

Every day, it seems, scientists learn something new about how our genes work. The latest insights into the dazzling and complex machinery of life itself.

Four years ago, a Duke University biologist named Randy Jirtle began an elegant little experiment that would ultimately lead him to confront one of life's biggest mysteries. He started with two groups of mice that gave birth to sets of identical babies carrying the same genes. The babies were raised the same way from birth. They should have looked alike but instead, they barely looked related. In the first group, the babies were overweight, prone to diabetes and cancer and covered in fur the color of rancid butter. The mice in the second group were beautiful: lean, healthy, brown. Same nature, same nurture, radically different outcomes. What was going on in there?

The difference, it turned out, wasn't due to the mice's genetic code, nor was it due to the environment. It lay instead in a mechanism that was mediating between the two. A gene in the sickly yellow babies was making a disease-causing protein called Agouti, which also affects coat color. The brown babies had the same gene, but it wasn't making much of anything. It had mostly stopped working. The brown babies' mothers had eaten a special diet during pregnancy: one rich in folic acid, which floods the body with tiny four-atom configurations called methyl groups. These methyl groups had infiltrated the growing brown mouse embryos and latched onto the flawed gene, shutting it down. This was the solution to the mystery: Jirtle had vividly illustrated why, at the biochemical level, the genetic sequence alone doesn't always equal destiny. Four humble atoms had been enough to override a serious defect in the brown babies' genomes. And what was true of the mice turned out to be true of men: there is much more to our nature than the plans laid in the genetic code.

Biologists have known about methyl groups for decades, and since the 1990s they have discovered several other types of chemical switches that can turn genes on and off. But only recently have they begun to understand that these switches are a crucial link between the DNA and the outside world. Their findings are now challenging some of science's most basic assumptions about the way life works. Researchers once saw the order of the base pairs in DNA as a sort of unchanging blueprint, but that was far too simplistic an interpretation. Almost immediately after conception, while the embryo is still just a few cells, it begins to pick up on subtle cues in its environment. It then canvasses its own genome, switching genes in different cells on or off according to the signals it receives. At this moment, "nature" becomes malleable, and genetically identical cells set off on different journeys. Throw the switches one way and the cells grow into a heart. Throw them another way and the cells metamorphose into a liver. Wait long enough and you'll generate a full-grown person with a bewildering array of cells, tissues and organs. The switches, scientists now know, are responsible for this process. They direct almost all the body's fundamental functions. As much as the genes themselves, they are the biological builders that make us who we are.

That's not always a good thing. Malfunctioning genetic switches play a role in the vast majority of noninfectious diseases, including cancer, obesity and neurological disorders. Some of the switches, once set, seem to get stuck for life. But others may be reversible. Drug companies have already developed chemotherapies that turn genes on and off in cancer cells. They hope to someday build on the same principles to design drugs for almost every illness with a genetic component. "We feel like the Egyptologists in search of Tutankhamun's tomb," says Dr. Andrew Allen, chief medical officer of Pharmion, a firm with several such drugs in the works. "We've reached an antechamber. We have the sense that there are wonderful things just around the corner." Those things may be the answers to some of biology's biggest puzzles—mysteries of life that science has yet to solve.

To crack these secrets, scientists will first have to adopt new ways of thinking about genes. As they have learned more about the switches, they have had to revise theories that go all the way back to the pre-DNA era. Genetics was born in 1866, when a monk named Gregor Mendel published a seminal paper that defined the term "gene" as the unit that passes down heritable traits. He argued that children inherit two copies of each gene—one from the mother and one from the father. Although one may have more influence than the other, both remain active throughout life. Mendel's laws eventually became widely accepted. Still, no one knew what genes were actually made of until 1953, when James Watson and Francis Crick revealed their simple but ingenious double-helix model of DNA.

In Watson and Crick's model, each gene is made of a long, continuous stretch of nucleic acids arranged in a specific order. The gene's function is to serve as a template for RNA, which in turn pieces together proteins, the body's building blocks. This model is still biology's guiding principle, the "central dogma": DNA makes RNA makes proteins. It is correct, but as scientists now know, it is not comprehensive. DNA must be doing something else as

well—because, as it turns out, only 1 percent or so of the genome is actually in the protein-making business.

Until recently, some scientists assumed that the rest of the genome was a hodgepodge of evolutionary leftovers that did very little of consequence. Part of it they called "junk DNA," and the rest of it they didn't even name. "I think some people were hoping that 99 percent of the genome could just be ignored," says biologist Eric Lander, founding director of the Broad Institute, a collaboration of Harvard University and the Massachusetts Institute of Technology. Over the last decade, though, researchers have realized that this forgotten part of the genome is, in fact, profoundly important. It contains the machinery that flips the switches, manipulating much of the rest of the genome.

Most of the machinery follows Mendel's laws. But not all of it does. Some of it violates the notion that both copies of a gene operate throughout life. During the tango of conception, the sperm and egg both try to lead: they argue over a small set of genes in which one copy, from the mother or the father, will be permanently switched off, leaving the other copy to work solo. This week, the journal *Genome Research* will publish a study, led by Jirtle, suggesting that there are 156 of these solo genes in the body. Many are responsible for regulating other genes.

Scientists have been studying gene regulation for decades, but in the past few years, since the Human Genome Project was completed, they have drastically accelerated their pace. There is still a great deal to be learned, but a new discovery now appears in a major journal almost every week. "Every time you think you've solved the way things get regulated, you realize there's yet another layer of complexity," says biologist Rick Young of MIT and the Whitehead Institute for Biomedical Research. "That can be frustrating, but it's also exciting. It's so beautifully complicated."

Researchers have explored and exploited several types of genetic switches in the last few years. "Small interfering" and "microRNAs"—tiny free-floating nucleic-acid strings that can fool genes into shutting themselves down—are some of the most intriguing. Scientists have figured out how to mimic them using artificially created versions to turn genes off. The technique, called RNA interference (RNAi), won the Nobel Prize last year and it has now moved from academia to industry. Several firms have invented locally injectable RNAi therapies, and three weeks ago Quark Pharmaceuticals began to test in humans the world's first systematically injected RNAi. It turns off a gene called p53 that can cause unnecessary cell death in the kidneys; once the drug's work is done it exits the body, and p53 turns back on.

Methyl groups, the four-atom configurations that tamped down the Agouti gene in Jirtle's mice, are another influential category of switches. They may interfere with the DNA directly, like monkey wrenches in its machinery or, instead, they may interact with histones, proteins that serve as yet another type of switch. Young, the MIT biologist, made a surprising discovery about histones in July: at least a third of our genes have histone switches that hover somewhere between on and off, allowing the genes to start manufacturing their signature proteins but not letting them finish. Young notes that the human embryo must initiate many complex developmental processes in a short time period. Maybe, he says, the body keeps some of the genes involved in development "poised for action" so it can kick-start them quickly, when there's "little time to waste."

That speed, however, may come at a cost. Some of the genes that are left half-on are crucial in early development. When they're fully turned on—and that could happen accidentally if they're already halfway there—they can wipe out the cell's entire machinery, turning it into a blank slate that looks dangerously like a cancer stem cell. Young is currently exploring the hypothesis that our half-on, half-off genes are directly linked to cancer—they're necessary for development, but they also may predispose us to tumors later on.

This idea—that cancer is a necessary problem, an unavoidable consequence of our genes' need to switch on and off—is troubling, but it does make intuitive sense. The more we learn about the genome, the more complicated it turns out to be, and the more complicated a system is, the more potential there is for error. Cancer and other common diseases of regulation may thus be intrinsically built into our bodies—the price we pay for being such intricately built beings. "We cannot look at common diseases such as cancer as accidents of evolution," says Kari Stefansson, president of the Icelandic genetic firm DeCode. "We may have been designed by evolution in a very complex manner for the sole purpose of making sure we eventually die."

Life, death and human nature are complex questions, and we've always known the answers would be equally complex. For the first 50 years of modern DNA-driven genetics, it wasn't clear if we'd ever solve the mysteries. But

with our emerging understanding of the machinery that directs development and disease, scientists at least have some new places to look for clues. Let's hope the switches that turn on the genes also turn on the lights.