18

"Strangest Hybrid"

By the 1960s, scientists joked that HeLa cells were so robust that they could probably survive in sink drains or on doorknobs. They were everywhere. The general public could grow HeLa at home using instructions from a *Scientific American* do-it-yourself article, and both Russian and American scientists had managed to grow HeLa in space.

Henrietta's cells went up in the second satellite ever in orbit, which was launched by the Russian space program in 1960, and almost immediately afterward, NASA shot several vials of HeLa into space in the *Discoverer XVIII* satellite. Researchers knew from simulated zero-gravity studies using animals that space travel could cause cardiovascular changes, degradation of bone and muscle, and a loss of red blood cells. They also knew radiation levels were higher beyond the ozone layer. But they didn't know what effects any of this would have on humans: Would it cause cellular changes, or even cell death?

When the first humans went into orbit, Henrietta's cells went with them so researchers could study the effects of space travel, as well as the nutritional needs of cells in space, and how cancerous and

noncancerous cells responded differently to zero gravity. What they found was disturbing: in mission after mission, noncancerous cells grew normally in orbit, but HeLa became more powerful, dividing faster with each trip.

And HeLa cells weren't the only ones behaving strangely. Since the start of the decade, researchers had been noticing two new things about all cultured cells. First, it seemed that all normal cells growing in culture eventually died or underwent spontaneous transformation and became cancerous. This phenomenon was exciting for researchers trying to understand the mechanisms of cancer, because it suggested that they might be able to study the moment a normal cell becomes malignant. But it was disturbing for those trying to use cell culture to develop medical therapies.

George Hyatt, a Navy doctor working with the National Cancer Institute, had experienced this phenomenon firsthand. He'd cultured human skin cells for treating badly burned soldiers, then created a wound on a young volunteer officer's arm and smeared the cells across it, hoping they'd grow to form a new layer of skin. If it worked, it might mean doctors could use skin-cell transplants to treat wounds in the field. The cells did grow, but when Hyatt biopsied them a few weeks later, they were all cancerous. He panicked, removed the cells, and hadn't tried transplanting skin cells since.

The other unusual thing scientists had noticed about cells growing in culture was that once they transformed and became cancerous, they all behaved alike—dividing identically and producing exactly the same proteins and enzymes, even though they'd all produced different ones before becoming malignant. Lewis Coriell, a renowned cell culturist, thought he might have an explanation. He published a paper suggesting that perhaps "transformed" cells behaved the same not because they'd become cancerous, but because they'd been contaminated by something—most likely a virus or bacterium—that made them behave similarly. Almost as an aside, he pointed out one possibility that other researchers hadn't considered: all transformed cells seemed to behave identically to HeLa, he wrote, which could mean that HeLa was the contaminant.

Soon after his paper was published, Coriell and a few other top tissue culturists called an urgent meeting to talk about the state of their field, which they worried was becoming a disaster. They'd mastered the techniques of cell culture and simplified them to such a degree that, as one researcher put it, they'd "made it possible for even the rank amateur to grow a few cultures."

In recent years, using tissue samples from themselves, their families, and their patients, scientists had grown cells of all kinds—prostate cancer, appendix, foreskin, even bits of human cornea—often with surprising ease. Researchers were using that growing library of cells to make historic discoveries: that cigarettes caused lung cancer; how X-rays and certain chemicals transformed normal cells into malignant ones; why normal cells stopped growing and cancer cells didn't. And the National Cancer Institute was using various cells, including HeLa, to screen more than thirty thousand chemicals and plant extracts, which would yield several of today's most widely used and effective chemotherapy drugs, including Vincristine and Taxol.

Despite the importance of this research, many scientists seemed cavalier about their cultures. Few kept clear records of which cells grew from which donors, and many mislabeled their cultures, if they labeled them at all. For scientists doing research that *wasn't* cell-specific, like investigating the effects of radiation on DNA, not knowing what kind of cell they were working on might not affect the outcome of their research. But if cells were contaminated or mislabeled in research that *was* cell-specific—as much research was—the results would be worthless. Regardless, the culturists who called the meeting said, precision was essential in science, and researchers should know what cells they were using, and whether they were contaminated.

According to Robert Stevenson, one of the scientists involved in the meeting, their goal was to keep the field from "degenerating into complete chaos." The group encouraged researchers to use protective

measures, like working under hoods with suction that pulled air and potential contaminants into a filtration system. And they recommended that the NIH establish a reference collection of cells: a central bank where all cultures would be tested, cataloged, and stored under maximum security, using state-of-the-art sterile techniques. The NIH agreed, and formed a Cell Culture Collection Committee made up of tissue culturists, including William Scherer, Lew Coriell, and Robert Stevenson. Their mission was to establish a nonprofit federal cell bank at the American Type Culture Collection (ATCC), which had been distributing and monitoring the purity of bacteria, fungi, yeast, and viruses since 1925, but never cultured cells.

The scientists on the Collection Committee set out to create the Fort Knox of pure, uncontaminated cell culture. They transported cultures in locked suitcases and developed a list of criteria all cells had to meet before being banked: each had to be tested for any possible contamination, and they all had to come directly from the original source.

Cell number one in the ATCC's collection was the L-cell, the original immortal mouse cell line grown by Wilton Earle. For cell number two, the committee contacted Gey asking for a sample from the original HeLa culture. But in his initial excitement, Gey had given all of the original HeLa cells to other researchers and kept none for himself. He eventually tracked some down in the lab of William Scherer, who'd used some of the original HeLa sample in their polio research.

Initially the committee could only test samples for viral and bacterial contamination, but soon a few of its members developed a test for cross-species contamination, so they could determine whether cultures labeled as being from one animal type were actually from another. They quickly found that of ten cell lines thought to be from nine different species—including dog, pig, and duck—all but one were actually from primates. They promptly relabeled those cultures, and it seemed they'd gotten the situation under control without attracting any bad publicity.

The media, it turned out, was far more interested in a bit of HeLa-related news that was almost as sensational as Alexis Carrel's immortal chicken heart. And it all started with cell sex.

In 1960, French researchers had discovered that when cells were infected with certain viruses in culture, they clumped together and sometimes fused. When they fused, the genetic material from the two cells combined, as with sperm meeting egg. The technical name for this was *somatic cell fusion,* but some researchers called it "cell sex." It was different from sperm-and-egg sex in several important ways: somatic cells were cells of the body, like skin cells, and their union produced offspring every few hours. Perhaps most important, cell sex was entirely controlled by researchers.

Genetically speaking, humans are terrible research subjects. We're genetically promiscuous—we mate with anyone we choose—and we don't take kindly to scientists telling us who to reproduce with. Plus, unlike plants and mice, it takes us decades to produce enough offspring to give scientists much meaningful data. Since the mid-1800s, scientists had studied genes by breeding plants and animals in specific ways—a smooth pea with a wrinkled one, a brown mouse with a white one—then breeding their offspring to see how genetic traits passed from one generation to the next. But they couldn't study human genetics the same way. Cell sex solved that problem, because it meant researchers could combine cells with any traits they wanted and study how those traits were passed along.

In 1965 two British scientists, Henry Harris and John Watkins, took cell sex an important step further. They fused HeLa cells with mouse cells and created the first human-animal hybrids—cells that contained equal amounts of DNA from Henrietta and a mouse. By doing this, they helped make it possible to study what genes do, and how they work.

In addition to the HeLa-mouse hybrid, Harris fused HeLa with chicken cells that had lost their ability to reproduce. His hunch was

that when those deactivated chicken cells fused with HeLa, something inside HeLa would essentially turn the chicken cell back on. He was right. He didn't know how it worked yet, but his discovery showed that something in cells regulated genes. And if scientists could figure out how to turn disease genes off, they might be able to create a form of gene therapy.

Soon after Harris's HeLa-chicken study, a pair of researchers at New York University discovered that human-mouse hybrids lost their human chromosomes over time, leaving only the mouse chromosomes. This allowed scientists to begin mapping human genes to specific chromosomes by tracking the order in which genetic traits vanished. If a chromosome disappeared and production of a certain enzyme stopped, researchers knew the gene for that enzyme must be on the most recently vanished chromosome.

Scientists in laboratories throughout North America and Europe began fusing cells and using them to map genetic traits to specific chromosomes, creating a precursor to the human genome map we have today. They used hybrids to create the first monoclonal antibodies, special proteins later used to create cancer therapies like Herceptin, and to identify the blood groups that increased the safety of transfusions. They also used them to study the role of immunity in organ transplantation. Hybrids proved it was possible for DNA from two unrelated individuals, even of different species, to survive together *inside* cells without one rejecting the other, which meant the mechanism for rejecting transplanted organs had to be *outside* cells.

Scientists were ecstatic about hybrids, but throughout the United States and Britain, the public panicked as the media published one sensational headline after the next:

MAN-ANIMAL CELLS ARE BRED IN LAB . . . THE NEXT STEP COULD BE TREE MEN . . . SCIENTISTS CREATE MONSTERS

The Times of London called the HeLa-mouse cells the "strangest hybrid form of life ever seen in the lab—or out of it." A *Washington Post* editorial said, "We cannot afford any artificially induced mouse-men."

It called the research "horrendous" and said the researchers should leave humans alone and "go back to their yeasts and fungi." One article ran with an image of a half-human, half-mouse creature with a long, scaly tail; another ran with a cartoon of a hippopotamus-woman reading the newspaper at a bus stop. The British press called the HeLa hybrids an "assault on life," and portrayed Harris as a mad scientist. And Harris didn't help the situation: he caused near-pandemonium when he appeared in a BBC documentary saying that the eggs of man and ape could now be joined to create a "mape."

Harris and Watkins wrote letters to editors complaining they'd been quoted out of context, their story sensationalized to "distort, misrepresent and terrify." They assured the public that they were just creating cells, not "trying to produce centaurs." But it didn't help. A public survey about their research was overwhelmingly negative, calling it pointless and dangerous, an example of "men trying to be gods." And the PR problem for cell culture was only going to get worse from there.