THE MYSTERIOUS EPIGENOME

What Lies Beyond DNA

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INTRODUCTION: BEYOND DNA

The new frontier. Those words rang out in political speeches during the campaign season of 1960 as a youthful presidential candidate began to stir the nation with a vision of courage and initiative, a vision of untapped possibilities and beckoning adventure. John F. Kennedy struck a rhetorical chord and the phrase resonated widely. Historians routinely refer to President Kennedy's administration as The New Frontier. After Kennedy's inauguration, the idea of a "new frontier" seemed to be widely embraced across the political spectrum. Its spirit transcended party politics. At its root, it captured a much broader narrative of our facing and seizing the challenges that loomed on the horizon.

On April 12, 1961, just eighty-three days after Kennedy took office, one of America's greatest scientific challenges burst onto the world scene when Russian cosmonaut Yuri Gagarin successfully orbited the earth in a spacecraft. The Russians, who had been "first in space" with their launch of the Sputnik satellite in October 1957, had now scored another spectacular first. Over the next six weeks, President Kennedy worked closely with NASA officials to draw up a comprehensive plan for expanded space exploration by the United States. This master plan was presented to a joint session of Congress on May 25, 1961. In one of his more memorable lines, the president said, "I believe that this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to the earth."[1]

That goal was reached in July 1969, when Neil Armstrong jumped from the ladder of the lunar module and landed on the dusty surface of the Sea of Tranquility. In the years since that historic milestone, the United States has tackled many other frontiers of science and technology. One of the most ambitious and promising projects was the Human Genome Project, launched in 1990, which aimed to map the entire human genome, right down to the exact sequence of adenine, thymine, cytosine, and guanine along the double helix. This herculean task—somewhat analogous to the goal of landing on the moon—took nearly a decade of labor by thousands of scientists and the expenditure of billions of dollars.

The first major goal was reached in 2000, when President Clinton called a news conference to announce that a rough draft of the genome had been assembled. After a few more years of refining and cross-checking the data, the project was completed in 2003 and a final draft of the genome was published. At last, scientists had delivered a complete map of our human DNA—right down to the positioning of tens of thousands of genes on the different chromosomes. Thanks to the coordinated efforts of geneticists around the globe, anyone could directly access online the exact spelling of the entire 3.1-billion-letter DNA database for *Homo sapiens.*

By most standards of scientific discovery, this project was a magnificent success. However, some of the practical promise of this project remains unfulfilled. For example, there has been little progress in the so-called gene therapies anticipated in the days when the project was being organized. As the headline of a recent front page article in the *New York Times* announced, "A Decade Later, Genetic Map Yields Few New Cures."

In the article, writer Nicholas Wade expresses disappointment that "medicine has yet to see any large part of the promised benefits. For biologists, the genome has yielded one insightful surprise after another.

But the primary goal of the $3 billion Human Genome Project—to ferret out the genetic roots of common diseases like cancer and Alzheimer's and then generate treatments—remains largely elusive. Indeed, after ten years of effort, geneticists are almost back to square one in knowing where to look for the roots of common disease."[2]

The Human Genome Project was an undeniable success in advancing our knowledge of the programming of the DNA hard drive, but its payout in terms of *health-enhancing strategies* seems to have fallen far short of the expectations raised in the early 1990s. How could this be? Is not the human genome a prime example of a new frontier that has been faced and conquered? How could this achievement produce such minimal results in terms of medical breakthroughs?

Spelling out the encyclopedic text of our DNA is indeed a major scientific achievement. Yet perhaps what has been missing, at least in connection with human health, is an equally important genome-related frontier—one that lies *beyond* DNA and is just now coming into focus.

In probing the operation of DNA, scientists have learned much more about a second biological encyclopedia of information that resides above the primary information stored within our DNA. Researchers have discovered a complex system in the cell—sophisticated "software" situated beyond DNA—that directs DNA's functions and is responsible for our embryonic development and the differentiation of a single, fertilized egg cell into more than two hundred cell types in a mature body. This higher control system is also implicated in aging processes, cancer, and many other diseases. It guides the expression of DNA, telling different kinds of cells to use different genes, and to use them in the precise ways that meet the needs of those different cells. This "information beyond DNA" plays a crucial role in each of our sixty trillion cells, telling the genes exactly when, where, and how they are to be expressed. Welcome to biology's mysterious new frontier—the *epigenome.*

How could this huge key to the function of DNA remain hidden for so long? President Kennedy once said, "The greater our knowledge increases, the more our ignorance unfolds." This truth applies just as powerfully to the world of biology and genome research as it does to physics or political theory. In any academic field, scholars are continually poking and probing into the obscure corners of the unknown; in doing so, they not only find out new truth, they also realize how much ignorance they harbored before the search began. In the case of DNA's depths of complexity, each discovery seems to raise fresh questions and new opportunities to see *what we don't know.*

In *The Mysterious Epigenome*, we shall focus our study on two revolutionary arenas. First, we will explain the latest news in the world of DNA, which is curled up like a chemically encoded hard drive in the nucleus of all plant and animal cells. Each month, it seems, brings yet another remarkable discovery of the unexpected richness of information embedded in DNA. We find these discoveries too exciting and too important not to share.

Second, interwoven with the stories of these recent DNA discoveries, we will recount how science has stumbled onto the master control system that sits above our genetic riches. We will describe the nooks and crannies of the wondrous epigenome that is now being diligently mapped and cataloged. Much of this system resides very close to our genes; it is dynamically connected to the double helix in the form of a multilayered system of tiny chemical tags. Thus, the term *epigenome* commonly refers to these control tags that are in close relationship with DNA. Yet, in our journey through the epigenome, we will use the word in a slightly broader sense. We will include all layers and levels of cell memory and stored information found beyond the DNA.

Picture the genome of DNA as a sailing ship sitting in calm waters, tied up to a dock, ready for a journey. When the winds arise, the captain wants to venture out to sea, so he wisely sets the sails to catch the wind and moves the rudder to direct the ship to its destination. In our analogy, then, the captain, sails, and rudder are the multilayer epigenome. We want to explore and understand every part of this biological "ship-at-sea," including the all-important DNA and every dimension of the cell's epigenetic programming that directs the expression of DNA.

We have chosen to emphasize the theme of human health, especially in relation to discoveries of the epigenome. Undoubtedly, the most exciting aspect of this explosion of epigenetic information is the potential for our proactive role in reprogramming our epigenome—to some extent at least—to allow for improved health for everyone. As we'll see, some aspects of this epigenetic improvement can even be passed on to future generations.

We have spent several years studying the new revolutionary picture of the genome and epigenome emerging from lab research. The deeper we penetrated into this realm, the more we sensed the time was ripe for a guided tour of both of these frontiers of biology. Our interest and qualifications for writing on this topic are linked to our work as research scientists and science writers, with specialties in ophthalmology and scientific rhetoric and argumentation. We previously collaborated on the book *Darwinism Under the Microscope*, and have also individually published other science books.

Our hope for you, the reader, is that this book will be but the start of an awe-inspiring journey, exploring the wonders of our cell's beckoning frontier. Let's take the plunge into our genome, our epigenome . . . and beyond!

Chapter One

SCIENCE'S SUPREME QUEST

Unlocking Our Master Codes

DNA, THE MASTER CODE OF LIFE, is flashing an impish smile. She has been a bit coy and evasive recently. Now we know why. She's been harboring some shocking scientific secrets.

During the past two decades, this delicate, spiral molecule has played a game of genetic hide-and-seek with scientists. Fortunately, she has whispered some helpful hints, and scattered clues on the fingerlike landscape of her chromosomes. One by one, those clues have started to fall into place. One can almost glimpse her nodding in delight as her sequestered mysteries are pried open.

Researchers have been stunned by many of these findings. One is the discovery of a sophisticated "splicing code" found embedded within the familiar DNA code. This set of instructions enables a single gene to perform the feat of knitting together a bewildering variety of different gene products—numbering in the hundreds and even thousands. It is like a brilliant chef producing a single "super recipe" from whose instructions cooks can produce three thousand different sumptuous dishes.

Another shock came in June 2007 when the ENCODE project, a combined effort of dozens of laboratories, turned up something totally unexpected. Previously, vast stretches of the human genome had been described as "junk DNA," based on the belief that 90 percent or more of our genetic sequences were sheer, useless gibberish. According to this pre-2007 view, these junky stretches of DNA (unlike functional genes) were not being opened up and translated into RNA copies. If this vast quantity of junk DNA were graded in terms of its vital function, it would receive an F. It was seen as useless debris—damaged goods that accumulated during long eons of evolution.

The ENCODE study, however, showed that this picture was radically false. The exact opposite conclusion about so-called junk DNA has now been substantiated. Those stretches of humble DNA are anything but junky. Much of their mysterious code is in fact being read and copied, and it is used in a wide variety of cellular functions. As scientists begin to grasp the vital functions of this genetic black box, much is yet to be learned. However, one thing is certain: the credibility of the junk DNA doctrine has been heavily damaged, almost certainly beyond repair, and textbooks are being rewritten to accommodate this surprising reversal.

A LIFE-CODE . . . BEYOND DNA?

One of the key DNA discoveries concerns a mysteriously intertwined "dance partner" in the elegant waltz of cellular life. The discovery of this chemical partner presents mind-boggling implications for our physical health and spiritual well-being. In a nutshell, we have now learned that our DNA responds to cues from a higher control system written into the cell, and the programming of this system can even change over time. Thus, our own healthy (or not-so-healthy) life habits can affect the way DNA is processed in our cells.

This may come as a surprise, because our DNA library, the genome, has been viewed as an ironclad inheritance for each of us. Thankfully, that's not the end of the story. Scientific sleuths have uncovered a sophisticated genetic control system, which they call the *epigenome*. We can think of it as a molecular computer code that has been lurking quietly inside living cells—*beyond our DNA*.

This built-in director, found in all of our cells, sits above our DNA and carefully controls how genes are expressed. This has been compared to a skilled musical director waving a baton in front of an orchestra. This remarkable system actually has several layers, or levels, that all seem to be tightly coordinated into one smooth system. Let's sketch a few of the key discoveries that have been confirmed as scientists plumbed the depths of the epigenome.

First, if one envisions the epigenome's role as the orchestra director of DNA, this is a director with metaphorical "eyes and ears." This biochemical conductor is sensitive to his biological environment. The quality of his directing can be changed as he picks up signals that tell him what is happening in the body's tissues and organs. For example, he can be strengthened in his daily work with a sensible diet, which supports his efficient DNA-directing, or he can be damaged and poisoned through binging, which leads to sloppy and even fatal waving of his wand. In fact, it appears a myriad of life habits can either strengthen or damage the DNA director. We will return to this in a moment.

Second, we've learned much about the clever mechanics that enable this system to work so efficiently. The director's functions are intricately woven together in a chemical software program, with its own set of codes composed of tiny signals and switches. At the heart of our book (between pages 80 and 81), we've placed detailed color images to show how these chemical signals might appear if we could see them directly through a nanoscale microscope. (We will refer to these images by letter throughout.)

Two of these epigenetic codes are embedded very close to the DNA in a double-tiered library of instructions—a database that governs the DNA-library hard drive. This dual-library differs from cell type to cell type, so that a brain cell's epigenome would be noticeably different from a muscle cell's epigenome. In the same way, both of these epigenetic libraries are different from those programmed into each of the other two hundred or so cell types. If we could zoom in on the intricate nooks of DNA's molecular landscape, we would see millions

Table 1.1. Genetics vs. Epigenetics		
Field of Study	Genetics	Epigenetics (Epigenomics)
Complete Library	Genome	Epigenome
Function	Codes for RNA & Proteins	Controls DNA Expression
Informational Format	DNA Language (in genes)	(1) Methyl tags on C-letters (2) Tagging of histone tails
Variation from Cell Type to Cell Type	None: the genome is identical in all cell types	Much variation: 200+ cell types, so 200+ epigenomes
Heritable Changes	Yes: mutations in germ cells are inherited	Yes: epigenetic modification can be passed on to successive generations
Changes by Lifestyle	No	Yes—many ways

of these chemical switches. Some epigenetic signals are hard to spot—they're very tiny and are written onto the double helix itself. A second epigenetic code involves five different markers, which are attached to the spools (called "histones") that DNA is coiled onto (see color images, figure A). Scientists have a name for this coiled-up DNA material: *chromatin*. This "packaged DNA," which makes up the stuff of our chromosomes and is buried deep inside the nucleus, is a prime focus of epigenetic research.

Moreover, several lines of evidence suggest that additional layers of subtly coded information are built into other parts of the cell, including the cell membrane and even the interior structural members of a cell. This strange new realm of functional information, written into parts of our cells that are distant from DNA, can be startling when one hears of it for the first time. It's a bit like discovering that the digital memory in a computer is not confined to the hard drive, but that millions of bits of vital data are inscribed in other specialized languages and codes which are embedded in the keyboard, screen, outer casing, and many other parts of the computer.

Just as this higher "control library" has been dubbed the *epigenome*, the study of this complex system is called *epigenomics* or, more commonly, *epigenetics*. (See table 1.1, which compares genetics with epigenetics.) A growing network of researchers is probing the mysteries of the epigenome, and the complexity of the system they're unraveling seems to grow with each passing month.

REPROGRAMMING FAMILY HEALTH FOR GENERATIONS

Perhaps the most sobering discovery that has emerged from this research is that crucial changes in a person's epigenetic code *can be inherited by succeeding generations.* In other words, scientists have found that our system of epigenetic control is not only modified and re-edited by our lifestyle, but these changes can also be locked in to some extent; they can be passed down to our children, and even to our grandchildren and perhaps beyond. One fascinating study was published by Dr. Lars Bygren of the Karolinska Institute, a highly regarded research facility in Stockholm. Bygren focused on the health histories of ninety-nine families in a tiny village in a remote agricultural region called Norrbotten in the northernmost part of Sweden.

As Bygren studied the life patterns in this village, where his own father grew up, he uncovered a stark reality. A pattern of binge-eating in years of abundant harvests seemed to have dealt a devastating blow that lasted for many decades, as it reprogrammed the epigenetic system of young boys in the village. By studying the patterns of diet and longevity in these lineages, Bygren concluded that an average of thirty-two years were cut from the life spans of the next two generations of farmers because of a single year of gluttony.

This research, originally reported in prestigious science journals, was laid out starkly in a January 2010 *Time* magazine cover story, titled "Why Your DNA Isn't Your Destiny," that surveyed the explosion of epigenetics research.[1]

The potential for influencing the efficiency of one's own DNA function—and especially for reshaping the health prospects of succeeding generations—is clearly headline news in the world of science. Yet it is much more than that. These discoveries have brought us to the edge of a scientific revolution in the biology of inheritance. Several lines of evidence, summarized in various books and research articles, have shown that many patterns of daily living—including diet, stress, smoking, and exercise—have the power to partially reprogram our epigenetic system and that of our offspring. How widespread is the fruit of such epigenetic changes (for good or ill) in the generations that follow? How many generations can reap the effects of these epigenetic alterations? Answers thus far are sketchy, though this is the focus of much current research. One thing is clear: *our epigenome is somewhat malleable and moldable.* We can tweak our epigenetic code, which then may produce either a positive or negative effect on our posterity as tiny chemical markers are modified. Several lines of evidence are delivering an epigenetic shock: the quality of our grandchildren's lives may be influenced by the way we live our lives today. As John Cloud concludes in the *Time* magazine article, "It will take geneticists and ethicists many years to work out all the implications, but be assured: the age of epigenetics has arrived."

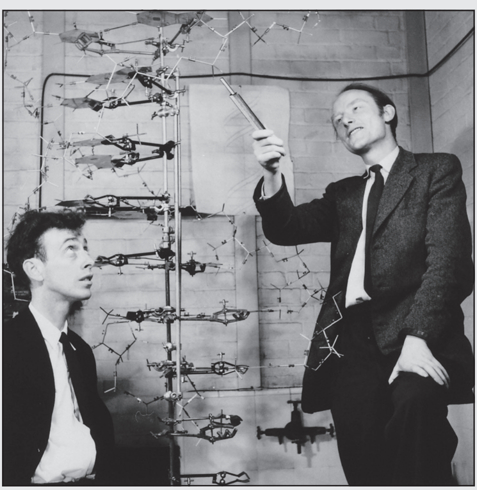
Of course, scientists have not downgraded the role of DNA or genetics in the day-to-day workings of cells. In one sense, DNA is still king; it is just as central to life today as it's always been. The library of DNA still plays a key role in ruling or shepherding the process of growth of a single fertilized cell into a gigantic sequoia, a mighty blue whale, or a healthy adult human. What is emerging today in molecular studies of genetics is a dual focus. First, we must track the intricate toiling of DNA in its ruling or shepherding process. Second, we must also track the higher control system, the epigenome—*which acts as the ruler* *and shepherd of the DNA*. Scientists will continue to probe the incredible genome, even as they explore and come to understand the mysterious epigenome.

It bears repeating: Because epigenetic inheritance weaves such deep changes in life and health, which does not easily happen in DNA itself, this new double focus in biology is opening a huge window of opportunity for improved human health for generations to come.

The Riddles of DNA

Over the past decade, based on an explosion of new data, scientists have had to revise their most basic notions of the double helix. Much of what was taught as fact about DNA in biology classes a few years ago has now been tossed into history's dustbin of discarded myths.

A radically revised picture of life is now taking shape. We glimpse a panorama far richer and more complex than the simple sketch inherited from the biological revolution that roared to life in 1953. That's when DNA pioneers James Watson and Francis Crick announced they had uncovered the elegant double-helix structure.



James Watson and Francis Crick, codiscoverers of DNA's double-helix structure.

Since then, nearly six decades of feverish research into DNA have passed, during which time Watson and Crick continued to play key roles. Watson even helped launch the Human Genome Project in the early 1990s, which by 2000 had produced a complete draft of all 3.1 billion letters in the miniaturized DNA hard drive found in human cells.

Until 2007, scientists assumed that only 3 percent of our DNA contained recognizable genes. These genes serve as digital files (construction templates or recipes) for assembling the complex protein molecules that do most of the work in our cells. It was commonly asserted that more than 90 percent of human DNA, devoid of gene patterns for proteins, was flawed or useless. But because it seemed to do little harm, it was passed along through the generations. This mysterious and disparaged DNA was described as "junk DNA."

Stainless steel DNA sculpture that Watson donated to Clare College at Cambridge University. It sits in a field not far from the Cavendish Laboratory where Watson and Crick made their discovery.

Then the shock. By mid-June 2007, a global project called ENCODE had completed an extensive exploration of the human genome and published 28 papers, which outlined a pattern of DNA activity that was entirely unexpected. Far from describing a genome "jammed with junk," the study showed that between 74 percent and 93 percent of the DNA spiral-ladder in human cells seems to be opened up routinely in our cells. It is read and then copied into the half-ladder RNA format.

Many of these mysterious RNA molecules—including some quite tiny ones—spring into action and are used in a variety of vital functions. The news summary released by the National Institutes of Health said, "The findings challenge the traditional view of our genetic blueprint as a tidy collection of independent genes, pointing instead to a complex network in which genes, along with regulatory elements and other types of DNA sequences that do not code for proteins, interact in overlapping ways not yet fully understood."[2] One scientist focusing on the collapse of the "junk DNA" model estimated that our human genome may contain as many as 450,000 RNA genes—a vast, lurking load of DNA information that was virtually invisible a few years ago.

OUR GOAL: TO PROBE AND QUESTION

Our purpose in writing *The Mysterious Epigenome* is to recount the discoveries that have opened up a transformed picture of our genome and its crucial companion, the epigenome. In a clear and accessible way, we will survey the nuts and bolts of these systems. As we sketch a picture of this molecular landscape, we will highlight recent findings about DNA, and we'll show how the epigenome's switches and gadgets work with the help of complex machinery.

To complete this tour of discovery, we will take the reader on a fictional field trip to a high-tech cellular display, along with a pair of trips into the cell using a miniaturized exploration sub. With the help of a bit of "frame-shifting technology," submarines will zip right into the cell and visit its spherical DNA-packed nucleus. These journeys are portrayed in the setting of a new biological research laboratory in Chicago. Although this lab and its scientists are fictitious, they are inspired by the very real Biologic Institute, a research facility near Seattle, Washington. In fact, we can assure you that the scientific information in these sections is as accurate as a geneticist's lab report.

Because we are dealing with such foundational discoveries, we decided to ask the relevant "So what?" questions throughout the book. First, what is the practical impact of these new truths on our physical health and way of life? How can we live life to the fullest while ensuring that our lifestyle promotes not only our own wellness but also that of family members who will inherit our epigenetic code? Because of the urgency of these questions, we devote space to the emerging picture of the health and fitness implications of the epigenome.

Equally important—ultimately more important by far—is the question of how these findings affect our spiritual health. How does the new breathtakingly complex view of the genome/epigenome system affect our view of origins? After reviewing the newest scientific evidence, we will ask *what* or *who* designed this massive multilevel system. It would be a simple failure of nerve if we did not delve into the design implications that flow from this scientific vista. How do these discoveries reopen old questions about whether life is "designed with a purpose in mind"? If a highly integrated system of complex information is at the root of our marvelous gifts of intelligence, creativity, and love, the idea of purpose simply cannot be ignored. Because this kind of question moves into the smoke-filled terrain of the debate between Darwinism and intelligent design, such scientific questions and controversies not only excite the mind but also have the potential to arouse our emotions.

DARWIN OR DESIGN?

Because of this built-in emotional factor, we approach with special care the issue of how cellular complexity arose. This area can be difficult because for many people, Darwin and Darwinism have come to symbolize such cherished values as scientific enlightenment, critical reasoning, and educational progress. The moment one sets forth deep empirical problems with Darwinian theory (which we do at times), one risks being instantly dismissed or marginalized. Even some leading evangelical Christians have argued that we should make peace with the Darwinian scenario of life's development. They claim that the evidence for Darwinian evolution is solid.[3] Yet is this claim plausible? Can a proclamation of the "triumph of Darwin" stand in light of the experimental evidence set forth in such works as *The Edge of Evolution* by biologist Michael Behe or *Signature in the Cell* by philosopher of science Stephen Meyer? We think not.

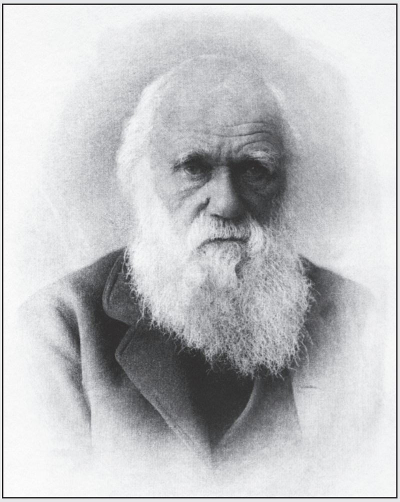
These developments, and many more, have posed a deep and formidable challenge to Darwinian theory. More scientists than ever, not only in the Americas but also in Europe and Asia, are asking if it is plausible that mindless, undirected processes of nature were responsible for building all of the cell's high-tech hardware and its *software codes* as well. This is precisely what Darwinism claims to have shown, and those claims are now under enormous stress from the weight of new data. Using Darwin's own words, is it possible that evolutionary theory will be found "not fit to survive" the onslaught of evidence? Is the handiwork of a brilliant designer now on display for all to see?

Darwin himself had no way to glimpse the tiny machines and digital libraries that modern science has uncovered in the past century of biochemistry. He and his contemporaries viewed the cell as a fairly simple substance. (See the sidebar, "Darwin's Limitations.") But when one fast-forwards from Darwin's day to the twenty-first century, there is a drastic change in perspective. In recent years, as biologists and geneticists have worked in concert to penetrate the mysterious intricacies of the cell, phrases such as "staggering complexity" and "infinite complexity" have appeared in the literature.[4] The unexpectedly sophisticated nano-world that has opened in front of them has greeted scientists with shocking discoveries. DNA is more information-rich than we imagined—and it is tethered to an overarching high-tech software system.

In recent years, a cascade of evidence has put stress on cherished assumptions. It has raised exciting new questions about the origin of cellular complexity. What is nature saying to us all? Let's take a look.

Darwin's Limitations

Let's note an irony about Darwin's monumental *Origin of Species*, published more than 150 years ago. Darwin's book, brilliantly argued and clearly revolutionary for its time, was nevertheless hamstrung with a blurred and simplistic view of the complexity of life. Today, when researchers question the adequacy of Darwinian theory, with its great emphasis on the role of natural selection in explaining the rise of complexity, they are asking the hard questions. Instead of asking simply, "What did Darwin discover about the development of life?" they are also now asking, "What didn't Darwin know about the basic structures of life's complexity that we now have to face?"



Charles Darwin

Armed with an inquisitive, brilliant mind, Darwin was nevertheless hampered by inferior instruments for observing life under the microscope. As a result, when viewing a cell, he and his colleagues concluded that it was a relatively simple object. One of his contemporaries, Ernst Haeckel (1834–1919), an eminent German embryologist and devout Darwinist, agreed with this assessment. He called the cell a "simple little lump of albuminous combination of carbon"[5]—in other words, just a tiny sac of gray, biological goo. These conclusions caused Darwin and scientists of his day to misunderstand the cell's significance. Instead of understanding it as the horrendously complex building block of all life forms, they saw the cell as a simple entity, and felt free to attribute to it purely material factors.

DISCUSSION QUESTIONS

1. Since the 1970s scientists have been describing the genome as containing much "junk DNA" within its chromosomes. Then the results of the ENCODE project were published. What surprising discovery was made known about "junk DNA"?
2. What are some of the everyday analogies that have been used to compare the relationship of DNA (the genome) with the epigenome?
3. What does it mean when it is said that "the epigenome has eyes and ears"?
4. Imagine that you can compare the genome, and also the epigenome, from two different types of cells—say, a nerve cell and muscle cell. Would you expect the two genome libraries to be identical? How about the two epigenomes—would you expect them to be identical?
5. What surprising discoveries did Dr. Bygren make about the epigenome, as he looked back into the history of the genetics of farm families in northern Sweden?
6. Referring to table 1.1, where genetics and epigenetics are compared, what contrasts between the two systems surprised you the most?