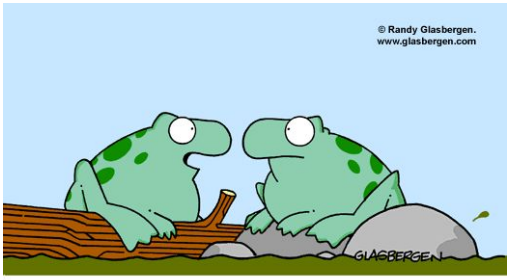
MARANATHA
HIGH SCHOOL
A COLLEGE PREPARATORY CHRISTIAN SCHOOL

AP Biology 2019 Summer Assignment

Welcome to AP Biology!



"Looks aren't everything. It's what's inside you that really matters. A biology teacher told me that."

The two main goals of AP Biology are to help you develop a conceptual framework for modern biology and to gain a deeper appreciation of science as a process (as opposed to an accumulation of facts). Because of the rapid pace of discovery in the life sciences our primary emphasis is on developing an understanding of unifying concepts that connect the major topics of biology. The AP Biology Curriculum centers around the four Big Ideas and you will need to not only know these but also understand how they all relate:

Big Idea 1: The process of evolution drives the diversity and unity of life.
Big Idea 2: Biological systems utilize free energy and molecular building blocks to grow, to reproduce and to maintain dynamic homeostasis.
Big Idea 3: Living systems store, retrieve, transmit and respond to information essential to life processes.
Big Idea 4: Biological systems interact, and these systems and their interactions possess complex properties.

What to do before the first day of school:

- **My email is d_newkirk@mhs-hs.org**. If you encounter problems with your summer assignments, you can contact me at this address.
- Purchase the books listed on Maranatha's bookstore webpage.
- AP Biology was designed by a select group of college professors and high school science teachers to be equivalent to an introductory college biology course. Visit the College Board site below to explore what an AP Biology course is like:
  - https://apstudent.collegeboard.org/exploreap?affiliateId=apcentral&bannerId=exploreap1
- We have a small problem in AP Biology. Each year new advances in science are discovered but the length of the school year (and when the AP Biology Test occurs) stays the same. What does this mean? We are short on time. In order to cover ALL of the material, you are responsible for reviewing the Chemistry section on your own. Here is what you are to do:
  - **AP Biology Summer 2019 Part 1: Print and complete the Chemistry Review Worksheet:** As an AP Biology student the expectation is that if you don't know it, find it out. Here are a few helpful resources:
    - Watch the following YouTube videos. These three videos are great chemistry reviews.
    - https://www.youtube.com/watch?v=MYuh5yErdfA
    - https://www.youtube.com/watch?v=Juw7HBg0zZs
    - https://www.youtube.com/watch?v=FbaXQ8u6IP8
  - **AP Biology Summer 2019 Part 2:** Print and complete this packet consisting of reading selections and questions.
- **Optional**: Contribute to and participate in discussions in our course's Flipboard magazine: http://flip.it/IyPAj

I am truly looking forward to working with you next year!
Best regards,

Mr. Newkirk

NAME:_____

AP: CHAPTER 2 & 3 CHEMICAL CONTEXT OF LIFE & WATER

1. What are the most common elements in the human?

2. Helium has an atomic number of 2 and atomic mass of 4. Explain.

3. Define isotope and give some examples.

4. How are isotopes used in biology?

5. What happens when electrons change levels?

6. What is the significance of valence numbers?

AP: CHAPTER 4 CARBON & THE MOLECULAR DIVERSITY OF LIFE

1. Define organic chemistry.

2. What are the major groups of organic compounds studied in biology?

3. Describe some of the shapes of carbon skeletons.

4. Define the following:

   Isotopes:

   Geometric Isotopes:

   Enantiomers:

5. Why are enantiomers of biological interest?

6. What is the significance of functional groups?

7. For each of the functional groups, complete the chart:

Group	Formula	Comments
Hydroxyl		
Carbonyl		aldehyde
Carbonyl		keytone
Carboxyl		
Amino		
Sulfhydryl		
Phosphate		

AP: CHAPTER 5A MACROMOLECULES

1.Define the following:

monomer:

polymer:

condensation reaction:

hydrolysis:

2. Which foods do you think will enter the blood the quickest? Why?

3. What are the general roles of carbohydrates?

4. List some monosaccharides with their molecular formulas.

5. Double sugars are called _____

List the monosaccharides that form each:

Maltose:

Sucrose:

Lactose:

6. Polymers of sugars form _____

7. Which forms of polysaccharide is best for each function:

Strength of structure _____

Storage and sugar release _____

What theme is this addressing? _____

8. How does the alpha differ from the beta form of glucose and why is it significant to animals?

_____

_____

_____

9. How do the role and structure of the following polysaccharides compare?

Starch:

Glycogen:

Cellulose:

10. Ninety percent of Asians, 75% of African-Americans, and a much smaller percent of northern Europeans are lactose intolerant. Why do you suppose we see this pattern?

_____

_____

_____

AP: CHAPTER 5B MACROMOLECULES

1. What is the characteristic common to lipids?

2. Lipids are synthesized by the chemical reaction _____
and broken down by the reaction _____

3. What makes fats hydrophobic?

4. State at least two differences between saturated and unsaturated fats.

5. How do phospholipids interact in an aqueous solution?

6. Make a diagram of phospholipid interactions that form membranes.

7. Sketch the common building block of steroids.

8. List several functions of proteins.

9. What are the three properties used to classify amino acids?

10. Sketch two amino acids side-by-side, on one of them label the functional groups, then show how the two can be joined together.

11. What determines the primary structure of a protein?

12. Describe the four levels of protein structure: (IMPORTANT!)

Name	Description	Detailed Sketch
Primary Structure		
Secondary Structure		
Tertiary Structure		
Quaternary Structure		

13. What happens to a protein during denaturation?

_____

_____

14. What are the building blocks of nucleic acids? _____

15. Briefly describe two functions of DNA in the cell.

_____

_____

_____

AP Biology Summer Assignment: Part 2

Preface: I cannot emphasize enough how important it is that you carefully read these passages. I have included the questions below primarily to ensure that you actually do read and also to highlight some of the more crucial concepts, but the primary purpose of the assignment is for you to encounter important biological ideas in a palatable and even entertaining medium. Zimmer and Sapolsky are renowned for their ability to articulate scientific information in an engaging and clear manner, and I sincerely hope that you find the reading enjoyable. **I recommend reading each selection straight through in its entirety before going back and answering the questions.**

"E. Coli and the Elephant"

1. What does the "E" stand for in E. Coli? Why?
2. Explain what Kluyver meant by his exclamation in 1926: "From the elephant to butyric acid bacterium—it is all the same!"
3. What did Thomas Morgan demonstrate using *Drosophila melanogaster*
4. What did Beadle and Tatum discover in 1941 by studying *Neurospora crassa*?
5. The section on pages 7-12 is titled "The Unity of Life." What unifies life?
6. What did Delbruck learn from sick *E. coli*? What was making the bacteria sick?
7. What was Avery (and his colleagues) primary contribution to the field of genetics?
8. Alfred Hershey and Martha Chase conducted one of the most famous experiments of all time. Describe the experiment and what they concluded.
9. Matthew Meselson and Frank Stahl "conducted what came to be known as the beautiful experiment in biology." Explain.
10. "What is true for *E.coli* is true for the elephant." Explain.
11. Describe three ways in which *E. coli* is much more complex than scientists like Monod initially believed.
12. "The first species whose metabolism scientists mapped in fine detail was *E.coli*. What does it mean to map a metabolism?
13. "As *E.coli* juggles iron, captures energy, and transforms sugar into complex molecules, it seems to defy the universe." What does Zimmer mean by this statement, i.e. what is being defied? How is the universe actually not being defied?
14. In what sense is *E.coli* a microcosm of life as a whole, and therefore microcosm a good title for a book about *E.coli*?
15. What are two amazing characteristics of *E.coli's* propulsion system?
16. What "few elegant rules" allow *E.coli* to navigate its world successfully?
17. What is the "The Myth of the Tangled Spaghetti?" Why is it mythical?
18. Bacteria like *E.coli* can multiply at an incredible exponential rate. Why hasn't *E.coli* taken over and covered the planet?

"Genes, Claustrum, and Consciousness"

1. What is V. S. Ramachandran's favorite elegant idea?
2. Ravichandran believes that strategy that led to cracking the genetic code, might fruitfully be applied to what other question?
3. Briefly summarize the chain of events that led up to elucidating the structure of DNA.
4. "Watson and Crick didn't just describe DNA's structure, they explained its significance." What is the significance of DNA's structure recognized by Watson and Crick?
5. What is a claustrum?
6. What is histology?
7. What does the claustrum have to do with consciousness?

"Boltzmann's Explanation of the Second Law of Thermodynamics"

1. What is the second law of thermodynamics?
2. How did Boltzmann explain (i.e. provide theoretical foundation) the second law?
3. What is the cosmological question Susskind and other cosmology are still unable to answer?

"A Gene for Nothing"

1. How have people known for a long time that cloning a human to produce two or more people with identical genomes wouldn't resulted in "one multibodied consciousness among the clones, a mind meld, an army of photocopies of the same soul?"
2. "For many, genes and the DNA that comprises genes represent the holy grail of biology, the code of codes...The worship at the altar of the gene rests on two assumptions." What are those two assumptions?
3. How is the first assumption mentioned in #2 mistaken?
4. How is the second assumption mentioned in #2 mistaken?
5. What, specifically, does a gene 'do?'
6. Sections of DNA that code for a protein (exons) are usually broken up by sections of non-protein-coding DNA (interons). What is one the roles of this non-coding DNA?
7. Use a specific example to describe the biochemical mechanism by which the expression of a particular gene by be regulated by factors in the environment.
8. Using your new knowledge of major histocompatibility proteins, provide a biochemical mechanism to actually answer the question, "How do rodents use smell to distinguish friends from strangers?"
9. What percentage of DNA is non-coding?
10. According to Sapolsky, what does the phrase 'survival of the fittest' really mean?
11. Instead utilizing the language of the misinformed, what would be a more accurate way of stating the idea behind 'genes determine behavior?'
12. Instead of claiming "evolution is mostly about natural selection for different assemblages of genes," what is a more accurate way of expressing what evolution really does?

Two

E. COLI AND THE ELEPHANT

"LUXURIOUS GROWTH"

***ESCHERICHIA COLI* HAS LURKED WITHIN** our ancestors for millions of years, before our ancestors were even human. It was not until 1885 that our species was formally introduced to its lodger. A German pediatrician named Theodor Escherich was isolating bacteria from the diapers of healthy babies when he noticed a rod-shaped microbe that could produce, in his words, a "massive, luxurious growth." It thrived on all manner of food—milk, potatoes, blood.

Working at the dawn of modern biology, Escherich could say little more about his new microbe. What took place within *E. coli*—the transformation of milk, potatoes, or blood into living matter—was mostly a mystery in the 1880s. Organisms were like biological furnaces, scientists agreed, burning food as fuel and creating heat, waste, and organic molecules. But they debated whether this transformation required a mysterious vital spark or was just a variation on the chemistry they could carry out themselves in their laboratories.

Bacteria were particularly mysterious in Escherich's day. They seemed fundamentally different from animals and other forms of multicellular life. A human cell, for example, is thousands of times larger than *E. coli*. It has a complicated inner geography dominated by a large sac known as the nucleus, inside of which are giant structures called chromosomes. In bacteria, on the other hand, scientists could find no nucleus, nor much of anything else. Bacteria seemed like tiny, featureless bags of goo that hovered at the boundary of life and nonlife.

Escherich, a forward-thinking pediatrician, accepted a radical new theory about bacteria: far from being passive goo, they infected people and caused diseases. As a pediatrician, Escherich was most concerned with

diarrhea, which he called "this most murderous of all intestinal disease." A horrifying number of infants died of diarrhea in nineteenth-century Germany, and doctors did not understand why. Escherich was convinced—rightly—that bacteria were killing the babies. It would be no simple matter to find those pathogens, however, because the guts of the healthiest babies were rife with bacteria. Escherich would have to sort out the harmless species of microbes before he could recognize the killers.

"It would appear to be a pointless and doubtful exercise to examine and disentangle the apparently randomly appearing bacteria," he wrote. But he tried anyway, and in that survey he came across a harmless-seeming resident we now call *E. coli*.

Escherich published a brief description of *E. coli* in a German medical journal, along with a little group portrait of rod-shaped microbes. His discovery earned no headlines. It was not etched on his gravestone when he died, in 1911. *E. coli* was merely one of a rapidly growing list of species of bacteria that scientists were discovering. Yet it would become Escherich's great legacy to science.

Its massive, luxurious growth would bloom in laboratories around the world. Scientists would run thousands of experiments to understand its growth—and thereby to understand the fundamental workings of life. Other species would also do their part in the rise of modern biology. Flies, watercress, vinegar worms, and bread mold all had their secrets to share. But the story of *E. coli* and the story of modern biology are extraordinarily intertwined. When scientists were at loggerheads over some basic question of life—what are genes made of? do all living things have genes?—it was often *E. coli* that served as the expert witness. By understanding how *E. coli* produced its luxurious growth—how it survived, fed, and reproduced—biologists went a great way toward understanding the workings of life itself. In 1969, when the biologist Max Delbrück accepted a Nobel Prize for his work on *E. coli* and its viruses, he declared, "We may say in plain words, 'This riddle of life has been solved.' "

THE UNITY OF LIFE

Escherich originally dubbed his bacteria *Bacterium coli communis:* a common bacterium of the colon. In 1918, seven years after Escherich's death,

scientists renamed it in his honor. By the time it got a new name, it had taken on a new life. Microbiologists were beginning to rear it by the billions in their laboratories.

In the early 1900s, many scientists were pulling cells apart to see what they were made of, to figure out how they turned raw material into living matter. Some scientists studied cells from cow muscles, others sperm from salmon. Many studied bacteria, including *E. coli*. In all of the living things they dissected, scientists discovered the same basic collection of molecules. They focused much of their attention on proteins. Some proteins give life its structure—the collagen in skin, the keratin in a horse's hoof. Other proteins, known as enzymes, usher other molecules into chemical reactions. Some enzymes split atoms off molecules, and others weld molecules together.

Proteins come in a maddening diversity of complicated shapes, but scientists discovered that they also share an underlying unity. Whether from humans or bacteria, proteins are all made from the same building blocks: twenty small molecules known as amino acids. And these proteins work in bacteria much as they do in humans. Scientists were surprised to find that the same series of enzymes often carry out the same chemical reactions in every species.

"From the elephant to butyric acid bacterium—it is all the same!" the Dutch biochemist Albert Jan Kluyver declared in 1926.

The biochemistry of life might be the same, but for scientists in the early 1900s, huge differences seemed to remain. The biggest of all was heredity. In the early 1900s, geneticists began to uncover the laws by which animals, plants, and fungi pass down their genes to their offspring. But bacteria such as *E. coli* didn't seem to play by the same rules. They did not even seem to have genes at all.

Much of what geneticists knew about heredity came from a laboratory filled with flies and rotten bananas. Thomas Hunt Morgan, a biologist at Columbia University, bred the fly *Drosophila melanogaster* to see how the traits of parents are passed on to their offspring. Morgan called the factors that control the traits genes, although he had no idea what genes actually were. He did know that mothers and fathers both contributed copies of genes to their offspring and that sometimes a gene could fail to produce a trait in one generation only to make it in the next. He could breed a red-eyed fly with a white-eyed one and get a new generation of flies with only

red eyes. But if he bred those hybrid flies with each other, the eyes of some of the grandchildren were white.

Morgan and his students searched for molecules in the cells of *Drosophila* that might have something to do with genes. They settled on the fly's chromosomes, those strange structures inside the nucleus. When chromosomes are given a special stain, they look like crumpled striped socks. The stripes on *Drosophila* chromosomes, Morgan and his students discovered, are as distinctive as bar codes. Chromosomes mostly come in pairs, one inherited from each parent. And by comparing their stripes, Morgan and his students demonstrated that chromosomes can change from one generation to the next. As a fly's sex cells develop, each pair of chromosomes embrace and swap segments. The segments a fly inherited determined which genes it carried.

There was something almost mathematically abstract about these findings. George Beadle, one of Morgan's graduate students, decided to bring genes down to earth by figuring out exactly how they controlled a single trait, such as eye color. Working with the biochemist Edward Tatum, Beadle tried to trace cause and effect from a fly's genes to the molecules that make up the pigment in its eyes. But that experiment soon proved miserably complex. Beadle and Tatum abandoned flies for a simpler species: the bread mold *Neurospora crassa*.

Bread mold may not have obvious traits such as eyes and wings, but it does produce many enzymes, some of which build amino acids. To see how the mold's genes control those enzymes, Beadle and Tatum bombarded it with X-rays. They knew that when fly larvae are exposed to X-rays, the radiation mutates some of their genes. The mutations produce new traits—extra leg bristles or a different eye color—which mutant flies can pass down to their offspring.

Beadle and Tatum now created bread mold mutants. Some were unable to produce certain types of amino acids because they now lacked a key enzyme. But if Beadle and Tatum mated the mutant bread mold with a normal one, some of their offspring could make the amino acid once more. Beadle and Tatum concluded in 1941 that behind each enzyme in bread mold there is one gene.

A hazy but consistent picture of genes was emerging—at least a picture of the genes of animals, plants, and fungi. But there didn't seem to be a place for bacteria in the picture. The best evidence for genes came from

chromosomes, and bacteria seemed to have no chromosomes at all. Even if bacteria did have genes, scientists had little hope of finding them. Scientists could study a fly's genes thanks to the fact that flies reproduce sexually. A fly's chromosomes get cut up and shuffled in different combinations in its offspring. Scientists could not run this sort of experiment on bacteria, because bacteria did not have sex. They seemed to just grow and then split in two. Many researchers looked at bacteria as simply loose bags of enzymes—a fundamentally different kind of life.

It would turn out, however, that all life, bacteria included, shares the same foundation. *E. coli* would reveal much of that unity, and in the process it would become one of the most powerful tools biologists could use to understand life.

The transformation started with a simple question. Edward Tatum wondered if the one-gene, one-enzyme rule he discovered in mold applied to bacteria. He decided to run the mold experiment again, this time directing his X-rays at bacteria. For his experiment, Tatum chose a strain of *E. coli* called K-12. It had been isolated in 1922 from a California man who suffered from diphtheria, and it had been kept alive ever since at Stanford University, where it was used for microbiology classes.

Tatum's choice was practical. Like most strains of *E. coli*, K-12 is harmless. *E. coli* is also versatile enough to build all of its own amino acids and many other molecules. For food, it needs little more than sugar, ammonia, and some trace minerals. If *E. coli* used a lot of enzymes to turn this food into living matter, Tatum would have plenty of targets for his X-rays. He might succeed in creating only a few mutants of the sort he was looking for, but thanks to *E. coli*'s luxurious growth he'd be able to see them. A single mutant could give rise to a visible colony in a day.

Tatum pelted colonies of *E. coli* with enough X-rays to kill 9,999 of every 10,000 bacteria. Among the few survivors he discovered mutants that could grow only if he supplied them with a particular amino acid. Helped along, the mutants could even reproduce, and their offspring were just as crippled. Tatum had gotten the same results as he had with bread mold. It looked as if behind every enzyme in *E. coli* lurked a gene.

It was a profound discovery, but Tatum remained cautious about its significance. It now seemed that bacteria had genes, but he could not say for sure. The best way to prove that a species had genes was to breed males and females and study their offspring. But *E. coli* seemed sadly celibate.

"The term 'gene' can therefore be used in connection with bacteria only in a general sense," Tatum wrote.

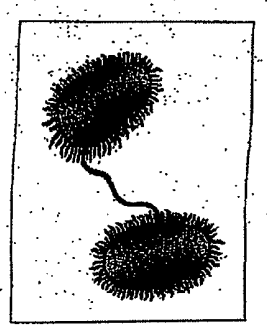
The connection became far stronger when a somber young student arrived at Tatum's lab at Yale. Joshua Lederberg was only twenty-one years old when he began to work with Tatum, but he had a grand ambition: to find out whether bacteria had sex. As part of his military service during World War II, Lederberg had spent time in a naval hospital on Long Island, where he examined malaria parasites from marines fighting in the Pacific. He had gazed down at the single-celled protozoans, which sometimes reproduced by dividing and sometimes by taking male and female forms and mating. Perhaps bacteria had this sort of occasional sex, and no one had noticed. Others might mock the idea as a fantasy, but Lederberg decided to take what he later called "the long-shot gamble in looking for bacterial sex."

When Lederberg heard about Tatum's work, he realized he could look for bacterial sex with a variation on Tatum's experiments. Tatum was amassing a collection of mutant *E. coli* K-12, including double mutants—bacteria that had to be fed two compounds to survive. Lederberg reasoned that if he mixed two different double mutants together, they might be able to pick up working versions of their genes through sex.

Lederberg started work at Yale in 1946. He selected a mutant strain that could make neither the amino acid methionine nor biotin, a B vitamin. The other strain he picked couldn't make the amino acids threonine and proline. Lederberg put the bacteria in a broth he stocked with all four compounds so that the mutant microbes could grow and multiply. They mingled in the broth for a few weeks, with plenty of opportunity for hypothetical sex.

Lederberg drew out samples of the bacteria and put them on fresh petri dishes. Now he withheld the four nutrients they could not make themselves: threonine, proline, methionine, and biotin. Neither of the original mutant strains could grow in the dishes. If their descendants were simply copies of their ancestors, Lederberg reasoned, they would stop growing as well.

But after weeks of frustration—of ruined plates, of dead colonies—Lederberg finally saw *E. coli* spreading across his dishes. A few microbes had acquired the ability to make all four amino acids. Lederberg concluded that their ancestors must have combined their genes in something



Two *E. coli* having bacterial sex

akin to sex. And in their sex they proved that they carried genes.

In the years that followed, the discovery would allow scientists to breed *E. coli* like flies and to probe genes far more intimately than ever before. Twelve years later, at the ancient age of thirty-three, Lederberg would share the Nobel Prize in Medicine with Tatum and Beadle. But in 1946, when he picked up his petri dishes and noticed the spots that appeared to be the sexual colonies he had dreamed of, Lederberg allowed himself just a single word alongside the results in his notebook: "*Hooray.*"

HOST AND PARASITE

While Lederberg was observing *E. coli* having sex, other scientists were observing it getting sick. And they were learning things that were just as important about the nature of life.

The first scientist to appreciate just how revealing a sick *E. coli* could be was not a biologist but a physicist. Max Delbrück had originally studied under Niels Bohr and the other pioneers of quantum physics. In the 1930s it seemed as if a few graceful equations could melt away many of the great mysteries of the universe. But life would not submit. Physicists like Delbrück were baffled by life's ability to store away all of the genes necessary to build a kangaroo or a liverwort in a single cell. Delbrück decided to make life—and in particular, life's genes—his study.

"The gene," Delbrück proposed, "is a polymer that arises by the repetition of identical atomic structures." To discover the laws of that polymer, he came to the United States, joining Morgan's laboratory to breed flies. But the physicist in Delbrück despised the messy quirks of *Drosophila*. He craved another system that could provide him with far more data and was far simpler. As luck would have it, another member of Morgan's lab, Emory Ellis, was studying the perfect one: the viruses that infect *E. coli*.

The viruses that infect *E. coli* were too small for Delbrück and Ellis

to see. As best anyone could tell, they infected their bacterial hosts and reproduced inside, killing the microbes and wandering off to find new victims. The new viruses seemed identical to the old, which suggested that they might carry genes. Delbrück and Ellis set out to chart the natural history of *E. coli*'s viruses.

To study the viruses—known as bacteriophages—Delbrück and Ellis could look only for indirect clues. If they added viruses to a dish of *E. coli*, the viruses invaded the bacteria and replicated inside them. The new viruses left behind the shattered remains of their hosts and infected new ones. Over a few hours spots formed on the dish where their victims formed transparent pools of carnage. "Bacterial viruses make themselves known by the bacteria they destroy," Delbrück said, "as a small boy announces his presence when a piece of cake disappears."

Although the signs of the viruses were indirect, there were a lot of them. Billions of new viruses could appear in a dish in a few hours. The power of Delbrück and Ellis's system attracted a small flock of young scientists. They called themselves the Phage Church, and Delbrück was their pope. The Phage Church demonstrated that *E. coli*'s bacteriophages were not all alike. Some could infect certain *E. coli* strains but not others. By triggering mutations in the viruses, the scientists could cause the viruses to infect new strains. The ability to infect *E. coli* passed down from virus to virus. Viruses, it became clear, had genes—genes that must be very much like those of their host, *E. coli*.

The genes of host and parasite are so similar, in fact, that scientists discovered certain kinds of viruses that could merge into *E. coli*, blurring their identities. These prophages, as they are called, can invade *E. coli* and then disappear. A prophage's hosts behave normally, growing and dividing like their virus-free neighbors. Yet scientists found that the prophages survived within *E. coli*, which passed them down from one generation to the next. To rouse a prophage, the scientists needed only to expose a dish of infected *E. coli* to a flash of ultraviolet light. The bacteria abruptly burst open with hundreds of new prophages, which began to infect new hosts, leaving behind the clear pools of destruction. Two had become one, only to become two again.

THE STUFF OF GENES

In the merging dance of *E. coli* and its viruses, the Phage Church discovered clues to some of life's great questions. And for them there was no greater question than what genes are made of.

Until the 1950s, most scientists suspected that proteins were the stuff of genes. They had no direct evidence but many powerful hints. Genes exist in all living things, even bacteria and viruses, and proteins appeared to be in all of them as well. Scientists studying flies had located genes in the chromosomes, and chromosomes contain proteins. Scientists also assumed that the molecules from which genes are made had to be complicated, since genes somehow gave rise to all the complexity of life. Proteins, scientists knew, often are staggeringly intricate. All that remained was to figure out how proteins actually function as genes.

The first major challenge to this vague consensus came in 1944, when a physician announced that genes are not in fact made of protein. Oswald Avery, who worked at the Rockefeller Institute in New York, studied the bacteria *Pneumococcus*. It comes in both a harmless form and a dangerous one that can cause pneumonia. Earlier experiments had hinted that genes control the behaviors of the different strains. If scientists killed the dangerous strain before injecting it into mice, it did not make the mice sick. But if the dead strain was mixed with living harmless *Pneumococcus*, an injection killed the mice. The harmless strain had been transformed into pathogens, and their descendants remained deadly. In other words, genetic material had moved from the dead strain to the live one.

Avery and his colleagues isolated compound after compound from the deadly strain and added each one to the harmless strain. Only one molecule, they found, could make the harmless strain deadly. It was not a protein. It was something called deoxyribonucleic acid, DNA for short.

Scientists had known of DNA for decades but didn't know what to make of it. In 1869, a Swiss biochemist named Johann Miescher had discovered a phosphorus-rich goo in the pus on the bandages of wounded soldiers. The goo came to be known as nucleic acid, which scientists later discovered comes in two nearly identical forms: ribonucleic acid (RNA) and deoxyribonucleic acid. The phosphorus in DNA helps form a backbone, along with oxygen and sugar. Connected to this backbone are four kinds of compounds, known as bases, rich in carbon and nitrogen.

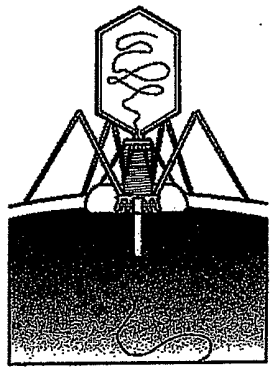
DNA was clearly important to life, because scientists could find it in just about every kind of cell they looked at. It could even be found in fly chromosomes, where genes were known to reside. But many researchers thought DNA simply offered some kind of physical support for chromosomes—it might wind around genes like cuffs. Few thought DNA had enough complexity to be the material of genes. DNA was, as Delbrück once put it, "so *stupid* a substance."

Stupid or not, DNA is what genes are made of, Avery concluded. But his experiments failed to win over hardened skeptics, who wondered if his purified DNA had actually been contaminated by some proteins.

It would take another decade of research on *E. coli* and its viruses to start to redeem DNA's reputation. While Avery was sifting *Pneumococcus* for genes, Delbrück's Phage Church was learning how to see *E. coli*'s viruses. The viruses were no longer mathematical abstractions but hard little creatures. Using the newly invented electron microscope, Delbrück and his colleagues discovered that bacteriophages are elegantly geometrical shells. After a phage lands on *E. coli*, it sticks a needle into the microbe and injects something into its new host. The shell remains sitting on *E. coli*'s surface, an empty husk, while the virus's genes enter the microbe.

The life cycle of *E. coli*'s viruses opened up the chance to run an elegantly simple experiment. Alfred Hershey and Martha Chase, two scientists at the Cold Spring Harbor Laboratory on Long Island, created viruses with radioactive tracers in their DNA. They allowed the viruses to infect *E. coli* and then pulled off their empty husks in a fast-spinning centrifuge. Hershey and Avery searched for radioactivity and found it only within the bacteria, not the virus shells.

Hershey and Chase then reversed the experiment, spiking the protein in the viruses with radioactive tracers. Once the viruses had infected *E. coli*, only the empty shells were radioactive. A



A virus inserts its DNA into *E. coli*.

decade after Avery's experiment, Hershey and Chase confirmed his conclusion: genes are made of DNA.

No one was more excited by the new results than a young American biologist named James Watson. Watson was only twenty when he was initiated into the Phage Church, blasting *E. coli*'s viruses with X-rays for his dissertation work. He was taught the conventional view that genes are made of proteins, but his own research was drawing his attention to DNA. He saw Hershey and Chase's experiment as "a powerful new proof that DNA is the primary genetic material."

In order to understand how DNA acts as genetic material, however, it was necessary to figure out its structure. Watson was working at the time at the University of Cambridge, where he quickly teamed up with Francis Crick, a British physicist who also wanted to understand the secret of life. Together they pored over clues about DNA and tinkered with arrangements of phosphates, sugars, and bases. In February 1953, they suddenly figured out its shape. They assembled a towering model of steel plates and rods. It was a twisted ladder of sugar and phosphates, with bases for rungs.

The structure was beautiful, simple, and eloquent. It seemed to practically speak for itself about how genes work. Each phosphate strand is studded with billions of bases, arrayed in a line like a string of text. The text can have an infinite number of meanings, depending on how the bases are arranged. By this means, DNA stores the information necessary for building any protein in any species.

The structure of DNA also suggested to Watson and Crick how it could be reproduced. They envisioned the strands being pulled apart, and a new strand being added to each. Building a new DNA strand would be simplified by the fact that each kind of base can bond to only one other kind. As a result, the new strands would be perfect counterparts.

It was a beautiful idea, but it didn't have much hard evidence going for it. Max Delbrück worried about what he called "the untwiddling problem." Could a double helix be teased apart and transformed into two new DNA molecules without creating a tangled mess? Delbrück tried to answer the question but failed. Success finally came in 1957, to a graduate student and a postdoc at Caltech, Matthew Meselson and Frank Stahl. With the help of *E. coli*, they conducted what came to be known as the most beautiful experiment in biology.

Meselson and Stahl realized that they could trace the replication of

DNA by raising *E. coli* on a special diet. *E. coli* needs nitrogen to grow, because the element is part of every base of DNA. Normal nitrogen contains fourteen protons and fourteen neutrons, but lighter and heavier forms of nitrogen also exist, with fewer or more neutrons. Meselson and Stahl fed *E. coli* ammonia laced with heavy nitrogen in which each atom carried a fifteenth neutron. After the bacteria had reproduced for many generations, they extracted some DNA and spun it in a centrifuge. By measuring how far the DNA moved as it was spun, they could calculate its weight. They could see that the DNA from *E. coli* raised on heavy nitrogen was, as they had expected, heavier than DNA from normal *E. coli*.

Meselson and Stahl then ran a second version of the experiment. They moved some of the heavy-nitrogen *E. coli* into a flask where they could feed on normal nitrogen, with only fourteen neutrons apiece. The bacteria had just enough time to divide once before Meselson and Stahl tossed their DNA in the centrifuge. If Watson and Crick were right about how DNA reproduced, Meselson and Stahl knew what to expect. Inside each microbe, the heavy strands would have been pulled apart, and new strands made from light nitrogen would have been added to them. The DNA in the new generation of *E. coli* would be half heavy, half light. It should form a band halfway between where the light and heavy forms did. And that was precisely what Meselson and Stahl saw.

Watson and Crick might have built a beautiful model. But it took a beautiful experiment on *E. coli* for other scientists to believe it was also true.

A UNIVERSAL CODE

The discovery of *E. coli*'s sex life gave scientists a way to dissect a chromosome. It turned out that *E. coli* has a peculiar sort of sex, with one microbe casting out a kind of molecular grappling hook to reel in a partner. Its DNA moves into the other microbe over the course of an hour and a half. Élie Wollman and François Jacob, both at the Pasteur Institute in Paris, realized that they could break off this liaison. They mixed mutants together and let them mate for a short time before throwing them into a blender. Depending on how long the bacteria were allowed to mate, the recipient might or might not get a gene it needed to survive. By timing how long it took various genes to enter *E. coli*, Wollman and Jacob could

create a genetic map. It turned out that *E. coli*'s genes are arrayed on a chromosome shaped in a circle.

Scientists also discovered that along with its main chromosome *E. coli* carries extra ringlets of DNA, called plasmids. Plasmids carry genes of their own, some of which they use to replicate themselves. Some plasmids also carry genes that allow them to move from one microbe to another. *E. coli* K-12's grappling hooks, for example, are encoded by genes on plasmids. Once the microbes are joined, a copy of the plasmid's DNA is exchanged, along with some of the chromosome itself.

As some scientists mapped *E. coli*'s genes, others tried to figure out how their codes are turned into proteins. At the Carnegie Institution in Washington, D.C., researchers fed *E. coli* radioactive amino acids, the building blocks of proteins. The amino acids ended up clustered around pellet-shaped structures scattered around the microbe, known as ribosomes. Loose amino acids went into the ribosomes, and full-fledged proteins came out. Somehow the instructions from *E. coli*'s DNA had to get to the ribosomes to tell them what proteins to make.

It turned out that *E. coli* makes special messenger molecules for the job. The first step in making a protein requires an enzyme to clamp on to a gene and crawl along its length. It builds a single-stranded version of the gene from RNA. This RNA can then move to a ribosome, delivering its genetic message.

How a ribosome reads that message was far from clear, though. RNA, like DNA, is made of four different bases. Proteins are combinations of twenty amino acids. *E. coli* needs some kind of dictionary to translate instructions written in the language of genes into the language of proteins.

In 1957, Francis Crick drafted what he imagined the dictionary might look like. Each amino acid was encoded by a string of three bases, known as a codon. Marshall Nirenberg and Heinrich Matthaei, two scientists at the National Institutes of Health, soon began an experiment to see if Crick's dictionary was accurate. They ground up *E. coli* with a mortar and pestle and poured its innards into a series of test tubes. To each test tube they added a different type of amino acid. Then Nirenberg and Matthaei added the same codon to each tube: three copies of uracil (a base found in RNA but not in DNA). They waited to see if the codon would recognize one of the amino acids.

In nineteen tubes nothing happened. The twentieth tube was filled with the amino acid phenylalanine, and only in that tube did new proteins

form. Nirenberg and Matthaei had discovered the first entry in life's dictionary: UUU equals phenylalanine. Over the next few years they and other scientists would decipher *E. coli*'s entire genetic code.

Having deciphered the genetic code of a species for the first time, Nirenberg and his colleagues then compared *E. coli* to animals. They filled test tubes with the crushed cells of frogs and guinea pigs, and added codons of RNA to them. Both frogs and guinea pigs followed the same recipe for building proteins as *E. coli* had. In 1967, Nirenberg and his colleagues announced they had found "an essentially universal code."

Nirenberg would share a Nobel Prize for Medicine the following year. Delbrück got his the year after. Lederberg, Tatum, and many others who worked on *E. coli* were also summoned to Stockholm. A humble resident of the gut had led them to glory and to a new kind of science, known as molecular biology, that unified all of life. Jacques Monod, another of *E. coli*'s Nobelists, gave Albert Kluyver's old claim a new twist, one that many scientists still repeat today.

"What is true for *E. coli* is true for the elephant."

THE SHAPE OF LIFE

With the birth of molecular biology, genes came to define what it means to be alive. In 2000, President Bill Clinton announced that scientists had completed a rough draft of the human genome—the entire sequence of humans' DNA. He declared, "Today, we are learning the language in which God created life."

But on their own, genes are dead, their instructions meaningless. If you coax the chromosome out of *E. coli*, it cannot build proteins by itself. It will not feed. It will not reproduce. The fragile loop of DNA will simply fall apart. Understanding an organism's genes is only the first step in understanding what it means for the organism to be alive.

Many biologists have spent their careers understanding what it means for *E. coli* in particular to be alive. Rather than starting from scratch with another species, they have built on the work of earlier generations. Success has bred more success. In 1997, scientists published a map of *E. coli*'s K-12's entire genome, including the location of 4,288 genes. The collective knowledge about *E. coli* makes it relatively simple for a scientist to create a mutant missing any one of those genes and then to learn from its behav-

ior what that gene is for. Scientists now have a good idea of what all but about 600 genes in *E. coli* are for. From the hundreds of thousands of papers scientists have published on *E. coli* comes a portrait of a living thing governed by rules that often apply, in one form or another, to all life. When Jacques Monod boasted of *E. coli* and the elephant, he was speaking only of genes and proteins. But *E. coli* turns out to be far more complex—and far more like us—than Monod's generation of scientists realized.

The most obvious thing one notices about *E. coli* is that one can notice *E. coli* at all. It is not a hazy cloud of molecules. It is a densely stuffed package with an inside and an outside. Life's boundaries take many forms. Humans are wrapped in soft skin, crabs in a hard exoskeleton. Redwoods grow bark, squid a rubbery sheet. *E. coli*'s boundary is just a few hundred atoms thick, but it is by no means simple. It is actually a series of layers within layers, each with its own subtle structure and complicated jobs to carry out.

E. coli's outermost layer is a capsule of sugar teased like threads of cotton candy. Scientists suspect it serves to frustrate viruses trying to latch on and perhaps to ward off attacks from our immune system. Below the sugar lies a pair of membranes, one nested in the other. The membranes block big molecules from entering *E. coli* and keep the microbe's molecules from getting out. *E. coli* depends on those molecules reacting with one another in a constant flurry. Keeping its 60 million molecules packed together lets those reactions take place quickly. Without a barrier, the molecules would wander away from one another, and *E. coli* would no longer exist.

At the same time, though, life needs a connection to the outside world. An organism must draw in new raw materials to grow, and it must flush out its poisonous waste. If it can't, it becomes a coffin. *E. coli*'s solution is to build hundreds of thousands of pores, channels, and pumps on the outer membrane. Each opening has a shape that allows only certain molecules through. Some swing open for their particular molecule, as if by password.

Once a molecule makes its way through the outer membrane, it is only half done with its journey. Between the outer and inner membranes of *E. coli* is a thin cushion of fluid, called the periplasm. The periplasm is loaded with enzymes that can disable dangerous molecules before they are able to pass through the inner membrane. They can also break down valuable molecules so that they can fit in channels embedded in the inner membrane. Meanwhile, *E. coli* can truck its waste out through other channels. Matter flows in and out of *E. coli*, but rather than making a random, lethal surge, it flows in a selective stream.

E. coli has a clever solution to one of the universal problems of life. Yet solutions have a way of creating problems of their own. *E. coli*'s barriers leave the microbe forever on the verge of exploding. Water molecules are small enough to slip in and out of its membranes. But there's not much room for water molecules inside *E. coli*, thanks to all the proteins and other big molecules. So at any moment more water molecules are trying to get into the microbe than are trying to get out. The force of this incoming water creates an enormous pressure inside *E. coli*, several times higher than the pressure of the atmosphere. Even a small hole is big enough to make *E. coli* explode. If you prick us, we bleed, but if you prick *E. coli*, it blasts.

One way *E. coli* defends against its self-imposed pressure is with a corset. It creates an interlocking set of molecules that form a mesh that floats between the inner and outer membranes. The corset (known as the peptidoglycan layer) has the strength to withstand the force of the incoming water. *E. coli* also dispatches a small army of enzymes to the membranes to repair any molecules damaged by acid, radiation, or other abuse. In order to grow, it must continually rebuild its membranes and peptidoglycan layer, carefully inserting new molecules without ever leaving a gap for even a moment.

E. coli's quandary is one we face as well. Our own cells carefully regulate the flow of matter through their walls. Our bodies use skin as a barrier, which must also be pierced with holes—for sweat glands, ear canals, and so on. Damaged old skin cells slough off as the underlying ones grow and divide. So do the cells of the lining of our digestive tract, which is essentially just an interior skin. This quick turnover allows our barriers to heal quickly and fend off infection. But it also creates its own danger. Each time a cell divides, it runs a small risk of mutating and turning cancerous. It's not surprising, then, that skin cancer and colon cancer are among the most common forms of the disease. Humans and *E. coli* alike must pay a price to avoid becoming a blur.

THE RIVER THAT RUNS UPHILL

Barriers and genes are essential to life, but life cannot survive with barriers and genes alone. Put DNA in a membrane, and you create nothing

more than a dead bubble. Life also needs a way to draw in molecules and energy, to transform them into more of itself. It needs a metabolism.

Metabolisms are made up of hundreds of chemical reactions. Each reaction may be relatively simple: an enzyme may do nothing more than pull a hydrogen atom off a molecule, for instance. But that molecule is then ready to be grabbed by another enzyme that will rework it in another way, and so on through a chain of reactions that can become hideously intricate—merging with other chains, branching in two, or looping back in a circle. The first species whose metabolism scientists mapped in fine detail was *E. coli*.

It took them the better part of the twentieth century. To uncover its pathways, they manipulated it in many ways, such as feeding it radioactive food so that they could trace atoms as *E. coli* passed them from molecule to molecule. It was slow, tough, unglamorous work. After James Watson and Francis Crick discovered the structure of DNA, their photograph appeared in *Life* magazine: two scientists flanking a tall, bare sculpture. There was no picture of the scientists who collectively mapped *E. coli*'s metabolism. It would have been a bad photograph anyway: hundreds of people packed around a diagram crisscrossed with so many arrows that it looked vaguely like a cat's hairball. But for those who know how to read that diagram, *E. coli*'s metabolism has a hidden elegance.

The chemical reactions that make up *E. coli*'s metabolism don't happen spontaneously, just as an egg does not boil itself. It takes energy to join atoms together, as well as to break them apart. *E. coli* gets its energy in two ways. One is by turning its membranes into a battery. The other is by capturing the energy in its food.

Among the channels that decorate *E. coli*'s membranes are pumps that hurl positively charged protons out of the microbe. *E. coli* gives itself a negative charge in the process, attracting positively charged atoms that happen to be in its neighborhood. It draws some of them into special channels that can capture energy from their movement, like an electric version of a waterwheel. *E. coli* stores that energy in the atomic bonds of a molecule called adenosine triphosphate, or ATP.

ATP molecules float through *E. coli* like portable energy packs. When *E. coli*'s enzymes need extra energy to drive a reaction, they grab ATP and draw out the energy stored in the bonds between its atoms. *E. coli* uses the energy it gets from its membrane battery to get more energy from its

food. With the help of ATP, its enzymes can break down sugar, cutting its bonds and storing the energy in still more ATP. It does not unleash all the energy in a sugar molecule at once. If it did, most of that energy would be lost in heat. Rather than burning up a bonfire of sugar, *E. coli* makes surgical nicks, step by step, in order to release manageable bursts of energy.

E. coli uses some of this energy to build new molecules. Along with the sugar it breaks down, it also needs a few minerals. But it has to work hard to get even the trace amounts it requires. *E. coli* needs iron to live, for example, but iron is exquisitely scarce. In a living host most iron is tucked away inside cells. What little there is outside the cells is usually bound up in other molecules, which will not surrender it easily. *E. coli* has to fight for iron by building iron-stealing molecules, called siderophores, and pumping them out into its surroundings. As the siderophores drift along, they sometimes bump into iron-bearing molecules. When they do, they pry away the iron atom and then slide back into *E. coli*. Once inside, the siderophores unfold to release their treasure.

While iron is essential to *E. coli*, it's also a poison. Once inside the microbe, a free iron atom can seize oxygen atoms from water molecules, turning them into hydrogen peroxide, which in turn will attack *E. coli*'s DNA. *E. coli* defends itself with proteins that scoop up iron as soon as it arrives and store it away in deep pockets. A single one of these proteins can safely hold 5,000 iron atoms, which it carefully dispenses, one atom at a time, as the microbe needs them.

Iron is not the only danger *E. coli*'s metabolism poses to itself. Even the proteins it builds can become poisonous. Acid, radiation, and other sorts of damage can deform proteins, causing them to stop working as they should. The mangled proteins wreak havoc, jamming the smooth assembly line of chemistry *E. coli* depends on for survival. They can even attack other proteins. *E. coli* protects itself from itself by building a team of assassins—proteins whose sole function is to destroy old proteins. Once an old protein has been minced into amino acids, it becomes a supply of raw ingredients for new proteins. Life and death, food and poison—all teeter together on a delicate fulcrum inside *E. coli*.

As *E. coli* juggles iron, captures energy, and transforms sugar into complex molecules, it seems to defy the universe. There's a powerful drive throughout the universe, known as entropy, that pushes order toward disorder. Elegant snowflakes melt into drops of water. Teacups shatter. *E. coli*

seems to push against the universe, assembling atoms into intricate proteins and genes and preserving that orderliness from one generation to the next. It's like a river that flows uphill.

E. coli is not really so defiant. It is not sealed off from the rest of the universe. It does indeed reduce its own entropy, but only by consuming energy it gets from outside. And while *E. coli* increases its own internal order, it adds to the entropy of the universe with its heat and waste. On balance, *E. coli* actually increases entropy, but it manages to bob on the rising tide.

E. coli's metabolism is something of a microcosm of life as a whole. Most living things ultimately get their energy from the sun. Plants and photosynthetic microbes capture light and use its energy to grow. Other species eat the photosynthesizers, and still other species eat them in turn. *E. coli* sits relatively high up in this food web, feeding on the sugars made by mammals and birds. It gets eaten in turn, its molecules transformed into predatory bacteria or viruses, which get eaten as well. This flow of energy gives rise to forests and other ecosystems, all of which unload their entropy on the rest of the universe. Sunlight strikes the planet, heat rises from it, and a planet full of life—an *E. coli* for the Earth—sustains itself on the flow.

A SENSE OF WHERE YOU ARE

Life's list grows longer. It stores information in genes. It needs barriers to stay alive. It captures energy and food to build new living matter. But if life cannot find that food, it will not survive for long. Living things need to move—to fly, squirm, drift, send tendrils up gutter spouts. And to make sure they're going in the right direction, most living things have to decide where to go.

We humans use 100 billion neurons bundled in our heads to make that decision. Our senses funnel rivers of information to the brain, and it responds with signals that control the movements of our bodies. *E. coli*, on the other hand, has no brain. It has no nervous system. It is, in fact, thousands of times smaller than a single human nerve cell. And yet it is not oblivious to its world. It can harvest information and manufacture decisions, such as where it should go next.

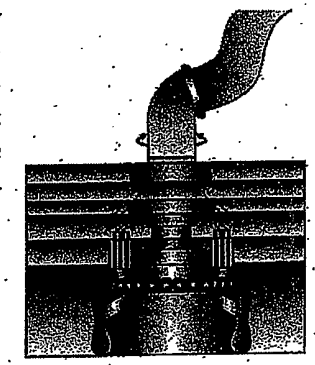
E. coli swims like a spastic submarine. Along the sides of its cigar-shaped body it sprouts about half a dozen propellers. They're shaped like whips, trailing far behind the microbe. Each tail (or, as microbiologists call it, flagellum) has a flexible hook at its base, which is anchored to a motor. The motor, a wheel-shaped cluster of proteins, can spin 250 times a second, powered by protons that flow through its pores into the microbe's interior.

Most of the time, *E. coli*'s motors turn counterclockwise, and when they do their flagella all bundle together into a cable. They behave so neatly because each flagellum is slightly twisted in the same direction, like the ribbons on a barber's pole. The cable of flagella spin together, pushing against the surrounding fluid in the process, driving the microbe forward.

E. coli can swim ten times its body length in a second. The fastest human swimmers can move only two body lengths in that time. And *E. coli* wins this race with a handicap, because the physics of water is different for microbes than for large animals like us. For *E. coli*, water is as viscous as mineral oil. When it stops swimming, it comes to a halt in a millionth of a second. *E. coli* does not stop on a dime. It stops on an atom.

About every second or so, *E. coli* throws its motors in reverse and hurls itself into a tumble. When its motors spin clockwise, the flagella can no longer slide comfortably over one another. Now their twists cause them to push apart; their neat braid flies out in all directions. It now looks more like a fright wig than a barber's pole. The tumble lasts only a tenth of a second as *E. coli* turns its motors counterclockwise once more. The flagella fold together again, and the microbe swims off.

The first scientist to get a good look at how *E. coli* swims was Howard Berg, a Harvard biophysicist. In the early 1970s, Berg built a microscope that could follow a single *E. coli* as it traveled around a drop of water. Each tumble left *E. coli* pointing in a new random direction.



E. coli's flagellum is driven by motorlike proteins that spin in its membrane.

Berg drew a single microbe's path over the course of a few minutes and ended up with a tangle, like a ball of yarn in zero gravity. For all its busy swimming, Berg found, *E. coli* manages to wander only within a tiny space, getting nowhere fast.

Offer *E. coli* a taste of something interesting, however, and it will give chase. *E. coli*'s ability to navigate is remarkable when you consider how little it has to work with. It cannot wheel and bank a pair of wings. All it can do is swim in a straight line or tumble. And it can get very little information about its surroundings. It cannot consult an atlas. It can only sense the molecules it happens to bump into in its wanderings. But *E. coli* makes good use of what little it has. With a few elegant rules, it gets where it needs to go.

E. coli builds sensors and inserts them in its membranes so that their outer ends reach up like periscopes. Several thousand sensors cluster together at the microbe's front tip, where they act like a microbial tongue. They come in five types, each able to grab certain kinds of molecules. Some types attract *E. coli*, and some repel it. An attractive molecule, such as the amino acid serine, sets in motion a series of chemical reactions inside the microbe with a simple result: *E. coli* swims longer between its tumbles. It will keep swimming in longer runs as long as it senses that the concentration of serine is rising. If its tumbles send it away from the source of serine, its swims become shorter. This bias is enough to direct *E. coli* slowly but reliably toward the serine. Once it gets to the source, it stays there by switching back to its aimless wandering.

Scientists began piecing together *E. coli*'s system of sensing and swimming in the 1960s. They chose *E. coli*'s system because they thought it would be easy. They could take advantage of the long tradition of using mutant *E. coli* to study how proteins work. And once they had solved *E. coli*'s information processors, they would be able to take what they had learned and apply it to more complex processors, including our own brains. Forty years later they understand *E. coli*'s signaling system more thoroughly than that of any other species. Some parts of *E. coli*'s system turned out to be simple after all. *E. coli* does not have to compute barrel rolls or spiral dives. Its swim-and-tumble strategy works very well. Every *E. coli* may not get exactly where it needs to go, but many of them will. They will be able to survive and reproduce and pass the run-and-tumble strategy on to their offspring. That is all the success a microbe needs.

Yet in some important ways, *E. coli*'s navigation defies understanding. Its microbial tongue can detect astonishingly tiny changes in the concentration of molecules it cares about, down to one part in a thousand. The microbe is able to amplify these faint signals in a way that scientists have not yet discovered. It's possible that *E. coli*'s receptors are working together. As one receptor twists, it causes neighboring receptors to twist as well. *E. coli* may even be able to integrate different kinds of information at the same time—oxygen climbing, nickel falling, glucose wafting by. Its array of receptors may turn out to be far more than just a microbial tongue. It may be more like a brain.

THE MYTH OF THE TANGLED SPAGHETTI

E. coli's brainy tongue does not fit well into the traditional picture of bacteria as primitive, simple creatures. Well into the twentieth century, bacteria remained saddled with a reputation as relics of life's earliest stages. They were supposedly nothing more than bags of enzymes with some loose DNA tossed in like a bowl of tangled spaghetti. "Higher" organisms, on the other hand—including animals, plants, fungi—were seen as having marvelously organized cells. They all keep their DNA neatly wound up around spool-shaped proteins and bundled together into chromosomes. The chromosomes are tucked into a nucleus. The cells have other compartments, in which they carry out other jobs, such as generating energy or putting the finishing touches on proteins. The cells themselves have structure, thanks to a skeletal network of fibers crisscrossing their girth.

The contrast between these two kinds of cells—sloppy and neat—seemed so stark in the mid-1900s that scientists used it to divide all of life into two great groups. All species that carried a nucleus were eukaryotes, meaning "true kernels" in Greek. All other species—including *E. coli*—were now prokaryotes. Before the kernel there were prokaryotes, primitive and disorganized. Only later did eukaryotes evolve, bringing order to the world.

There's a kernel of truth to this story. The last common ancestor of all living things almost certainly didn't have a nucleus. It probably looked vaguely like today's prokaryotes. Eukaryotes split off from prokaryotes

more than 3 billion years ago, and only later did they acquire a full-fledged nucleus and other distinctive features. But it is all too easy to see more differences between prokaryotes and eukaryotes than actually exist. The organization of eukaryotes jumps out at the eye. It is easy to see the chromosomes in a human cell, the intricately folded Golgi apparatus, the sausage-shaped mitochondria. The geography is obvious. But prokaryotes, it turns out, have a geography as well. They keep their molecules carefully organized, but scientists have only recently begun to discover the keys to that order.

Many of those keys were first discovered in *E. coli*. *E. coli* must grapple with several organizational nightmares in order to survive, but none so big as keeping its DNA in order. Its chromosome is a thousand times longer than the microbe itself. If it were packed carelessly into the microbe's interior, its double helix structure would coil in on itself like twisted string, creating an awful snarl. It would be impossible for the microbe's gene-reading enzymes to make head or tail of such a molecule.

There's another reason why *E. coli* must take special care of its DNA: the molecule is exquisitely vulnerable to attack. As the microbe turns food into energy, its waste includes charged atoms, which can crash into DNA, creating nicks in the strands. Water molecules are attracted to nicks, where they rip the bonds between the two DNA strands, pulling the chromosome apart like a zipper.

Only in the past few years have scientists begun to see how *E. coli* organizes its DNA. Their experiments suggest that it folds its chromosome into hundreds of loops, held in place by tweezerlike proteins. Each loop twists in on itself, but the tweezers prevent the coiling from spreading to the rest of the chromosome. When *E. coli* needs to read a particular gene, a cluster of proteins moves to the loop where the gene resides. It pulls the two strands of DNA apart, allowing other proteins to slide along one of the strands and produce an RNA copy of the gene. Still other proteins keep the strands apart so that they won't snarl and tangle during the copying. Once the RNA molecule has been built, the proteins close the strands of the DNA again. *E. coli*'s tweezers also make the damage from unzipping DNA easier to manage. When a nick appears in the DNA, only a single loop will come undone because the tweezers keep the damage from spreading farther. *E. coli* can then use repair enzymes to stitch up the wounded loop.

E. coli faces a far bigger challenge to its order when it reproduces. To reproduce, it must create a copy of its DNA, pull those chromosomes to either end of its interior, and slice itself in half. Yet *E. coli* can do all of that with almost perfect accuracy in as little as twenty minutes.

The first step in building a new *E. coli*—copying more than a million base pairs of DNA—begins when two dozen different kinds of enzymes swoop down on a single spot along *E. coli*'s chromosome. Some of them pull the two strands of DNA apart while others grip the strands to prevent them from twisting away or collapsing back on each other. Two squadrons of enzymes begin marching down each strand, grabbing loose molecules to build it a partner. The squadrons can add a thousand new bases to a DNA strand every second. They manage this speed despite running into heavy traffic along the way. Sometimes they encounter the sticky tweezers that keep DNA in order; scientists suspect that the tweezers must open to let the replication squadrons pass through, then close again. The squadrons also end up stuck behind other proteins that are slowly copying genes into RNA and must wait patiently until they finish up and fall away before racing off again. Despite these obstacles, the DNA-building squadrons are not just fast but awesomely accurate. In every 10 billion bases they add, they may leave just a single error behind.

As these enzymes race around *E. coli*'s DNA, two new chromosomes form and move to either end of the microbe. Although scientists have learned a great deal about how *E. coli* copies its DNA, they still debate how exactly the chromosomes move. Perhaps they are pulled, perhaps they are pushed. However they move, they remain tethered like two links in a chain. A special enzyme handles the final step of snipping them apart and sealing each back together. Once liberated, the chromosomes finish moving apart, and *E. coli* can begin to divide itself in two.

The microbe must slice itself precisely, in both space and time. If it starts dividing before its chromosomes have moved away, it will cut them into pieces. If it splits itself too far toward either end, one of its offspring will have a pair of chromosomes and the other will have none. These disasters almost never take place. *E. coli* nearly always divides itself almost precisely at its midpoint, and almost always after its two chromosomes are safely tucked away at either end.

A few types of proteins work together to create this precise dance. When *E. coli* is ready to divide, a protein called FtsZ begins to form a ring

along the interior wall of the microbe at midcell. It attracts other proteins, which then begin to close the ring. Some proteins act like winches, helping to drag the chromosomes away from the closing ring. Others add extra membrane molecules to seal the ends of the two new microbes.

FtsZ proteins form their ring without consulting a map of the microbe, without measuring it with a ruler. Instead, it appears that FtsZ is forced by other proteins to form the ring at midcell. Another protein, called MinD, forms into spirals that grow along the inside wall of the microbe. The MinD spiral can scrape off any FtsZ it encounters attached to the wall. But the MinD spiral itself is fleeting. Another protein attaches to the back end of the spiral and pulls the MinD proteins off the wall one at a time.

A pattern emerges: the MinD spiral grows from one end toward the middle but falls apart before it gets there. The dislodged MinD proteins float around the cell and begin to form a new spiral at the other end. But as the MinD spiral grows toward the middle again, its back end gets destroyed once more. The MinD spiral bounces back and forth, taking about a minute to move from one end of the microbe to the other.

The bouncing MinD spiral scrapes away FtsZ from most of the cell. Only in the middle can FtsZ have any hope of forming the ring. And even there FtsZ is blocked most of the time by the chromosome and its attendant proteins. Only after the chromosome has been duplicated and the two copies are moving away from the middle is there enough room for FtsZ to take hold and start cutting the microbe in two.

E. coli may not have the obvious anatomy of a eukaryote cell, but it has a structure nevertheless. It is a geography of rhythms, a map of flux.

OFF THE CLIFF

E. coli caught Theodor Escherich's eye thanks to its gift for multiplication—the way a single microbe can give rise to a massive, luxurious growth in a matter of hours. If the bacteria Escherich discovered had continued to reproduce at that rapid rate, they would have soon filled his flasks with a solid microbial mass. In a few days they could have taken over the Earth. But *E. coli* did something else. It began to grow more slowly, and then, within a day, it stopped.

All living things could, in theory, take over the planet. But we do not

wade through forests of puffballs or oceans of fleas. A species' exponential growth quickly slams into the harsh reality of this finite world. As *E. coli*'s population grows denser, the bacteria use up oxygen faster than fresh supplies can arrive. Their waste builds up around them, turning toxic. This collision with reality can be fatal. As *E. coli* runs out of its essential nutrients, its ribosomes get sloppy, producing misshapen protein that attacks other molecules. The catastrophe can ripple out across the entire microbe. To continue to grow under such stress would be suicidal, like driving a car over a cliff.

Instead, *E. coli* slams on the brakes. In a matter of seconds it stops reading its genes and destroys all the proteins it's in the midst of building. It enters a zombielike state called the stationary phase. The microbe begins to make proteins to defend against heat, acid, and other insults even as it stops making the enzymes necessary for feeding. To keep dangerous molecules from slipping through its membranes, *E. coli* closes off many of its pores. To protect its DNA, *E. coli* folds it into a kind of crystalline sandwich. All of these preparations demand a lot of energy, which the microbe can no longer get from food. So *E. coli* eats itself, dismantling some of its own energy-rich molecules. It even cannibalizes many of its ribosomes, so it can no longer make new proteins.

The threats faced by a starving *E. coli* are much like the ones our own cells face as we get old. Aging human cells suffer the same sorts of damage to their genes and ribosomes. People who suffer Alzheimer's disease develop tangles of misshapen proteins in their brains—proteins that are deformed in much the same way some proteins in starving *E. coli* are deformed. Life not only grows and reproduces. It also decays.

Although humans and microbes face the same ravages of time, it's the microbe that comes out the winner. If scientists pluck out a single *E. coli* in a stationary phase and put it in a flask of fresh broth, it will unpack its DNA, build new proteins, and resume its life with stately grace. Scientists can leave a colony of *E. coli* in a stationary phase for five years and still resurrect some viable microbes. We humans never get such a second chance.

provides its own observational adventures, including the unique opportunity to close the circle by investigating the neurological mechanism through which the observer observes and comes to know the cosmos.

GENES, CLAUSTRUM, AND CONSCIOUSNESS

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What's my favorite elegant idea? The elucidation of DNA's structure is surely the most obvious, but it bears repeating. I'll argue that the same strategy used to crack the genetic code might prove successful in cracking the "neural code" of consciousness and self. It's a long shot, but worth considering.

The ability to grasp analogies, and to see the difference between deep and superficial ones, is a hallmark of many great scientists. Francis Crick and James Watson were no exception. Crick himself cautioned against the pursuit of elegance in biology, given that evolution proceeds happenstantially. "God is a hacker," he said, adding (according to my colleague Don Hoffman), "Many a young biologist has slit his own throat with Occam's razor." Yet his own solution to the riddle of heredity ranks with natural selection as biology's most elegant discovery. Will a solution of similar elegance emerge for the problem of consciousness?

It is well known that Crick and Watson unraveled the double-helical structure of the DNA molecule: two twisting complementary strands of nucleotides. Less well known is the chain of events culminating in this discovery.

First, Mendel's laws dictated that genes are particulate (a first approximation, still held to be accurate). Then Thomas Morgan showed that fruit flies zapped with X-rays became mutants with punctate changes in their chromosomes, yielding the clear con-

clusion that the chromosomes are where the action is. Chromosomes are composed of histones and DNA; as early as 1928, the British bacteriologist Fred Griffith showed that a harmless species of bacterium, upon incubation with a heat-killed virulent species, changes into the virulent species. This was almost as startling as a pig walking into a room with a sheep and two sheep emerging. Later, Oswald Avery showed that DNA was the transformative principle here. In biology, knowledge of structure often leads to knowledge of function—one need look no further than the whole of medical history. Inspired by Griffith and Avery, Crick and Watson realized that the answer to the problem of heredity lay in the structure of DNA. Localization was critical, as, indeed, it may prove to be for brain function.

Crick and Watson didn't just describe DNA's structure, they explained its significance. They saw the analogy between the complementarity of molecular strands and the complementarity of parent and offspring—why pigs beget pigs and not sheep. At that moment, modern biology was born. There are similar correlations between brain structure and mind function, between neurons and consciousness. (I'm stating the obvious here only because there are some philosophers, called "new mysterians," who believe the opposite.)

After his triumph with heredity, Crick turned to what he called the "second great riddle" in biology—consciousness. There were many skeptics. I remember a seminar Crick gave on consciousness at the Salk Institute here in La Jolla. He'd barely started when a gentleman in attendance raised a hand and said, "But Dr. Crick, you haven't even bothered to *define* the word 'consciousness' before embarking on this." Crick's response was memorable: "I'd remind you that there was never a time in the history of biology when a bunch of us sat around the table and said, 'Let's first *define* what we mean by life.' We just went out there and discovered what it

was—a double helix. We leave matters of semantic hygiene to you philosophers."

Crick did not, in my opinion, succeed in solving consciousness (whatever it might mean). Nonetheless, he was headed in the right direction. He had been richly rewarded earlier in his career for grasping the analogy between biological complementarities, the notion that the structural logic of the molecule dictates the functional logic of heredity. Given his phenomenal success using the strategy of structure-function analogy, it is hardly surprising that he imported the same style of thinking to study consciousness. He and his colleague Christof Koch did so by focusing on a relatively obscure structure called the claustrum.

The claustrum is a thin sheet of cells underlying the insular cortex of the brain, one on each hemisphere. It is histologically more homogeneous than most brain structures, and unlike most brain structures (which send and receive signals to and from a small subset of other structures), the claustrum is reciprocally connected with almost every cortical region. The structural and functional streamlining might ensure that when waves of information come through the claustrum, its neurons will be exquisitely sensitive to the timing of the inputs.

What does this have to do with consciousness? Instead of focusing on pedantic philosophical issues, Crick and Koch began with their naive intuitions. "Consciousness" has many attributes—continuity in time; a sense of agency or free will; recursiveness, or "self-awareness," etc. But one attribute that stands out is subjective unity: You experience all your diverse sense impressions, thoughts, willed actions, and memories as a unity—not as jittery or fragmented. This attribute of consciousness, with the accompanying sense of the immediate present, or the "here and now," is so obvious that we don't usually think about it; we regard it as axiomatic.

So a central feature of consciousness is its unity—and here is a brain structure that sends and receives signals to and from practically all other brain structures, including the right parietal (involved in polysensory convergence and embodiment) and the anterior cingulate (involved in the experience of "free will"). Thus the claustrum seems to unify everything anatomically, and consciousness does so mentally. Crick and Koch recognized that this might not be a coincidence: The claustrum may be central to consciousness—indeed, it may embody the idea of the Cartesian theater, taboo among philosophers—or at least be the conductor of the orchestra. It is this kind of childlike reasoning that often leads to great discoveries. Obviously, such analogies don't replace rigorous science, but they're a good place to start. Crick and Koch's idea may be right or wrong, but it's elegant. If it's right, they have paved the way to solving one of the great mysteries of biology. Even if it's wrong, students entering the field would do well to emulate their style. Crick was right too often to ignore.

I visited him at his home in La Jolla in July of 2004. He saw me to the door as I was leaving and, as we parted, gave me a sly, conspiratorial wink: "I think it's the claustrum, Rama. That's where the secret is." A week later, he passed away.

OVERLAPPING SOLUTIONS

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The elegance of the brain lies in its inelegance. For centuries, neuroscience attempted to neatly assign labels to the various parts of the brain: This is the area for language, this for morality, this for tool use, color detection, face recognition, and so on. The search for an orderly brain map started off as a viable endeavor but turned out to be misguided.

The deep and beautiful trick of the brain is more interesting: It possesses multiple, overlapping ways of dealing with the world. It is a machine built of conflicting parts. It is a representative democracy that functions by *competition* among parties who all believe they know the right way to solve the problem.

As a result, we can get mad at ourselves, argue with ourselves, curse at ourselves, and contract with ourselves. We can feel conflicted. These sorts of neural battles lie behind marital infidelity, relapses into addiction, cheating on diets, breaking of New Year's resolutions—all situations in which some parts of a person want one thing and other parts another.

These are things that modern machines simply do not do. Your car cannot be conflicted about which way to turn: It has one steering wheel commanded by one driver, and it follows directions without complaint. Brains, on the other hand, can be of two minds, and often many more. We don't know whether to turn toward the cake or away from it, because there are several sets of hands on the steering wheel of behavior.

Take memory. Under normal circumstances, memories of daily

is especially so for the increasing proportion of men and women who choose to delay having children until middle age (if then).

I realize that rapid change in a society's moral compass needs more than the removal of influences maintaining the status quo; it also needs an active impetus. What is the impetus in this case? It is simply the pain and suffering that arises when the possessiveness and jealousy inherent in the monogamous mind-set butt heads with the asynchronous shifts of affection and aspiration inherent in the response of human beings to their evolving social interactions. Gratuitous suffering is anathema to all. Thus, the realization that this particular category of suffering is wholly gratuitous has not only irresistible moral force (via the principle of reflective equilibrium) but also immense emotional utility.

The writing is on the wall.

BOLTZMANN'S EXPLANATION OF THE SECOND LAW OF THERMODYNAMICS

LEONARD SUSSKIND

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"What is your favorite deep, elegant, or beautiful explanation?" That's a tough question for a theoretical physicist; theoretical physics is all about deep, elegant, beautiful explanations, and there are many to choose from.

Personally, my favorites are explanations that get a lot for a little. In physics, that means a simple equation or a very general principle. I have to admit, though, that no equation or principle appeals to me more than Darwinian evolution, with the selfish-gene mechanism thrown in. To me, it has what the best physics explanations have: a kind of mathematical inevitability. But there are many people who can explain evolution better than I, so I will stick to what I know best.

The guiding star for me, as a physicist, has always been Ludwig Boltzmann's explanation of the second law of thermodynamics—the law that says that entropy never decreases. To the physicists of the late 19th century, this was a very serious paradox. Nature is full of irreversible phenomena—things that easily happen but could not possibly happen in reverse order. However, the fundamental laws of physics are completely reversible: Any solution of Newton's equations can be run backwards and it's still a solution. So if entropy can increase, the laws of physics say it must be able to decrease. But experience says otherwise. For example, if you watch a movie of a

nuclear explosion in reverse, you know very well that it's fake. As a rule, things go one way and not the other. Entropy increases.

What Boltzmann realized is that the second law—entropy never *decreases—is not a law in the same sense as Newton's law of gravity* or Faraday's law of induction. It's a probabilistic law that has the same status as the following obvious claim: If you flip a coin a million times, you will not get a million heads. It simply won't happen. But is it possible? Yes, it is; it violates no law of physics. Is it likely? Not at all. Boltzmann's formulation of the second law was very similar. Instead of saying entropy does not decrease, he said entropy *probably* doesn't decrease. But if you wait around long enough in a closed environment, you will eventually see entropy decrease; by accident, particles and dust will come together and form a perfectly assembled bomb. How long? According to Boltzmann's principles, the answer is the exponential of the entropy created when the bomb explodes. That's a very long time, a lot longer than the time it takes to flip a million heads in a row.

I'll give you a simple example to see how it's possible for things to be more probable one way than the other, despite both being possible. Imagine a high hill that comes to a narrow point—a needle point—at the top. Now imagine a bowling ball balanced at the top of the hill. A tiny breeze comes along. The ball rolls off the hill, and you catch it at the bottom. Next, run it in reverse: The ball leaves your hand, rolls up the hill, and with infinite finesse, comes to the top—and stops! Is it possible? It is. Is it likely? It is not. You would have to have almost perfect precision to get the ball to the top, let alone to have it stop dead-balanced. The same is true with the bomb. If you could reverse every atom and particle with sufficient accuracy, you could make the explosion products reassemble themselves. But a tiny inaccuracy in the motion of just one single particle and all you would get is more junk.

Here's another example: Drop a bit of black ink into a tub of water. The ink spreads out and eventually makes the water gray. Will a tub of gray water ever clear up and produce a small drop of ink? Not impossible, but very unlikely.

Boltzmann was the first to understand the statistical foundation for the second law, but he was also the first to understand the inadequacy of his own formulation. Suppose you came upon a tub that had been filled a zillion years ago and had not been disturbed since. You notice the odd fact that it contains a somewhat localized cloud of ink. The first thing you might ask is, What will happen next? The answer is that the ink will almost certainly spread out more. But by the same token, if you ask what most likely took place a moment before, the answer would be the same: It was probably more spread out a moment ago than it is now. The most likely explanation would be that the ink blob is just a momentary fluctuation.

Actually, I don't think you'd come to that conclusion at all. A much more reasonable explanation is that, for reasons unknown, the tub started not so long ago with a concentrated drop of ink, which then spread. Understanding why ink and water go one way becomes a problem of "initial conditions." What set up the concentration of ink in the first place?

The water and ink is an analogy for the question of why entropy increases. It increases because it's most likely that it will increase. But the equations say that it's also most likely that it increases toward the past. To understand why we have this sense of direction, one must ask the same question Boltzmann did: Why was the entropy very small at the beginning? What created the universe in such a special low-entropy way? That's a cosmological question we are still very uncertain about.

I began telling you what my favorite explanation is, and I ended up telling you what my favorite unsolved problem is. I apologize for not following the instructions. But that's the way of all good explanations. The better they are, the more questions they raise.

didn't have the slightest shred of science supporting it, having been discredited before Darwin's time. This didn't prevent Lysenko from gaining vast influence over Stalin and agricultural planning. A bizarre episode in science that would just leave one shaking one's head in bemusement if Lysenkoism hadn't played a role in the death by starvation of vast numbers of Soviet citizens.

Further reading: the issue of *People* magazine cited above, of course, and as long as we're at it, the entire collection of *People* magazines. And for the best read on the science of this piece, see Matt Ridley's *Nature via Nurture: Genes, Experience, & What Makes Us Human* (New York: HarperCollins, 2003).

A Gene for Nothing

Remember Dolly the Sheep, the first mammal cloned from adult cells, in 1996? She was lovely, really an inspiration. She endured endless state dinners at the White House, all grace and cordiality. Then there was her triumphant ticker-tape parade down Broadway that won over even the most hardened New Yorker. Her appearances in those ubiquitous billboard ads for Guess? jeans (jeans, genes—get it? Those advertising guys are just awesome sometimes). Rollerblading at Disneyland for charity with the cast from *Friends.* Throughout the media circus, she was poised, patient, even-tempered, the epitome of what we look for in a celebrity and role model.

And despite that charm, people kept saying mean things about Dolly. Heads of state, religious leaders, editorialists, fell over themselves shortly after her debut to call her an aberration of nature, an insult to the sacred biological wonder of reproduction, something that should never remotely be considered in a human.

What was everyone so upset about? Some possibilities come to mind: (a) The Dolly Sheep/Dolly Parton connection unsettled everyone in a way that they just couldn't quite put their finger on. (b) Because the cloning technology that gave rise to Dolly could be extended to humans, we face the potential of droves of clones of someone running around, all with the exact same liver function. (c) Thanks to that technology, we might wind up with a bunch of clones who have the same brain.

Sure, the first two possibilities are creepy. But the dis-ease prompted by Dolly was overwhelmingly, remains overwhelmingly, about the third option. The same brain, the same neurons, the same genes directing those neurons, one multibodied consciousness among the clones, a mind meld, an army of photocopies of the same soul.

In actuality, people have known that this is not really the case ever since scientists discovered identical twins. Such individuals constitute genetic clones, just like Dolly and her mother (what was her name? Why does she get shortchanged in the media?), from whom that original cell was taken. Despite all those breathless stories about identical twins separated at birth who share all sorts of traits, like flushing the toilet before using it, twins do not have mind melds, do not behave identically. As one important example, if an identical twin is schizophrenic, the sibling, with the identical "schizophrenia gene(s)," has only about a 50 percent chance of having the disease. A similar finding comes from a fascinating experiment by Dan Weinberger of the National Institute of Mental Health. Give identical twins a puzzle to solve, and they might come up with answers that are more similar than one would expect from a pair of strangers. Hook those individuals up during the puzzle-solving to a brain-imaging instrument that visualizes metabolic demands in different regions of the brain, and the pattern of activation in the pair can differ dramatically, despite the same solution. Or get yourself some brains from identical twins. I don't mean pictures from a brain scanner. Get the real, squishy stuff, postmortem brains. Slice 'em, dice 'em, examine them with every kind of microscope, and every obsessive measure—the numbers of neurons in particular brain regions, the complexity of the branching cables coming out of those neurons, the numbers of connections among those neurons—and they all differ. Same genes, different brains.

The careful editorialists pointed this out about Dolly (and instead, some of the most disturbing issues about cloning raised by Dolly center on the possibilities of generating life simply for the purpose of

banking away transplant-compatible tissues). Nonetheless, that business about identical genes supposedly producing identical brains tugs at a lot of people. And other gene/behavior stories keep getting propelled to the front pages of newspapers. One popped up shortly before Dolly with the report, headed by a Stanford team, of a single gene, called fru, that determines the sexual behavior of male fruit flies. Courtship, opening lines, foreplay, whom they come on to—the works. Mutate that gene and, get this, you can even change the sexual orientation of the fly. And that wasn't front-page news because of our insatiable fly voyeurism. "Could our sexual behaviors be determined by a single gene as well?" every article asked. And a bit earlier, there was the hubbub about the isolation of a gene related to anxiety, and before that, one for risk-taking behavior, and a while before that, the splash about another gene, whose mutation in one family was associated with their violent antisocial behavior, and then before that . . .

Why do these command attention? For many, genes and the DNA that comprises genes represent the holy grail of biology, the code of codes (two phrases often used in lay-public discussions of genetics). The worship at the altar of the gene rests on two assumptions. The first concerns the autonomy of genetic regulation. This is a notion that biological information begins with genes and flows outward and upward. DNA as the alpha, the initiator, the commander, the epicenter from which biology emanates. Nobody tells a gene what to do. It's always the other way around. The second assumption is that when genes give a command, biological systems listen. In that view, genes instruct your cells as to their structure and function. And when those cells are neurons, those functions include thought and feelings and behavior. And thus we are finally identifying the biological factors, so this thinking goes, that make us do what we do.

This view was put forward in a lead piece in the *The New Yorker* by a literature professor named Louis Menand. Mr. Menand ruminated on those anxiety genes, when "one little gene is firing off a sig-

nal to bite your fingernails" (the first assumption about the autonomy of genes, firing off whenever some notion pops into their head). He considers what this does to our explanatory systems. How do we reconcile societal, economic, psychological explanations of behavior with those ironclad genes? "The view that behavior is determined by an inherited genetic package"—the second assumption, genes as irresistible commanders—"is not easily reconciled with the view that behavior is determined by the kinds of movies a person watches." And what is the solution? "It is like having the Greek gods and the Inca gods occupying the same pantheon. Somebody's got to go."

In other words, if you buy into genes firing off and determining our behaviors, such modern scientific findings are simply incompatible with the environment having an influence. Sumpin's gotta go.

Now, I'm not quite sure what sort of genetics they teach in Mr. Menand's English department, but the sumpin's-gotta-go loggerhead is what most behavioral biologists have been trying to unteach for decades. Apparently with only limited success. Which is why it's worth another try.

Okay. You've got nature—neurons, brain chemicals, hormones, and, of course, at the bottom of the cereal box, genes. And then there's nurture, all those environmental breezes gusting about. And the biggest cliché in this field is how it is meaningless to talk about nature or nurture, only about their interaction. And somehow, that truism rarely sticks. Instead, somebody's got to go, and when a new gene is trotted out that when "firing off," "determines" a behavior, environmental influences are inevitably seen as something irrelevant that have to go. And soon, poor sweet Dolly became a menace to our autonomy as individuals, and there are perceived to be genes that control whom you go to bed with and whether you feel anxious about it.

Let's try to undo the notion of genes as neurobiological and behavioral destiny by examining those two assumptions. Let's begin with the second one, the notion that genes equal inevitability, generate commands that drive the function of cells, including those in our

head. What exactly do genes do? A gene, a stretch of DNA, does not produce a behavior. Or an emotion, or even a fleeting thought. It produces a protein, where a specific DNA sequence that constitutes a gene codes for a specific type of protein. Now, some of these proteins certainly have lots to do with behavior and feelings and thoughts. Proteins include some hormones and neurotransmitters (chemical messengers between neurons), the receptors that receive hormonal and neurotransmitter messages, the enzymes that synthesize and degrade those messengers, many of the intracellular messengers triggered by those hormones, and so on. All vital for a brain to do its business. But the key is that it is extremely rare that things like hormones and neurotransmitters cause a behavior. Instead, they produce tendencies to respond to the environment in certain ways.

This is critical. Let's consider anxiety. When an organism is confronted with some sort of threat, it typically becomes vigilant, searches to gain information about the nature of the threat, struggles to find an effective coping response. And once a signal indicates safety—the lion has been evaded, the traffic cop buys the explanation and doesn't issue a ticket—the organism can relax. But this is not what occurs in an anxious individual. Instead, there is a frantic skittering among coping responses—abruptly shifting from one to another without checking whether anything has worked, an agitated attempt to cover all the bases and attempt a variety of responses simultaneously. Or there is an inability to detect when the safety signal occurs, and the restless vigilance keeps going. By definition, anxiety makes little sense outside the context of what the environment is doing to an individual. In that framework, the brain chemicals and, ultimately, the genes relevant to anxiety don't make you anxious. They make you more responsive to anxiety-provoking situations, make it harder to detect safety signals in the environment.

The same theme continues in other realms of our behaviors as well. The exciting (made-of-protein) receptor that seems to have something to do with novelty-seeking behavior doesn't actually make you seek

novelty. It makes you more excitable in response to a novel environment than the folks without that receptor variant. And those (genetically influenced) neurochemical abnormalities of depression don't make you depressed. They make you more vulnerable to stressors in the environment, to deciding that you are helpless in circumstances where you are not (this particular point will be returned to in detail in essay five). Over and over it's the same theme.

One may retort that, in the long run, we are all exposed to anxiety-provoking circumstances, all exposed to the depressing world around us. If we are all exposed to those same environmental factors, yet it is only the people who are genetically prone toward, say, depression who get depressed, that is a pretty powerful vote for genes. In that scenario, the "genes don't cause things, they just make you more sensitive to the environment" becomes empty and semantic.

The problems there, however, are twofold. First, not everyone who has a genetic legacy of depression gets depressed (only about 50 percent—the same punch line as for individuals with a genetic legacy of schizophrenia), and not everyone who has a major depression has a genetic legacy for it. Genetic status is not all that predictive, in and of itself.

Second, only on a superficial level do we share the same environments. For example, the incidence of the genes related to depression is probably roughly equal throughout the world. However, geriatric depression is epidemic in our society and virtually nonexistent in traditional societies in the developing world. Why? Remarkably different environments in different societies, in which old age can mean being a powerful village elder or an infantilized has-been put out to a shuffleboard pasture. Or the environmental differences can be more subtle. Periods of psychological stress involving loss of control and predictability during childhood are recognized to predispose toward adult depression. Two children may have had similar childhood lessons in "there's bad things out there that I can't control"—both may have seen their parents divorce, lost a grandparent, tearfully

buried a pet in the backyard, experienced a bully who got away with endlessly menacing them. Yet the temporal patterning of their two experiences is unlikely to be identical, and the child who experiences all those stressors over one year instead of over six years is far more likely to come with the cognitive distortion "There're bad things out there that I can't control, and in fact, I can't control anything" that sets you up for depression. The biological factors coded for by genes in the nervous system don't typically determine behavior. Instead, they influence the way you respond to the environment, and those environmental influences can be extremely subtle. Genetic vulnerabilities, tendencies, predispositions, biases. . . . but rarely genetic inevitabilities.

It's also important to realize the inaccuracy of the first assumption about behavioral genetics, the notion of genes as autonomous initiators of commands, as having minds of their own. To see the fallacy of this, it's time to look at two startling facts about the structure of genes, because they blow that assumption out of the water and bring environmentalism back into this arena big-time.

A chromosome is made of DNA, a vastly long string of it, a long sequence of letters coding for genetic information. People used to think that the first eleventy letters of the DNA message would comprise Gene 1. A special letter sequence signaled the end of that gene, and then the next eleventy and a half letters coded for Gene 2, and so on, through tens of thousands of genes. And in the pancreas, Gene 1 might specify the construction of insulin, and in your eyes, Gene 2 might specify protein pigments that give eyes their color, and Gene 3, active in neurons, might make you aggressive. Ah, caught you: might make you more *sensitive* to aggression-provoking stimuli in the environment. Different people would have different versions of Genes 1, 2, 3, and some versions worked better than others, were more evolutionarily adaptive. The final broad feature was that an army of biochemicals would do the scut work, transcribing the genes, reading the DNA sequences, and thus following the instructions as to

how, eventually, to construct the appropriate proteins. Sure, we would torture our students with an entire year's worth of trivial details about that transcription process, but the basic picture suffices.

Except that that's not really how things work. The real picture, while different, does not initially seem earth-shattering. Instead of one gene coming immediately after another and all of that vast string of DNA devoted entirely to coding for different proteins, long stretches of DNA don't get transcribed. Sometimes those stretches even split up a gene into subsections. Nontranscribed, noncoding DNA. What's it for? Some of it doesn't seem to do anything. "Junk DNA," long, repetitious sequences of meaningless gibberish. But some of that noncoding DNA does something interesting indeed. It's the instruction manual for how and when to activate those genes. These stretches have a variety of names—regulatory elements, promoters, repressors, responsive elements. And different biochemical messengers bind to those regulatory elements and thereby alter the activity of the gene immediately "downstream"—immediately following in the string of DNA.

Aha, the death of the gene as the autonomous source of information, as having a mind of its own. Instead, other factors regulate when and how genes function. And what regulates this genetic activity? Often the environment.

A first example of how that might work. Suppose something stressful happens to some primate. There's a drought and not much to eat, forcing the animal to forage miles each day for food. As a result, it secretes stress hormones from its adrenals called glucocorticoids. Among other things, glucocorticoid molecules enter fat cells, bind to glucocorticoid receptors. These hormone/receptor complexes then find their way to the DNA and bind to a particular regulatory stretch of DNA, one of those operating instructions. As a result, a gene downstream is activated, which produces a protein that, indirectly, inhibits that fat cell from storing fat. A logical thing to do—while that primate is starving and walking the grasslands in search of

a meal, this is the time to divert energy to working muscles, not to fat cells.

This constitutes a cleverly adaptive mechanism by which the environment triggers a genetic response that modifies metabolism. This is a very different scenario for thinking about where information originates in these cascades. In effect, these regulatory elements introduce the possibility of environmentally modulated if/then clauses: *if* the environment is tough and you're working hard to find food, *then* make use of your genes to divert energy to exercising muscle. And if a human refugee wanders miles from home with insufficient food because of civil strife, then the same is probably occurring—the behavior of one human, the sort of environment that that individual generates, can change the pattern of gene activity in another person.

Let's get a fancier example of how these regulatory elements of DNA are controlled by environmental factors. Suppose that Gene 4037 (a gene that has a real name, but I'll spare you the jargon), when left to its own devices, is transcriptionally active, generating the protein that it codes for. However, a regulatory element comes just before 4037 in the DNA string, and typically a particular messenger binds to the regulatory element, shutting down Gene 4037. Fine. How about the following: That inhibitory messenger is sensitive to temperature. In fact, if the cell gets hot, that messenger goes to pieces, unwinds, and comes floating off the regulatory element. What happens? Freed from the inhibitory regulation, Gene 4037 suddenly becomes active. Maybe it's a gene that works in the kidney and codes for a protein relevant to water retention. Boring—another metabolic story, this one having to do with how a warm environment triggers a metabolic adaptation that staves off dehydration. But suppose, instead, Gene 4037 codes for an array of proteins that have something to do with sexual behavior. What have you just invented? Seasonal mating. Winter is waning, each day gets a little warmer, and in relevant cells in the brain, pituitary, or gonads, genes like 4037 are gradually becoming active.

Finally, some threshold is passed, and wham, everyone starts rutting and ovulating, snorting and pawing at the ground, and generally carrying on. If it is the right time of year, then use those genes to increase the likelihood of mating. (Actually, in most seasonal maters, the environmental signal for mating is the amount of daily light exposure—the days are getting longer—rather than temperature—the days are getting warmer. But the principle is the same.)

A final, elegant version of this principle. Every cell in your body has a distinctive protein signature that marks it as belonging to you, a biochemical fingerprint. These "major histocompatability" proteins are important—this is how your immune system tells the difference between you and some invading bacteria and is why an organ transplanted into you that has a very different signature gets rejected. Now, some of those signature proteins can detach from cells, can get into your sweat glands, wind up in your sweat, and help to make for a distinctive odor signature. And for a rodent, now that's important stuff. You can design receptors in olfactory cells in a rodent's nose that can distinguish between odor proteins that are similar to its own versus ones that are totally novel. That's easy to construct—the greater the similarity, the tighter the protein fits into the receptor, like a key in a lock (to hark back to one of our great high-school science clichés). What have you just invented? A means to explain something that rodents do effortlessly—distinguish between the smells of relatives and strangers.

Keep tinkering with this science project. Now, couple those olfactory receptors to a cascade of messengers inside the cell that gets you to the DNA, to the point of binding to those regulatory elements. What might you want to construct? How about: if an olfactory receptor binds an odorant indicating a relative, then trigger a cascade that ultimately inhibits the activity of genes related to reproduction. You've just invented a mechanism to explain how animals tend not to mate with close relatives. Or you can construct a different cascade: if an olfactory receptor binds an odorant indicating a relative, then

inhibit genes that are normally active that regulate the synthesis of testosterone. And what you've just come up with is a means by which rodents get bristly and aggressive when a strange male stinks up their burrow, but not when it's the scent of their kid brother. Or you can design the olfactory receptors to distinguish between odor signatures of same-sex individuals versus those of the opposite sex, and before you know it, this is a mechanism to regulate reproductive physiology. If you smell someone of the opposite sex, then start that cascade that ultimately gears up those genes down in the gonads—and there's reasonably good evidence that that mechanism works in humans as well as in rodents.

In each of these examples, you can begin to see the logic, a beautiful sort of elegance that couldn't be improved on much by teams of engineers. And now for the two facts about this regulation of genes that dramatically change how to view genes. First, when it comes to cells in mammals, by the best estimates available, more than 95 percent of DNA is noncoding. *Ninety-five percent.* Sure, a lot of that is the junk packing-material DNA, but your average gene comes with a huge instruction manual about how to operate it, and the operator is often environmental. With that sort of percentage, if you think about genes and behavior, you have to think about how the environment regulates genes and behavior.

And here's the second fact. A big deal when it comes to genes and evolution and behavior is the genetic variation between individuals. By this, I mean that the DNA sequence coding for any given gene often varies from one person to the next, and this often translates into proteins that differ in how well they do their job. This is the grist for natural selection: Which is the most adaptive version of some (genetically influenced) trait? Given that evolutionary change occurs at the level of DNA, "survival of the fittest" really means "reproduction of individuals whose DNA sequences make for the most adaptive collection of proteins." And the startling second fact is that when you examine variability in DNA sequences among individuals, the non-

coding regions of DNA are considerably more variable than are the regions that code for genes. Okay, a lot of that noncoding variability is attributable to the junk packing-material DNA that is free to drift genetically over time, because it doesn't do much. After all, two violins must look fairly similar, whether one is a Stradivarius and the other a Guarneri, whereas packing material can be as different as old newspaper or Styrofoam peanuts or bubble wrap. But there seems to be enormous amounts of variability in regulatory regions of DNA as well.

What does this mean? Hopefully, we've now gotten past "genes determine behavior" to, more typically, "genes modulate how one responds to the environment." What that business about 95 percent of DNA being noncoding implies is that it is at least as valid to think something like "genes can be convenient tools used by environmental factors to influence behavior." And what that second fact about variability in noncoding regions means is that "evolution is mostly about natural selection for different assemblages of genes" is not as accurate as thinking that "evolution is mostly about natural selection for different genetic sensitivities and responses to environmental influences."

By now, ideally, it should seem mighty difficult to separate genetic and environmental factors into neat, separate piles. Just as it should be. Sure, some cases of behaviors are overwhelmingly under genetic control. Just consider all those mutant flies hopping into the sack with some cartoon cricket. And some mammalian behaviors can be pretty heavily under genetic regulation as well. As a remarkable example, there are closely related species of voles that differ as to whether they are monogamous or polygamous, and it all has to do with the receptor for a particular sex-related hormone in one part of the brain—monogamous male voles have that receptor there, polygamous voles don't. In an amazing piece of tinkering, some scientists expressed that receptor in the brains of the polygamous males—who were now monogamous (with it not being clear whether making males monogamous should count as gene "therapy").

These cases of single genes truly having a major influence on a behavior are usually cases where the behavior is carried out in pretty much the same way by everyone. This is a necessity. If you plan to pass on copies of your genes, there can't be much tolerance for variability in these behaviors. For example, just as all violins have to be constructed in fairly similar ways if they are going to do their job, all male primates have to go about the genetically based behavior of pelvic thrusting in fairly similar ways if they plan to reproduce successfully. (Yup, I just compared violins with pelvic thrusts. Yet more evidence for why those science majors should be forced to take an English class now and then.) But by the time you get to courtship or emotions or creativity or mental illness or you name it, it's an intertwining of biological and environmental components that utterly defeats the notion that somebody's got to go, and it's not going to be genes.

Maybe the best way to finish is to give another, particularly striking example of how individuals with identical genes can, nonetheless, come up with very different behaviors. I'm a bit hesitant to reveal this, as the finding has only recently surfaced, and it hasn't been published yet. But, what the hell, it's such an interesting finding, I have to mention it. Remember the massive public opinion poll that was carried out in 1996, the one that canvassed the opinions of every sheep throughout the British Isles? The researchers recently broke the code and identified the questionnaires from Dolly and her mother. And get a load of this bombshell: Dolly's mother voted Tory, listed the Queen Mum as her all-time favorite royal, worried most about mad cow disease ("Is this good or bad for sheep?"), enjoyed Gilbert and Sullivan, and endorsed the statement "Behavior? It's all nature." And as for Dolly? Voted Green Party, thought Prince William was the cutest, worried most about "the environment," listened to the Spice Girls, and endorsed the statement "Behavior? Nature. Or nurture. Whatever." You see, there's more to behavior than just genes.

NOTES AND FURTHER READING

Dolly, sadly, died in 2003 at age seven, very young for a sheep. She seemed to suffer from some sort of syndrome of premature aging—"a sheep in lamb's clothes" in one striking, poignant description. This precocity occurred for reasons that are still not fully understood but may have to do with her DNA being prematurely worn. The ends of the DNA that constitute chromosomes are called telomeres. With each round of cell division, telomeres get a bit shorter, and when they get below a certain threshold of length, cell division ceases. It could well be that Dolly started off life with the telomeric "clock" in each of her cells already at her mother's age. Suffering from a variety of ailments, she was put to sleep, and her early demise stands as a cautionary note for cloning enthusiasts.

Numerous basic textbooks go over the broad features of how genes are organized and how they function. For one of the classic texts, see Darnell J, Lodish H, and Baltimore D, *Molecular Cell Biology* (New York: Scientific American Books, 1990).

For information about how the heritability of schizophrenia and of major depression are both about 50 percent, see Barondes S, *Mood Genes: Hunting for Origins of Mania and Depression* (New York: Oxford University Press, 1999).

The subject of fruit flies and genes about sexual orientation is reviewed in Baker B, Taylor B, and Hall J, "Are complex behaviors specified by dedicated regulatory genes? Reasoning from Drosophila," *Cell* 105 (2001): 13. The study where polygamous voles were made monogamous is Lim M, Wang Z, Olazabel D, Ren X, Terwilliger E, and Young I, "Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene," *Nature* 429 (2004): 754.

For an overview of the genetics of behavior (including anxiety and risk-taking behavior), see Plomin R, *Behavioral Genetics*, 3rd ed. (New York: W. H. Freeman, 1997).

For two superb overviews of how the function of genes cannot be understood outside the context of environment, see Moore D, *The Dependent Gene: The Fallacy of "Nature versus Nurture"* (New York: Owl Books, 1999) and Ridley M, *Nature via Nurture* (New York: HarperCollins, 2003).