by challenging the presumed "infallibility" of the Church. Science eventually displaced the Church as Western civilization's source of wisdom for understanding the mysteries of the universe.

Geneticists experienced a comparable shock when, contrary to their expectations of over 120,000 genes, they found that the entire human genome consists of fewer than 25,000 genes. (Pennisi 2003a and 2003b; Pearson 2003; Goodman 2003) More than eighty percent of the presumed and *required* DNA does not exist! The missing genes proved to be more troublesome than the missing eighteen minutes of the Nixon tapes. The one-gene, one-protein concept was a fundamental tenet of genetic determinism. Now that the Human Genome Project has toppled the one-gene for

one-protein concept, our current theories of how life works have to be scrapped. No longer is it possible to believe that genetic engineers can, with relative ease, fix all our biological dilemmas. There are simply not enough genes to account for the complexity of human life or of human disease.



The Central Dogma. The dogma, also referred to as the Primacy of DNA, defines the flow of information in biological organisms. As indicated by the arrows, the flow is only in one direction, from DNA to RNA and then to protein. The DNA represents the cell's long-term memory, passed from generation to generation. RNA, an unstable copy of the DNA molecule, is the active memory that is used by the cell as a physical template in synthesizing proteins. Proteins are the molecular building blocks that provide for the cell's structure and behavior. DNA is implicated as the "source" that controls the character of the cell's proteins, hence the concept of DNA's primacy that literally means "first cause."

I may sound like Chicken Little shouting that the genetics sky is falling. However, you don't have to take my word for it. Chicken Big said the same thing. In a commentary on the surprising results of the Human Genome Project, David Baltimore, one of the world's preeminent geneticists and a Nobel Prize winner, addressed the issue of human complexity (Baltimore 2001):

"But unless the human genome contains a lot of genes that are opaque to our computers, it is clear that we do not gain our undoubted complexity over worms and plants by using more genes.

"Understanding what does give us our complexity—our enormous behavioral repertoire, ability to produce conscious action, remarkable physical coordination, precisely tuned alterations in response to external variations of the environments, learning, memory, need I go on?—remains a challenge for the future."

As Baltimore states, the results of the Human Genome Project force us to consider other ideas about how life is controlled. "Understanding what does give us our complexity . . . remains a challenge for the future." The sky *is* falling.

In addition, the results of the Human Genome Project are forcing us to reconsider our genetic relationship with other organisms in the biosphere. We can no longer use genes to explain why humans are at the top of the evolutionary ladder. It turns out there is not much difference in the total number of genes found in humans and those found in primitive organisms. Let's take a look at three of the most studied animal models in genetic research, a microscopic nematode roundworm known as *Caenorhabditis elegans*, the fruit fly, and the laboratory mouse.

The primitive *Caenorhabditis* worm serves as a perfect model for studying the role of genes in development and behavior. This rapidly growing and reproducing organism has a precisely patterned body comprised of exactly 969 cells and a simple brain of about 302 cells. Nonetheless it has a unique repertoire of behaviors and most importantly, it is amenable to genetic experimentation. The *aenorhabditis* genome consists of approximately 24,000 genes. (Blaxter 2003) The human body, comprised of over fifty trillion cells, contains only about 1,000 more genes than the lowly, spineless, thousand-celled microscopic worm.

The fruit fly, another favored research subject, has 15,000 genes. (Blaxter 2003; Celniker, et al, 2002) So the profoundly more complicated fruit fly has 9,000 fewer genes than the more primitive *Caenorhabditis* worm. And when it comes to the question of mice and men, we might have to think more highly of them or less of ourselves; the results of parallel genome projects reveal that humans and rodents have roughly the same number of genes!

Cell Biology 101

In retrospect, scientists should have known that genes couldn't provide the *control* of our lives. By definition, the brain is the organ responsible for controlling and coordinating the physiology and behavior of an organism. Conventional science, as revealed in a recent publication by the U. S. Department of Health and Human Services (2005), perceives that the nucleus is "basically the cell's brain." "It contains the equivalent of the cell's gray matter—its genetic material, or DNA. In the form of genes, each with a host of helper molecules, DNA determines the cell's identity, masterminds its activities and is the official cookbook for the body's proteins."

Since genes were presumed to "control" the traits of the cell and the nucleus is the organelle that contains virtually all the cell's DNA, considering the nucleus as the "brain" of the cell made sense.

But is the nucleus truly the cell's brain? If our assumption that the nucleus and its DNA-containing material is the "brain" of the cell, then removing the cell's nucleus, a procedure called enucleation, should result in the immediate death of the cell.

And now, for the big experiment . . . (Maestro, a drumroll if you please).

The scientist drags our unwilling cell into the microscopic operating arena and straps it down. Using a micromanipulator, the scientist guides a needle-like micropipette into position above the cell. With a deft thrust of the manipulator, our investigator plunges the pipette deep into the cell's cytoplasmic interior. By applying a little suction, the nucleus is drawn up into the pipette, and the pipette is withdrawn from the cell. Below the nucleus-engorged pipette lies our sacrificial cell—its "brain" torn out.

But *wait!* It's still moving! My God . . . the cell is still *alive!*

The wound has closed and like a recovering surgical patient, the cell begins to slowly stagger about. Soon the cell is back on its feet (okay, its pseudopods), fleeing the microscope's field with the hope that it will never see a doctor again.

Following enucleation, many cells can survive for up to two or more months without genes. Viable enucleated cells do not lie

about like brain-dead lumps of cytoplasm on life-support systems. These cells actively ingest and metabolize food, maintain coordinated operation of their physiologic systems (respiration, digestion, excretion, motility, etc.), retain an ability to communicate with other cells, and are able to engage in appropriate responses to growth and protection requiring environmental stimuli.

Unsurprisingly, enucleation is not without side effects. Without their genes, cells are not able to divide, nor are they able to reproduce any protein parts they lose through the normal wear and tear of the cytoplasm. The inability to replace defective cytoplasmic proteins contributes to mechanical dysfunctions that ultimately result in the death of the cell.

Our experiment was designed to test the idea that the nucleus is the "brain" of the cell. If the cell had died immediately following enucleation, the observations would have at least supported that belief. However, the results are unambiguous: enucleated cells still exhibit complex, coordinated, life-sustaining behaviors, which imply that the cell's "brain" is still intact and functioning.

The fact that enucleated cells retain their biological functions in the absence of genes is by no means a new discovery. Over a hundred years ago, classical embryologists routinely removed the nuclei from dividing egg cells and showed that a single, enucleated egg cell was able to develop as far as the blastula, an embryonic stage consisting of forty or more cells. Today, enucleated cells are used for industrial purposes as living "feeder" layers in cell cultures designed for virus vaccine production.

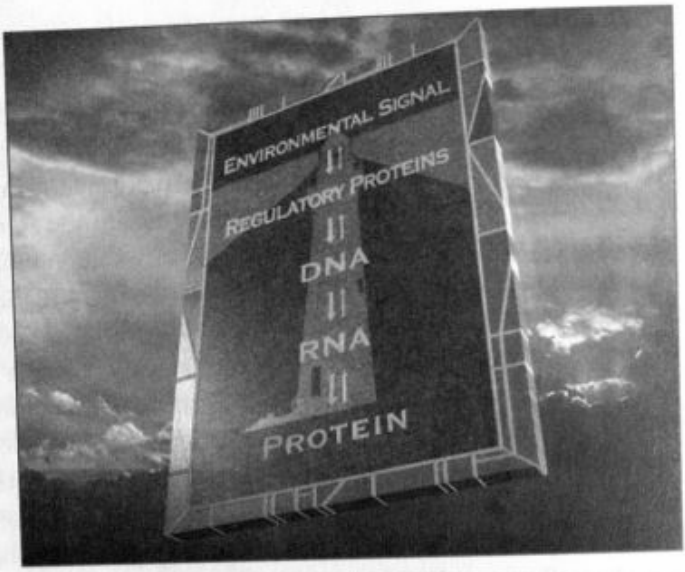
If the nucleus and its genes are not the cell's brain, then what exactly is DNA's contribution to cellular life? Enucleated cells die, not because they have lost their brain but because they have lost their reproductive capabilities. Without the ability to reproduce their parts, enucleated cells cannot replace failed protein building blocks, nor replicate themselves. So the nucleus is not the brain of the cell—the nucleus is the cell's gonad! Confusing the gonad with the brain is an understandable error because science has always been and still is a patriarchal endeavor. Males have often been accused of thinking with their gonads, so it's not entirely surprising that science has inadvertently confused the nucleus with the cell's brain!

Epigenetics: The New Science of Self-Empowerment

Genes-as-destiny theorists have obviously ignored hundred-year-old science about enucleated cells, but they cannot ignore new research that undermines their belief in genetic determinism. While the Human Genome Project was making headlines, a group of scientists were inaugurating a new, revolutionary field in biology called *epigenetics*. The science of epigenetics, which literally means "control above genetics," profoundly changes our understanding of how life is controlled. (Pray 2004; Silverman 2004) In the last decade, epigenetic research has established that DNA blueprints passed down through genes are not set in concrete at birth. Genes are not destiny! Environmental influences, including nutrition, stress, and emotions, can modify those genes without changing their basic blueprint. And those modifications, epigeneticists have discovered, can be passed on to future generations as surely as DNA blueprints are passed on via the double helix. (Reik and Walter 2001; Surani 2001; Watters 2006; Cloud 2010)

There is no doubt that epigenetic discoveries have lagged behind genetic discoveries. Since the late 1940s, biologists have been isolating DNA from the cell's nucleus in order to study genetic mechanisms. In the process they extract the nucleus from the cell, break open its enveloping membrane, and remove the chromosomal contents, half of which is made up of DNA and half of which is made up of regulatory proteins. In their zeal to study DNA, most scientists threw away the proteins, which we now know is the equivalent of throwing the baby out with the bathwater. Epigeneticists are bringing back the baby, by studying the chromosome's proteins, and those proteins are turning out to play as crucial a role in heredity as DNA.

In the chromosome, the DNA forms the core, and the proteins cover the DNA like a sleeve. When the genes are covered, their information cannot be "read." Imagine your bare arm as a piece of DNA representing the gene that codes for blue eyes. In the nucleus, this stretch of DNA is covered by bound regulatory proteins, which cover your blue-eye gene like a shirtsleeve, making it impossible to be read.



Primacy of Environment. The new science reveals that the information that controls biology starts with environmental signals that, in turn, control the activity of regulatory proteins on the DNA. Regulatory proteins direct the activity of genes. The DNA, RNA, and protein functions are the same as described in the Primacy of DNA chart. Note: the flow of information is no longer unidirectional. In the 1960s, Howard Temin challenged the Central Dogma with experiments that revealed RNA could go against the predicted flow of information and rewrite the DNA program. Originally ridiculed for his "heresy," Temin later won a Nobel Prize for describing reverse transcriptase, the molecular mechanism by which RNA can rewrite the genetic code. Reverse transcriptase is now notorious, for it is used by the AIDS virus' RNA to commandeer the infected cell's DNA. It is also now known that epigenetic changes in the DNA molecule, such as adding or removing methyl chemical groups, influence the binding of regulatory proteins. Proteins must also be able to buck the predicted flow of information, since protein antibodies in immune cells are involved with changing the DNA in the cells that synthesize them. The size of the arrows indicating information flow are intentionally not the same. There are tight restrictions on the reverse flow of information, a design that would prevent radical changes to the cell's genome.

How do you get that sleeve off? You need an environmental signal to spur the "sleeve" protein to change shape, i.e., detach from the DNA's double helix, allowing the gene to be read. Once the DNA is uncovered, the cell makes a copy of the exposed gene. As a result, the activity of the gene is "controlled" by the presence

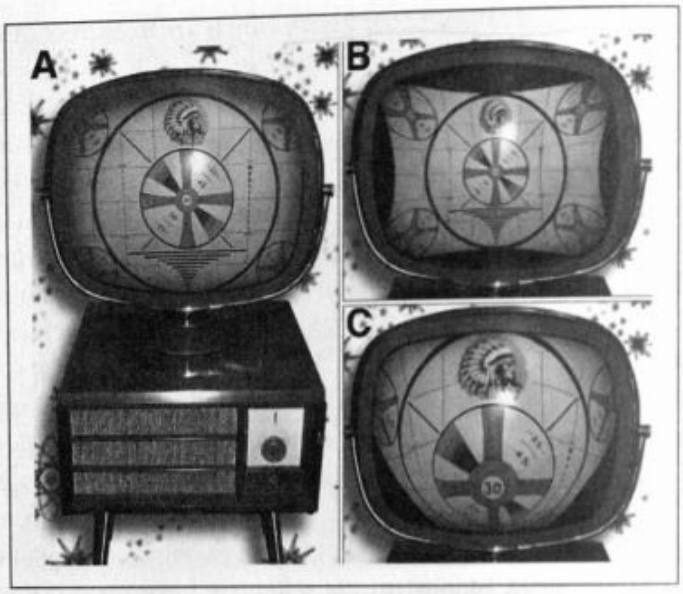
or absence of the ensleeving proteins, which are in turn controlled by environmental signals.

The story of epigenetic control is the story of how environmental signals control the activity of genes. It is now clear that the Primacy of DNA chart described earlier is outmoded. The revised scheme of information flow should now be called the "Primacy of the Environment." The new, more sophisticated flow of information in biology starts with an environmental signal, then goes to a regulatory protein and only then goes to DNA, RNA, and the end result, a protein.

The science of epigenetics has also made it clear that there are two mechanisms by which organisms pass on hereditary information. Those two mechanisms provide a way for scientists to study both the contribution of nature (genes) and the contribution of nurture (epigenetic mechanisms) in human behavior. If you only focus on the DNA blueprints, as scientists have been doing for decades, the influence of the environment is impossible to fathom. (Dennis 2003; Chakravarti and Little 2003)

Let's present an analogy, which hopefully will make the relationship between epigenetic and genetic mechanisms clearer. Are you old enough to remember the days when television programming stopped after midnight? After the normal programming signed off, a "test pattern" would appear on the screen. Most test patterns looked like a dartboard with a bull's eye in the middle, similar to the one pictured on the following page.

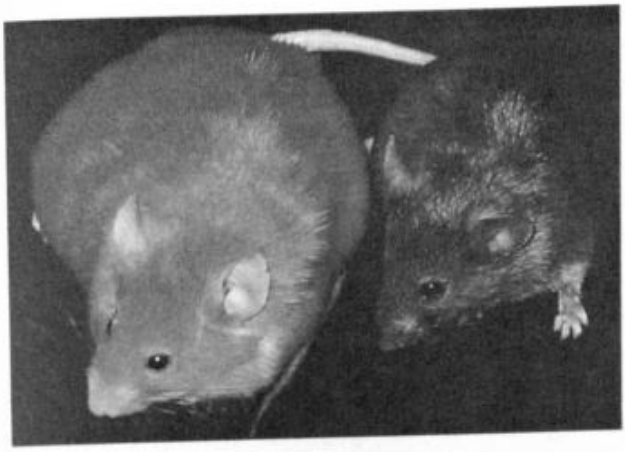
Think of the pattern of the test screen as the pattern encoded by a given gene, say the one for brown eyes. The dials and switches of the TV fine-tune the test screen by allowing you to turn it on and off and modulate a number of characteristics, including volume, color, hue, contrast, brightness, and vertical and horizontal holds. By adjusting the dials, you can alter the appearance of the pattern on the screen, while not actually changing the original broadcast pattern. This is precisely the role of regulatory proteins. Studies of protein synthesis reveal that epigenetic "dials" can create 2,000 or more variations of proteins from the same gene blueprint. (Bray 2003; Schmuker, et al, 2000)



In this epigenetic analogy, the test pattern on the screen represents the genetic code (program). While the TV's controls can change the appearance of the pattern (B and C), they do not change the original pattern of the broadcast (i.e., the gene). Epigenetic control modifies the read-out of a gene without changing the DNA code.

Parental Life Experiences Shape Their Children's Genetic Character

We now know that the environmentally influenced fine-tuning described above can be passed from generation to generation. A landmark Duke University study published in the August 1, 2003 issue of *Molecular and Cellular Biology* found that an enriched environment can even override genetic mutations in mice. (Waterland and Jirtle 2003) In the study, scientists looked at the effect of dietary supplements on pregnant mice with the abnormal "agouti" gene. Agouti mice have yellow coats and are extremely obese, which predisposes them to cardiovascular disease, diabetes, and cancer.



Agouti Sisters. One year old female genetically identical agouti mice. Maternal methyl donor supplementation shifts coat color of the offspring from yellow to brown and reduces the incidence of obesity, diabetes, and cancer. (Photo courtesy of Jirtle and Waterland©)

In the experiment, one group of yellow, obese, agouti mothers received methyl-group-rich supplements available in health food stores: folic acid, vitamin B12, betaine, and choline. Methyl-rich supplements were chosen because a number of studies have shown that the methyl chemical group is involved with epigenetic modifications. When methyl groups attach to a gene's DNA, it changes the way regulatory chromosomal proteins bind to the DNA molecule. If the proteins bind too tightly to the gene, the protein sleeve cannot be removed and the gene cannot be read. Methylating DNA can silence or modify gene activity.

This time the headlines "Diet Trumps Genes" were accurate. The mothers who got the methyl-group-rich supplements produced standard, lean, brown mice, even though their offspring had the same agouti gene as their mothers. The agouti mothers who didn't get the supplements produced yellow pups, which ate much more than the brown pups. The yellow pups wound up weighing almost twice as much as their lean, "pseudo-agouti" counterparts.

The University's photo, shown above, is striking. Though the two mice are genetically identical, they are radically different in appearance: one mouse is lean and brown and the other mouse

is obese and yellow. What you can't see in the picture is that the obese mouse is diabetic while its genetically identical counterpart is healthy.

Other studies have found epigenetic mechanisms to be a factor in a variety of diseases, including cancer, cardiovascular disease, and diabetes. In fact, only 5 percent of cancer and cardiovascular patients can attribute their disease directly to heredity. (Willett 2002; Silverman 2004) While the media made a big hoopla over the discovery of the BRCA1 and BRCA2 breast cancer genes, they failed to emphasize that ninety-five percent of breast cancers are not due to inherited genes. The malignancies in a significant number of cancer patients are derived from environmentally induced epigenetic alterations and not defective genes. (Kling 2003; Jones 2001; Seppa 2000; Baylin 1997) Recently, eminent scientist and physician Dean Ornish revealed that by just changing diet and lifestyle for 90 days, prostate cancer patients switched the activity of over 500 genes. Many of their gene changes inhibited biological processes critical in the formation of their tumors. (Ornish, et al 2008)

The epigenetic evidence has become so compelling that some brave scientists are even invoking the "L" word for Jean Baptiste de Lamarck, the much-scorned evolutionist, who believed that traits acquired as a result of environmental influence could be passed on. Philosopher Eva Jablonka and biologist Marion Lamb wrote in their 1995 book *Epigenetic Inheritance and Evolution—The Lamarckian Dimension:* "In recent years, molecular biology has shown that the genome is far more fluid and responsive to the environment than previously supposed. It has also shown that information can be transmitted to descendants in ways other than through the base sequence (code) of DNA." (Jablonka and Lamb 1995; Kaiser 2005)

We're back to where we started in this chapter, the environment. In my own work in the laboratory, I saw over and over the impact a changed environment had on the cells I was studying. But it was only at the end of my research career, at Stanford, that the message fully sank in. I saw that endothelial cells, which are the blood vessel-lining cells I was studying, changed their structure and function depending on their environment. When, for example, I added inflammatory chemicals to the tissue culture, the

endothelial cells rapidly became the equivalent of macrophages, the scavengers of the immune system. What was also exciting to me was that the cells transformed even when I destroyed their DNA with gamma rays. These endothelial cells were "functionally enucleated," yet they completely changed their biological behavior in response to inflammatory agents, just as they had when their nuclei were intact. These cells were clearly showing some "intelligent" control in the absence of their genes. (Lipton 1991; Butler, et al 2010)

Twenty years after my mentor Irv Konigsberg's advice to first consider the environment when your cells are ailing, I finally got it. DNA does not control biology, and the nucleus itself is not the brain of the cell. Just like you and me, cells are shaped by where they live. In other words, it's the environment, stupid.

CHAPTER 3

THE MAGICAL MEMBRANE

Now that we've looked at the protein assembly machinery of the cell, debunked the notion that the nucleus is the brain of the cellular operation, and recognized the crucial role the environment plays in the operation of the cell, we're on to the good stuff—the stuff that can make sense of your life and give you insight into ways of changing it.

This chapter puts forth my nominee for the true brain that controls cellular life—the membrane. I believe that when you understand how the chemical and physical structure of the cell's membrane works, you'll start calling it, as I do, the magical membrane. Or alternatively, capitalizing on the fact that part of the word is a homophone for brain, I refer to it in my lectures as the magical mem-Brain. And when you couple your understanding of the magical membrane with an understanding of the exciting world of quantum physics that I'll present in the next chapter, you will also understand how wrong the tabloids were in 1953. The secret of life does not lie in the famed double helix. Insight into the secret of life lies in understanding the elegantly simple biological mechanisms of the magical membrane—the mechanisms by which your body translates environmental signals into behavior.

When I started studying cell biology in the 1960s, the idea that the membrane was the cell's brain would have been considered laughable. And I have to concede that the membrane in those days was a sorry-looking Mensa candidate. The membrane seemed to

be just a simple, semi-permeable, three-layered skin that held the contents of the cytoplasm together. Think plastic wrap with holes.

One reason scientists misjudged the membrane is that it is so thin. Membranes are only seven millionths of a millimeter thick. In fact, they are so thin that they can only be seen with an electron microscope, which was developed after the Second World War. So it wasn't until the 1950s that biologists could even confirm that cell membranes exist. Up until that time, many biologists thought the cell's cytoplasm held together because it had a Jello-like consistency. With the aid of microscopes, biologists learned that *all* living cells have membranes and that all cell membranes share the same basic, three-layered structure. However, the simplicity of that structure belies its functional complexity.

Cell biologists gained insight into the amazing abilities of the cell membrane by studying the most primitive organisms on this planet, the prokaryotes. Prokaryotes, which include bacteria and other microbes, consist only of a cell membrane that envelops a droplet of soupy cytoplasm. Though prokaryotes represent life in its most primitive form, they have purpose. A bacterium does not bounce around in its world like a ball in a pinball machine. A bacterium carries out the basic physiologic processes of life like more complicated cells. A bacterium eats, digests, breathes, excretes waste matter, and even exhibits "neurological" processing. They can sense where there is food and propel themselves to that spot. Similarly, they can recognize toxins and predators and purposely employ escape maneuvers to save their lives. In other words, prokaryotes display intelligence!

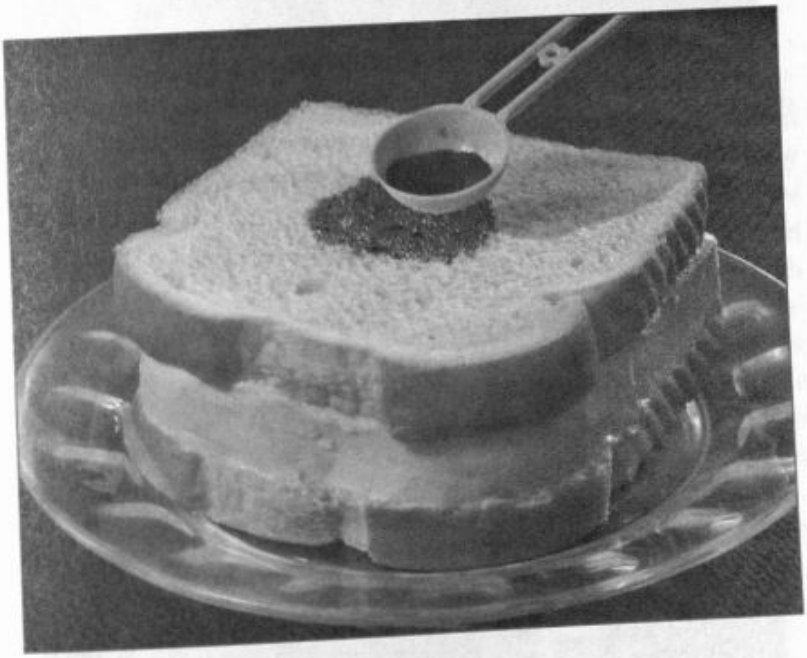
So what structure in the prokaryotic cell provides its "intelligence"? The prokaryotes' cytoplasm has no evident organelles, such as the nucleus and mitochondria, that are found in more advanced, eukaryotic cells. The most likely candidate for the prokaryote's brain is its cell membrane, the only organelle found in every living cell.

Bread, Butter, Olives, and Pimentos

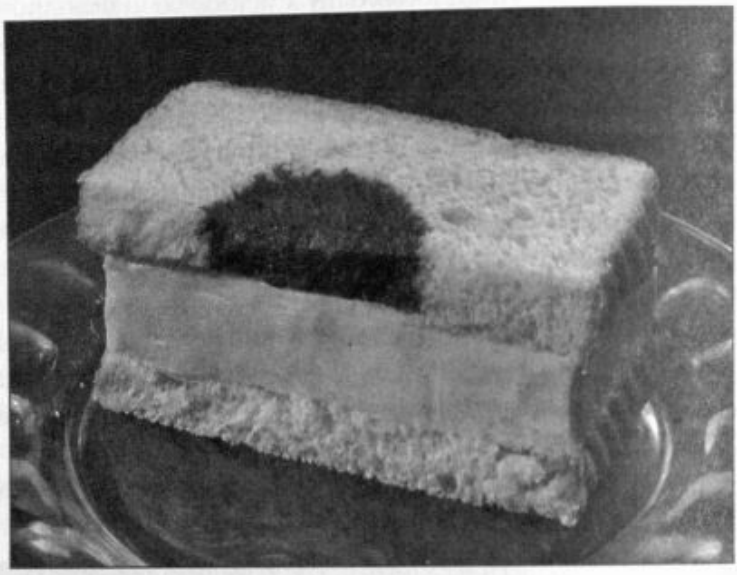
As I came to the realization that membranes were characteristic of all intelligent life, I focused my attention on understanding their structure and function. I came up with a gastronomic treat (just kidding) to illustrate the basic structure of the membrane. The treat consists of a bread and butter sandwich. To further refine the analogy, I added olives. Actually my instructive sandwich features two kinds of olives, ones stuffed with pimentos, the others pimento-free. Gourmands, don't groan. When I've left this sandwich out of my lectures, repeat members of the audience have asked me where it went!

Here's an easy experiment to show you how the "sandwich" membrane works. Make a bread-and-butter sandwich (at the moment free of olives). This sandwich represents a section of the cell membrane.

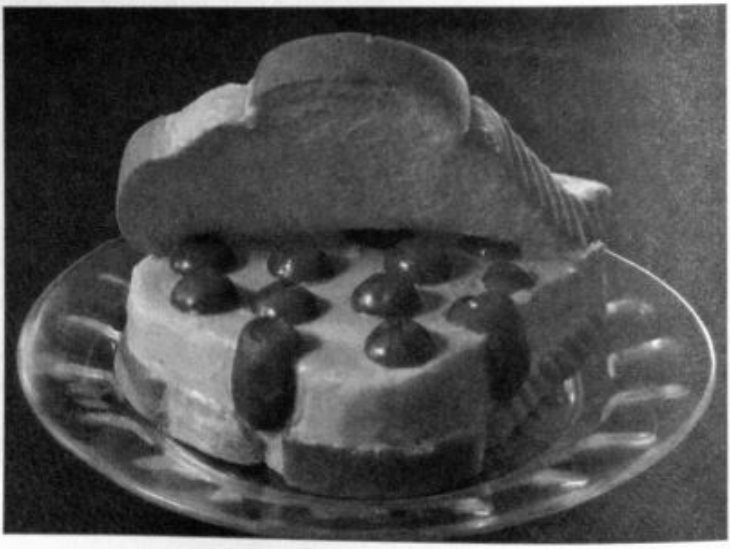
Now pour a teaspoon of colored dye on top of the sandwich.



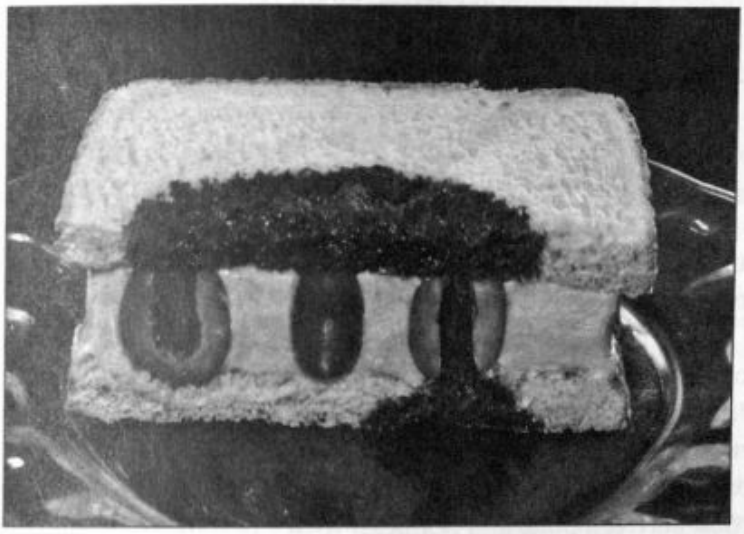
As illustrated below, the dye seeps through the bread but stops when it gets to the butter because the oily substance in the middle of the sandwich provides an effective barrier.



Now let's make a bread and butter sandwich with stuffed and unstuffed olives.



Now when we add the dye to the bread and slice the sandwich, we see a different result. When the dye hits a pimento-stuffed olive, it stops as surely as it stopped when it hit butter. But when the dye reaches an olive without a pimento, the pitted olive provides a channel through which the dye can flow freely across the middle of the sandwich, then through the bread to the plate.



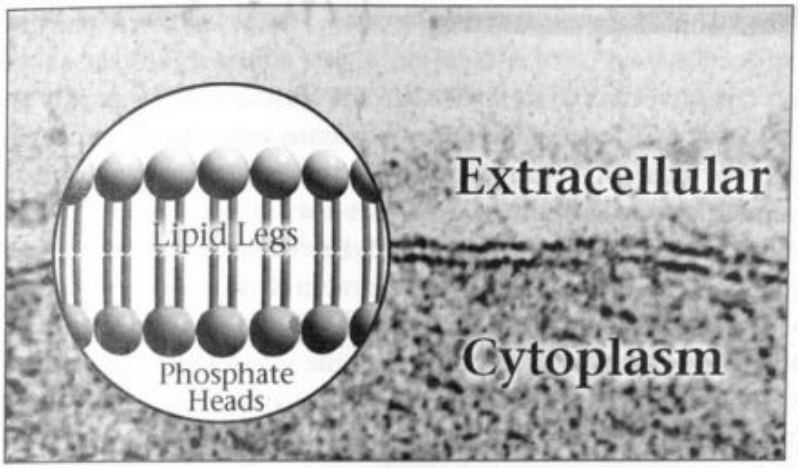
The plate in this analogy represents the cell's cytoplasm. By passing through the pimento-free olive, the dye penetrates the buttery layer to reach the other side of the "membrane" sandwich. The dye has successfully navigated the formidable, fatty, membrane barrier!

It is important for the cell to allow molecules to break through the barrier because in my sandwich analogy, the dye represents life-sustaining food. If the membrane were simply a bread and butter sandwich, it would provide a fortress-like barrier that keeps out the cacophony of innumerable molecular and radiant energy signals that make up a cell's environment. But the cell would die if the membrane were such a fortress because it would get no nutrients. When you add the pimento-free olives, which allow information and food into the cell, the membrane becomes a vital and ingenious mechanism enabling selected nutrients to penetrate the interior of the cell, just as the teaspoonful of dye made its way to the plate.

In real-life cellular biology, the bread-and-butter portion of the sandwich represents the membrane's phospholipids, one of the two major chemical components of the membrane. (The other major chemical components are the "olive" proteins, which we'll get to below.) I call phospholipids "schizophrenic" because they are composed of both polar and nonpolar molecules.

The fact that phospholipids contain both polar and nonpolar molecules may not sound like a recipe for schizophrenia to you, but I assure you it is. All the molecules in our universe can be divided into nonpolar and polar categories based on the type of chemical bonds that hold their atoms together. The bonds among polar molecules have positive and/or negative charges, hence their polarity. These molecules' positive and negative charges cause them to behave like magnets, attracting or repelling other charged molecules.

Polar molecules include water and things that dissolve in water. Nonpolar molecules include oil and substances that dissolve in oil; there are no positive or negative charges among their atoms. Remember the adage "water and oil don't mix"? Neither do oily nonpolar and watery polar molecules. To visualize the lack of interaction between polar and nonpolar molecules, think of your bottle of Italian salad dressing. You do your best to get vinegar and oil to bond by shaking the bottle, but when you set the bottle down, they separate. That's because molecules, like people, prefer environments that offer them stability. For their stability, polar (vinegar) molecules seek out watery polar environments and nonpolar (olive oil) molecules seek out nonpolar environments. Phospholipid molecules, comprised of both polar and nonpolar lipid regions, have a difficult time in seeking stability. The polarized phosphate portion of the molecule is motivated to seek water, while its nonpolar lipid portion abhors water and seeks stability by dissolving in oil.



Electron micrograph showing the cell membrane at the surface of a human cell. The dark-light-dark layering of the cell membrane is due to the ordering of the barrier's phospholipid molecules (inset). The lighter center of the membrane, the equivalent of the butter in our sandwich, represents the hydrophobic zone formed by the nonpolar legs of the phospholipids. The dark layers above and below the central lipid zone, the equivalent of the bread slices, represent the molecule's water-loving phosphate heads.

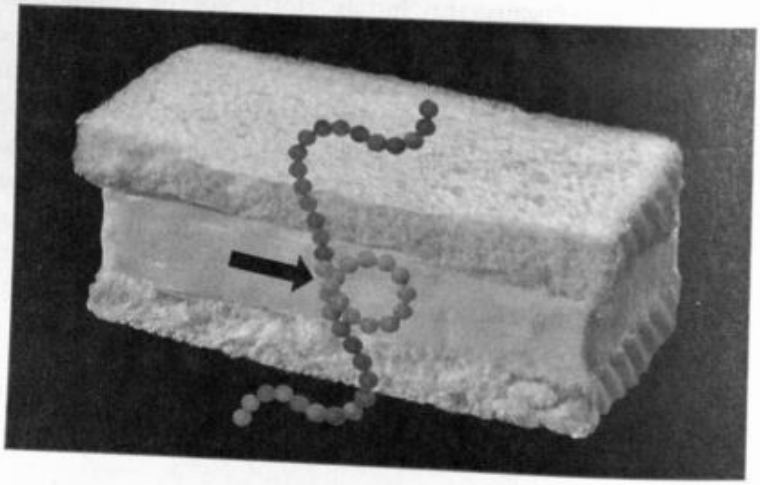
Getting back to our sandwich, the membrane's phospholipids are shaped like lollipops with an extra stick (see illustration above). The round part of the lollipop has polar charges among its atoms; it corresponds to the bread of our sandwich. The molecule's two stick-like portions are nonpolar; they correspond to the butter part of our sandwich. Because the "butter" portion of the membrane is nonpolar, it does not let positively or negatively charged atoms or molecules pass through it. In effect, this lipid core is an electrical insulator, a terrific trait for a membrane designed to keep the cell from being overwhelmed by every molecule in its environment.

But the cell could not survive if the membrane were the equivalent of a simple bread and butter sandwich. Most of the cell's nutrients consist of charged polar molecules that would not be able to get past the formidable nonpolar lipid barrier. Neither could the cell excrete its polarized waste products.

Integral Membrane Proteins

The olives in our sandwich are the truly ingenious part of the membrane. These proteins allow nutrients, waste materials, as well as other forms of "information" to be transported across the membrane. The protein "olives" allow not just any old molecules to get into the cell but only those molecules necessary for the smooth functioning of the cytoplasm. In my sandwich, the olives represent Integral Membrane Proteins (IMPs). These proteins embed themselves into the "butter" layer of the membrane, just as I have embedded olives in the illustration.

How do IMPs embed themselves into the butter? Remember that proteins are composed of a linear backbone assembled from linked amino acids. Of the twenty different amino acids, some are water-loving (hydrophyllic), polar molecules and some are water-fearing (hydrophobic), nonpolar molecules. When a region of the protein's backbone is made up of linked, hydrophobic amino acids, this segment of the protein seeks stability by finding an oil-loving environment like the membrane's lipid core (see arrow below). That's how hydrophobic parts of the protein integrate themselves into the middle layer of the membrane. Because some regions of a protein's backbone are made up of polar amino acids and other regions are nonpolar, the protein strand will weave itself in and out of the bread-and-butter sandwich.



There are lots of IMPs with lots of different names, but they can be subdivided into two functional classes: *receptor proteins* and *effector proteins*. Receptor IMPs are the cell's sense organs, the equivalent of our eyes, ears, nose, taste buds, etc. Receptors function as molecular "nano-antennas" tuned to respond to specific environmental signals. Some receptors extend inward from the membrane surface to monitor the internal milieu of the cell. Other receptor proteins extend from the cell's outer surface, monitoring external signals.

Like other proteins, which we discussed earlier, receptors have an inactive and an active shape and shift back and forth between those conformations as their electrical charges are altered. When a receptor protein binds with an environmental signal, the resulting alteration in the protein's electrical charges causes the backbone to change shape and the protein adopts an "active" conformation. Cells possess a uniquely "tuned" receptor protein for every environmental signal that needs to be read.

Some receptors respond to physical signals. One example is an estrogen receptor, which is specially designed to complement the shape and charge distribution of an estrogen molecule. When estrogen is in its receptor's neighborhood, the estrogen receptor locks on to it, as surely as a magnet picks up paper clips. Once the estrogen receptor and the estrogen molecule bind in a perfect "lock and key" fit, the receptor's electromagnetic charge changes and the protein shifts into its active conformation. Similarly, histamine receptors complement the shape of histamine molecules, and insulin receptors complement the shape of insulin molecules.

Receptor "antennas" can also read vibrational energy fields such as light, sound, and radio frequencies. The antennas on these "energy" receptors vibrate like tuning forks. If an energy vibration in the environment resonates with a receptor's antenna, it will alter the protein's charge, causing the receptor to change shape. (Tsong 1989) I'll cover this more completely in the next chapter, but I'd like to point out now that because receptors can read energy fields, the notion that only physical molecules can impact cell physiology is outmoded. Biological behavior can be controlled by invisible

forces, including thought, as well as it can be controlled by physical molecules like penicillin, a fact that provides the scientific underpinning for pharmaceutical-free energy medicine.

Receptor proteins are remarkable, but on their own they do not impact the behavior of the cell. While the receptor provides an awareness of environmental signals, the cell still has to engage in an appropriate, life-sustaining response, that is the venue of the effector proteins. Taken together, the receptor-effector proteins are a stimulus-response mechanism comparable to the reflex action that doctors typically test during physical examinations. When a doctor taps your knee with a mallet, a sensory nerve picks up the signal. That sensory nerve immediately passes on that information to a motor nerve that causes the leg to kick. The membrane's receptors are the equivalent of sensory nerves, and the effector proteins are the equivalent of action-generating motor nerves. Together, the receptor-effector complex acts as a switch, translating environmental signals into cellular behavior.

It is only in the last twenty years that scientists have realized the importance of the membrane's IMPs. They are in fact so important that studying the way IMPs work has become a field of its own called "signal transduction." Signal transduction scientists are busily classifying hundreds of complex information pathways that lie between the membrane's reception of environmental signals and the activation of the cell's behavior proteins. The study of signal transduction is catapulting the membrane to center stage, just as the field of epigenetics is highlighting the role of the chromosome's proteins.

There are different kinds of behavior-controlling effector proteins because there are lots of jobs that need to be done for the smooth functioning of the cell. Transport proteins, for example, include an extensive family of channel proteins that shuttle molecules and information from one side of the membrane barrier to the other. Which brings us back to the pimentos in our bread, butter, and olive sandwich. Many channel proteins are shaped like a tightly wound sphere, resembling the pimento-stuffed olives in our pictures. (See illustration page 49.) When the electrical charge

on the protein is altered, the protein changes shape, a change that creates an open channel running through the protein's core. Channel proteins are actually two olives in one, depending on their electrical charge. In the active mode, their structure resembles a pimento-free olive, with an open gate. In their inactive mode the proteins' shape resembles a pimento-stuffed olive that stays closed to the world outside the cell.

The activity of one specific channel type, sodium-potassium ATPase, merits special attention. Every cell has thousands of these channels built into the membrane. Collectively, their activity uses almost half of your body's energy every day. This channel opens and closes so frequently that it resembles a revolving door in a department store on the day of a big sale. Every time this channel revolves, it shuttles three positive-charged sodium atoms out of the cytoplasm and simultaneously admits two positive-charged potassium atoms into the cytoplasm from the environment.

Sodium-potassium ATPase not only uses up a lot of energy, it also creates energy as surely as store-bought batteries provide energy for Game Boys (at least until your kids wear them out). Actually, the energy-producing activity of sodium-potassium ATPase is a lot better than the batteries your kids wear out because it turns the cell into a constantly recharging biological battery.

Here's how sodium-potassium ATPase manages that trick. Every revolution of sodium-potassium ATPase throws more positive charges out than it lets in to the cell, and there are thousands of these proteins in each cell membrane. As these proteins go through hundreds of revolution cycles per second, the inside of the cell becomes negatively charged while the outside of the cell becomes positively charged. The negative charge below the membrane is referred to as the *membrane potential*. Of course the lipid, i.e., the butter portion of the membrane, does not let charged atoms cross the barrier, so the internal charge stays negative. The positive charge outside the cell and the negative charge inside make the cell essentially a self-charging battery whose energy is used to empower biological processes.

Another variety of effector proteins, cytoskeletal proteins, regulates the shape and motility of cells. A third variety, called enzymes, breaks down or synthesizes molecules, which is why

enzymes are sold in your local health food store as a digestive aid. When activated, all forms of effector proteins, including channels, cytoskeletal and enzyme proteins or their byproducts, can also serve as signals that activate genes. These IMPs or their byproducts provide signals that control the binding of the chromosome's regulatory proteins that form a "sleeve" around the DNA. In contrast to conventional wisdom, genes do not control their own activity. Instead it is the membrane's effector proteins, operating in response to environmental signals picked up by the membrane's receptors, which *control* the "reading" of genes so that worn-out proteins can be replaced or new proteins can be created.

How the Brain Works

Once I understood how IMPs worked, I had to conclude that *the cell's operations are primarily molded by its interaction with the environment, not by its genetic code.* There is no doubt that the DNA blueprints stored in the nucleus are remarkable molecules, which have been accumulated over three billion years of evolution. But as remarkable as these DNA blueprints are, they do not "control" the operations of the cell. Logically, genes cannot preprogram a cell or organism's life because cell survival depends on the ability to dynamically adjust to an ever-changing environment.

The membrane's function of interacting "intelligently" with the environment to produce behavior makes it the true brain of the cell. Let's put the membrane to the same "brain" test to which we put the nucleus. When you destroy its membrane, the cell dies just as you would if your brain were removed. Even if you leave the membrane intact, destroying only its receptor proteins, which can easily be done with digestive enzymes in the lab, the cell becomes "brain-dead." It is comatose because it no longer receives the environmental signals necessary for the operation of the cell. The cell also becomes comatose when the membrane's receptor proteins are left intact and its effector proteins are immobilized.

To exhibit "intelligent" behavior, cells need a functioning membrane with both receptor (awareness) and effector (action)

proteins. These protein complexes are the fundamental units of cellular intelligence. Technically they may be referred to as units of "perception." The definition of perception is "awareness of the elements of environment through physical sensation." The first part of the definition describes the function of receptor IMPs. The second part of the definition, the creation of a "physical sensation," sums up the role of the effector proteins.

By examining these basic units of perception, we have engaged in an ultimate reductionist exercise, taking the cell down to its fundamental nuts and bolts. In this regard it is important to note that at any given time there are up to hundreds of thousands of such switches in a cell membrane. Consequently, the behavior of a cell cannot be determined by examining any individual switch. The behavior of a cell can only be understood by considering the activities of *all* the switches at any given time. That is a holistic—not reductionist—approach, which I'll elaborate on in the next chapter.

At the cellular level, the story of evolution is largely the story of maximizing the number of basic units of "intelligence," the membrane's receptor/effector proteins. Cells became smarter by utilizing their outer membrane surface more efficiently and by expanding the surface area of their membranes so that more IMPs could be packed in. In primitive prokaryote organisms, the cell membrane's IMPs carry out all of its fundamental physiologic functions including digestion, respiration, and excretion. Later in evolution, portions of the surface membrane that carry out these physiologic functions go inside the cell, forming the membranous organelles that are characteristic of eukaryotic cytoplasm. That leaves more membrane surface area available to increase the number of perception IMPs. In addition, the eukaryote is thousands of times bigger than the prokaryote resulting in a tremendous increase in membrane surface area, i.e., a whole lot more room for IMPs. The end result is more awareness, which translates to greater survivability.

Through evolution, the cell membrane's surface expanded, but there was a physical limit to that expansion. There was a point at which the thin cell membrane was not strong enough to contain a larger mass of cytoplasm. Think what happens when you fill a balloon with water. As long as the balloon is not overfilled, it is strong

and can be passed around. However, if you exceed the balloon's water capacity, the balloon ruptures easily, spilling its contents, just as a membrane with too much cytoplasm would inevitably rupture. When the cell membrane reached that critical size, the evolution of the individual cell reached its limit. That's why for the first three billion years of evolution, single cells were the only organisms on this planet. That situation changed only when cells came up with another way to increase awareness. In order to get smarter, cells started banding together with other cells to form multicellular communities through which they could share their awareness, as I explained in Chapter 1.

To review, the functions required for a single cell to stay alive are the same functions required by a community of cells to stay alive. But cells started to specialize when they formed multicellular organisms. In multicellular communities, there is a division of labor. That division of labor is evident in the tissues and organs that carry out specialized functions. For example, in the single cell, respiration is carried out by the mitochondria. In a multicellular organism, the mitochrondrial equivalent for respiration are the billions of specialized cells that form the lungs. Here's another example: In the single cell, movement is created by the interaction of cytoplasmic proteins called actin and myosin. In a multicellular organism, communities of specialized muscle cells handle the job of generating motility, each endowed with massive quantities of actin and myosin proteins.

I repeat this information from the first chapter because I want to emphasize that while it is the job of the membrane in a single cell to be aware of the environment and set in motion an appropriate response to that environment, in our bodies those functions have been taken over by a specialized group of cells we call the nervous system. It is not a coincidence that the human nervous system is derived from the embryonic skin, the human counterpart of a cell's membrane.

Though we've come a long way from unicellular organisms, I believe, as I've mentioned before, that studying single cells is an instructive way of studying complicated multicellular organisms. Even the most complex human organ, the brain, will reveal its

secrets more readily when we know as much as we can about the membrane, the cell's equivalent of a brain.

The Secret of Life

As you've learned in this chapter, scientists have recently made great progress toward unraveling the complexity of the simple-looking membrane. But even twenty-five years ago, the rough outlines of the membrane's functions were known. In fact, it was 1985 when I first realized how understanding the workings of the membrane could be life changing. My eureka moment resembled the dynamics of super-saturated solutions in chemistry. These solutions, which look like plain water, are fully saturated with a dissolved substance. They are so saturated that adding just one more drop of the substance causes a dramatic reaction in which all of the dissolved materials instantly coalesce into a giant crystal.

In 1985, I was living in a rented house on the spice-drenched Caribbean island of Grenada teaching at yet another "off-shore" medical school. It was 2 A.M., and I was up revisiting years of notes on the biology, chemistry, and physics of the cell membrane. At the time I was reviewing the mechanics of the membrane, trying to get a grasp of how it worked as an information processing system. That is when I experienced a moment of insight that transformed me, not into a crystal, but into a membrane-centered biologist who no longer had any excuses for messing up his life.

At that early morning hour, I was redefining my understanding of the structural organization of the membrane. Staring first with the lollipop-like phospholipid molecules and noting that they arranged in the membrane like regimented soldiers on parade in perfect alignment. By definition, a structure whose molecules are arranged in regular, repeated pattern is defined as a crystal. There are two fundamental types of crystals. The crystals that most people are familiar with are hard and resilient minerals like diamonds, rubies, and even salt. The second kind of crystal has a more fluid structure even though its molecules maintain an organized pattern. Familiar examples of *liquid crystals* include digital watch faces and laptop computer screens.

To better understand the nature of a liquid crystal, let's go back to those soldiers on parade. When the marching soldiers turn a corner, they maintain their regimented structure, even though they're moving individually. They're behaving like a flowing liquid, yet they do not lose their crystalline organization. The phospholipid molecules of the membrane behave in a similar fashion. Their fluid crystalline organization allows the membrane to dynamically alter its shape while maintaining its integrity, a necessary property for a supple membrane barrier. So in defining this character of the membrane I wrote: "The membrane is a liquid crystal."

Then I started thinking about the fact that a membrane with just phospholipids would be simply a bread-and-butter sandwich without the olives. In the experiment described earlier, the colored dye could not get through the lipid butter layer. That bread and butter sandwich is a non-conductor. However, when you include the IMP "olives," you realize that the membrane conducts some things across while keeping other things out. So I continued writing my description of the membrane by adding: "The membrane is a *semiconductor.*"

Lastly, I wanted to include in my description the two most common kinds of IMPs. These are the receptors and a class of effectors called channels because they provide the all-important means for the cell to let in nutrients and let out waste matter. I was about to write that the membrane contains "receptors and channels" when I realized that a synonym for receptor is the word gate. So instead I completed my description by writing: "The membrane contains *gates* and *channels.*"

I sat back and reviewed my new description of the membrane: *"The membrane is a liquid crystal semiconductor with gates and channels."* What hit me right away was the fact that I had recently heard or read the very same phrase, though at the moment, I didn't know where I had come across it. One thing was for sure; it was not in the context of biological science.

As I leaned back in my chair, my attention was drawn to the corner of my desk where my new, smiley-face Macintosh, my first computer, was parked. Lying beside the computer was a copy of a bright red book called *Understanding Your Microprocessor.* I had just

bought this non-technical paperback guide to how computers work from a Radio Shack outlet. I grabbed the book and found in the introduction a definition of a computer chip that read: "A chip is a crystal semiconductor with gates and channels."

For the first second or two I was struck by the fact that the chip and cell membrane shared the same technical definition. I spent several more intense seconds comparing and contrasting biomembranes with silicon semiconductors. I was momentarily stunned when I realized that the identical nature of their definitions was not a coincidence. The cell membrane was indeed a structural and functional equivalent (homologue) of a silicon chip!

Twelve years later, in 1997, an Australian research consortium headed by B. A. Cornell published an article in *Nature* that confirmed my hypothesis that the cell membrane is a homologue of a computer chip. (Cornell, et al, 1997) The researchers isolated a cell membrane and attached a piece of gold foil under it. They then flooded the space between the gold foil and the attached membrane with a special electrolyte solution. When the membrane's receptors were stimulated by a complementary signal, the channels opened and allowed the electrolyte solution to flow across the membrane. The gold foil served as a transducer, an electrical pickup device, which converted the electrical activity of the channel into a digital readout on a screen. This device, created for the study, demonstrates that the cell membrane not only looks like a chip but also functions like one. Cornell and associates successfully turned a biological cell membrane into a digital-readout computer chip.

So what's the big deal, you ask? The fact that the cell membrane and a computer chip are homologues means that it is both appropriate and instructive to better fathom the workings of the cell by comparing it to a personal computer. The first big-deal insight that comes from such an exercise is that computers and cells are *programmable*. The second corollary insight is that the programmer lies *outside* the computer/cell. Biological behavior and gene activity are dynamically linked to information from the environment, which is downloaded into the cell.

The point: a cell is a "programmable chip" whose behavior and genetic activity are primarily controlled by environmental signals, not genes.

I had been trained as a nucleus-centered biologist as surely as Copernicus had been trained as an Earth-centered astronomer, so it was with a jolt that I realized that the gene-containing nucleus does not program the cell. Environmental data is entered into the cell/computer via the membrane's receptors, which represent the cell's "keyboard." Receptors trigger the membrane's effector proteins, which act as the cell/computer's "Central Processing Unit" (CPU).

The function of the computer's CPU is to convert incoming data into the binary code language used by the computer's operating system. The receptor-effector protein complexes represent a functional complement of a computer's CPU processor. Incoming environmental information is passed from the receptor to the effector protein, which in turn, converts the incoming signal into the behavioral language of biology.

I realized in those early morning hours that even though biological thought at that time was still preoccupied with genetic determinism, leading-edge cell research, which continues to unfold the mystery of the Magical Membrane in ever more complex detail, tells a far different story.

At that moment of transformation, I was frustrated because there was no one with whom I could share my excitement. I was alone out in the country. My house didn't have a telephone. Because I was teaching at a medical school, I realized that there would undoubtedly be some students studying in the library. I hastily threw some clothes on and raced off to the school to tell someone, anyone, of this exciting new insight.

Running into the library, out of breath, wild-eyed with my hair flying in all directions, I was the epitome of the absent-minded professor. I spotted one of my first-year medical students and ran up to him proclaiming, "You have to hear this! This is great shit!" I remember in the back of my mind how he pulled away from me, almost in fear of this raving, mad scientist who wildly broke the silence of the sleepy library. I immediately began to spew forth my new understanding of the cell, using the complex, polysyllabic jargon of a conventional cell biologist. When I finished my explanation and was silent, I was waiting to hear his congratulations

or at least a "bravo," but nothing was forthcoming. He was now wide-eyed himself. All he could say was, "Are you okay, Dr. Lipton?"

I was crushed. The student had not understood a word I had said. In hindsight, I realized that as a first-semester medical student, he did not have enough scientific background or vocabulary to make any sense out of my apparent rantings. However, the wind was knocked out of my sails. I held the key to the secret of life, and there was no one who could understand me! I confess I didn't have much better luck with most of my colleagues who had been schooled in polysyllabic jargon. So much for the Magical Membrane.

Over the years I gradually honed my presentation about the Magical Membrane and continued to refine it so that first-year medical students and lay people can understand it. I've also continued to update it with the latest research. In so doing, I've found much more receptive audiences among a wider range of people. I have also found audiences receptive to the spiritual implications of my eureka moment. Shifting to membrane-centered biology was exciting for me, but it wouldn't have been enough to send me screaming to the library. That Caribbean moment not only transformed me into a membrane-centered biologist, it also transformed me from an agnostic scientist into a card-carrying mystic who believes that eternal life transcends the body.

I'll get to the spiritual part of the story in the Epilogue. For the moment, let me reiterate the lessons of the Magical Membrane, which put the control of our lives not in the genetic roll of the dice at conception but in our own hands. We are the drivers of our own biology, just as I am the driver of this word processing program. We have the ability to edit the data we enter into our biocomputers, just as surely as I can choose the words I type. When we understand how IMPs control biology, we become masters of our fate, not victims of our genes.