E. coli and the Elephant

By Carl Zimmer

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In 2006 a horrible train of headlines chugged through the news. People across the United States were becoming terribly sick to their stomachs. Some were going to the hospital with bloody diarrhea. A few were dying. The cause was an outbreak of E. coli, carried in the leaves of spinach and lettuce plants. Friends and family knew that I was writing an entire book at the time about E. coli, and they thought it would be all about the new outbreak. To them the only thing to know about E. coli was that it could kill them. Whenever I got the chance, I’d try to explain that I was actually writing a book about life itself, about what it means to be alive, and that E. coli was serving as my guide. They’d nod quietly and politely change the subject.

There is a vast gulf between what most people think of when they hear the name Escherichia coli and what scientists think of. For scientists, Escherichia coli is an oracle. Over the past seven decades, experiments on the microbe have revealed many of the most important lessons about how life works. The science of molecular biology was born in Petri dishes of E. coli. A string of scientists traveled to Stockholm to accept Nobel Prizes for the work they did with the microbe. They learned what genes are made of and how their information is transformed into the millions of different molecules that make up living matter. Subsequent generations have continued to study it with more and more powerful tools, and today research on E. coli is helping to decipher even deeper mysteries. The very existence of Ecolihub is a testament to its importance. There’s so much information about E. coli in the scientific literature--hundreds of thousands of scientific papers, for starters--that an online database is the only way to navigate its ocean of data with confidence.

Escherichia coli was discovered in 1885 by a German pediatrician named Theodor Escherich. Escherich was trying to understand what was causing fatal intestinal diseases in children, and he decided the first step would be to inventory the many species of bacteria that live in the intestines of healthy children. He could then compare them to the microbes he’d find in sick children and pinpoint the pathogens. Among the harmless bacteria he discovered was a rod-shaped microbe that could grow quickly in a flask, and was able to feed on a wide range of food, including, he wrote, blood, milk, and potatoes. Escherich dubbed it Bacillus communis coli--the common bacteria of the colon. After his death it was renamed in his honor.

E. coli lives harmlessly by the billions in us. We are infected by these peaceful strains within a few days of birth, and we remain hosts to E. coli for our entire lives. All warm-blooded animals carry E. coli, and their droppings circulate the bacteria back into the environment--into the soil and streams and lakes, where the microbe can survive for months or even years. Harmless strains of E. coli do best on a diet of sugar. In our guts, they typically feed on the sugar in the waste released by other bacteria that can break down complex molecules found in plant matter. They cooperate and compete with their fellow E. coli inside us. The bacteria can work together to build complex structures called biofilms, which are like microbial cities. And they can wage war against other colonies of E. coli by producing lethal toxins (lethal to E. coli, not to us).

The strains of E. coli that make headlines are ones that have evolved into pathogens. Some inject disease-causing molecules into our intestinal cells, causing diarrhea. Others are harmless in the intestines but become dangerous if they manage to get into the urinary tract, causing damage all the way up to the kidneys. The one most famous in the United States, which caused the lettuce and spinach outbreaks of 2006 along with other outbreaks in contaminated hamburger, is known as E. coli O157:H7. It may come as a surprise to learn that it causes relatively little harm. A few dozen people a year typically die from it each year in the United States. Other strains of E. coli that cause dysentery in children (sometimes known as Shigella) kill over a million people a year worldwide. But the disease-causing strains of the bacteria, while famous and devastating, are in the distinct minority in the world of E. coli.

Indeed, it was E. coli’s very harmlessness that helped make it science’s favorite microbe. In the early 1900s scientists were studying a number of species to understand the fundamentals of biology. Experiments on the fruit fly Drosophila melanogaster first revealed the structure of chromosomes and the nature of mutations, for example. Microbiologists studied a number of bacteria. But a few scientists chose E. coli to study, and their tremendous successes made E. coli a standard model organism.

At Caltech, for example, the German physicist-turned-biologist Max Delbruck wanted a simple system he could study in order to understand the nature of genes. He tried Drosophila but found it hideous complex. It so happened that another scientist in his lab, Emory Ellis, was interested in studying cancer-causing viruses. Because viruses as a whole were so mysterious at the time, Ellis decided to study the viruses that infect bacteria. Previous researchers had studied viruses that infect E. coli; E. coli was harmless and easy to grow; and Ellis could scoop up sewer water and find viruses that could infect it.

Delbruck joined Ellis in studying E. coli and its viruses. They showed that a single virus could infect E. coli, and then 20 minutes later the microbe would burst open as 60 new viruses streamed out. Ellis and Delbruck could not videotape this process; instead, they had to design experiments of exquisite elegance, noting the effects of viruses by the clear spots they created where they killed off a number of E. coli in a Petri dish. Delbruck later collaborated with Salvador Luria of Indiana University on equally elegant experiments to show that E. coli spontaneously mutated and became resistant to viruses.

These successes helped Delbruck enlist an entire community of like-minded scientists who used E. coli and its viruses to dissect genes. They confirmed that DNA was the stuff of genes, for example, and they also proved that DNA is replicated by splitting its double strands and using each of them as a template for building a new partner.

Another reason for E. coli’s success was the discovery that it sometimes has a bacterial version of sex. Joshua Lederberg, a young graduate student in the mid-1940s, suspected that bacteria might mingle their genes as sexually-reproducing animals do. If they did, Lederberg realized, he could use bacteria to study genes in much the same way scientists used Drosophila--by breeding parents with different sets of genes and then studying how the genes mixed in their offspring. To prove that bacteria did have sex, however, Lederberg would need a special sort of microbe--one that he knew lived at Yale University, in the laboratory of Edward Tatum.

Tatum had created a collection of mutant E. coli. He had done so because he wanted to test the idea that a single gene encoded a single enzyme. Tatum and his colleague George Beadle had already shown this to be the case in experiments on bread mold. But mold--a fungus--is actually much more like us than like bacteria. So Tatum and Beadle set out to expand the one-gene-one-enzyme rule. They needed a fast-growing, safe microbe that could make many of its own amino acids, the building blocks of proteins. They planned to create mutant versions of the microbes by bombarding them with X-rays. A mutation might cripple a gene that was essential for building an amino acid. They could then pinpoint the mutation by finding bacteria that could only grow if their diet was enriched with a single amino acid. Tatum realized E. coli would be a good species to study. (He used a strain isolated from a patient in 1922, known as K-12. K-12 remains today the most studied strain of E. coli.) Tatum and Beadle created mutant strains of E. coli K-12 and discovered that, indeed, a single mutation could make the bacteria unable to make a single amino acid.

Lederberg joined Tatum’s lab at Yale and began to experiment with strains which had acquired two mutations. He mixed strains together with different sets of mutations and discovered that on rare occasion, the microbes traded genes. The bacteria, which had once been unable to survive without two amino acids, had given rise to new bacteria that could do very well on their own. Later, scientists would discover that E. coli, like many other kinds of bacteria, can build a tube that can pump some of its DNA into a recipient. It takes hours until the process is complete. During that time, scientists began to put the bacteria in a blender to spin them apart. They could discover which genes had been transferred in that time, and use those results to map the genes of E. coli along its circular chromosome.

Once these sorts of studies emerged, other scientists snapped up E. coli for their own experiments. They did not need to reinvent the wheel in order to investigate some basic question of biology; they could stand on the shoulders of scientists like Delbruck and Lederberg. And once scientists discovered something about E. coli, they would often discover that the same held true for all living things. E. coli uses a particular code to translate its genes into proteins, for example. Once scientists broke E. coli’s code, they found that every other species they examined used an almost identical one. Researchers discovered that certain proteins in E. coli can switch off genes and switch them on in response to specific signals. The same kind of switching takes place in other species as well. It’s the reason our bone cells make bone, for example, while our blood cells make hemoglobin, despite the fact that they all have genes for making both substances. As the Nobel-prize-winning biologist Jacques Monod once quipped, “What is true for E. coli is true for the elephant.”

Many of the pioneers of E. coli biology, including Delbruck, Tatum, and Lederberg, went on to win Nobel Prizes for their research. Since then, scientists have learned how to carry out experiments on many other species to ask basic questions about biology. But E. coli continues to be a favorite. Because scientists have amassed so much knowledge about it, for example, they may be able to figure out how its 4000-odd genes interact as a system, one that can withstand fluctuations in the environment while being able to change its behavior when necessary. Other scientists are observing E. coli evolve, scanning its genome to pinpoint the mutations favored by natural selection. They are trying to determine whether evolution is predictable or dominated by chance. And this sort of knowledge has also allowed scientists to harness E. coli’s biological creativity. By inserting genes into the microbe and adjusting its own DNA, they have transformed it into a biochemical factory, capable of producing compounds ranging from human insulin to jet fuel. E. coli may have a lot of company in the lab these days, but with advances such as these, it will continue to mean much more to scientists than a bad case of food poisoning. Ecolihub may be able to help the rest of us appreciate the difference too.