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LIFE | IDEAS | THE SATURDAY ESSAY

The Breakdown in Biomedical Research

Contaminated samples, faulty studies and inadequate training have created a crisis in laboratories and industry, slowing the quest for new treatments and cures

ILLUSTRATION: DOUG CHAYKA

By **RICHARD HARRIS**
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Later this month, HBO will air a movie starring Oprah Winfrey about the story of Henrietta Lacks, an African-American woman who died of cervical cancer in 1951 but whose cells live on today in laboratories around the world. The film, based on Rebecca Skloot's best-selling book "The Immortal Life of Henrietta Lacks," explores the Lacks family's struggle to get recognition for the crucial contribution that the Maryland woman inadvertently made to science. Her cancerous cells, dubbed HeLa, were extracted and cultured at the Johns Hopkins Hospital in Baltimore and became the first perpetual supply of cancer cells to be used in medical research.

But there is more to the story of HeLa than this compelling personal angle. The cells neatly illustrate a serious problem in biomedical research: Because they reproduce so quickly and have been mishandled so frequently over the years, HeLa cells have proved to be a serious contaminant. They have ruined countless experiments, fooling generations of scientists who hadn't realized that the cells had crept into their flasks. One careless moment in the lab can let HeLa overtake and crowd out other cells, so that scientists who think they are studying liver cancer, for example, are in fact doing nothing of the sort.

Such contamination is just one of the many problems now confronting biomedical research. Scientists point to what they call the "reproducibility crisis"—that is, studies whose results can't be duplicated and are untrustworthy if not invalid. The issue isn't just wasted time and money. Many observers now think that biomedical research world-wide has been so compromised that it is slowing and diverting the search for new

treatments and cures.

Henrietta Lacks's cells became the first perpetual supply of cancer cells to be used in medical research. *PHOTO: GETTY IMAGES*

Dealing with the crisis, which has been in evidence for more than a decade now, has become a priority in the field. The first step, however, is to understand its origins, which are manifold, ranging from inadequate training and poor lab techniques to a funding squeeze that creates perverse incentives for professional advancement.

Failure is an essential part of science, and no one expects researchers to get everything right on the first try. Scientific discovery is usually self-correcting in the long run, with useful information, treatments and drugs emerging even from experiments that don't work out. But false starts can slow progress.

How much of biomedical research is actually wrong? John Ioannidis, an epidemiologist and health-policy researcher at Stanford, was among the first to sound the alarm with a 2005 article in the journal PLOS Medicine. He showed that small sample sizes and bias in study design were chronic problems in the field and served to grossly overestimate positive results. His dramatic bottom line was that "most published research findings are false."

'It's tempting for scientists (like everyone else) to see what they want to see in their findings.'

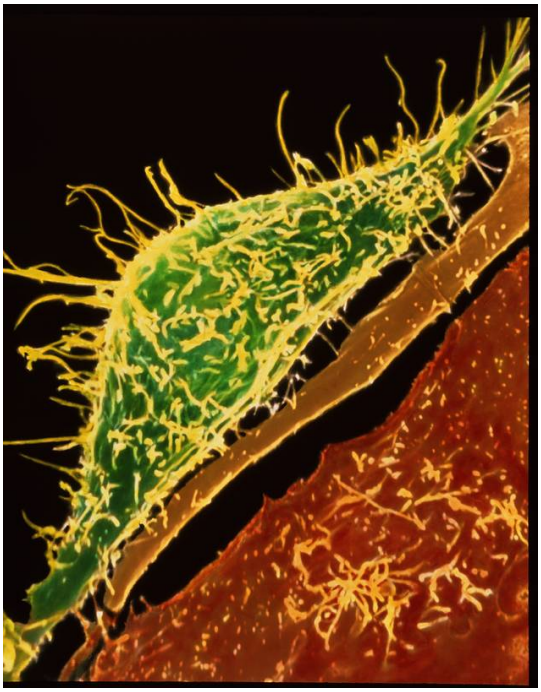
The problem is especially acute in laboratory studies with animals, in which scientists often use just a few animals and fail to select them randomly. Such errors inevitably introduce bias. Large-scale human studies, of the sort used in drug testing, are less likely to be compromised in this way, but they have their own failings: It's tempting for scientists (like everyone else) to see what they want to see in their findings, and data may be cherry-picked or massaged to arrive at a desired conclusion.

A paper published in February in the journal PLOS One by Estelle Dumas-Mallet and colleagues at the University of Bordeaux tracked 156 biomedical studies that had been the subject of stories in major English-language newspapers. Follow-up studies, they showed, overturned half of those initial positive results (though such disconfirmation rarely got follow-up news coverage). The studies dealt with a wide range of issues, including the biology of attention-deficit hyperactivity disorder, new breast-cancer susceptibility genes, a reported link between pesticide exposure and Parkinson's disease, and the role of a virus in autism.

Reviews by pharmaceutical companies have delivered equally grim numbers. In 2011, scientists at Bayer published a paper in the journal Nature Reviews Drug Discovery showing that they could replicate only 25% of the findings of various studies. The following year, C. Glenn Begley, the head of cancer research at Amgen, reported in the journal Nature that he and his colleagues could reproduce only six of 53 seemingly promising studies, even after enlisting help from some of the original scientists.

With millions of dollars on the line, industry scientists overseeing clinical trials with human subjects have a stronger incentive to follow high standards. Such studies are often designed in cooperation with the U.S. Food and Drug Administration, which ultimately reviews the findings. Still, most clinical trials produce disappointing results, often because the lab studies on which they are based were themselves flawed.

There are many different reasons for this crisis, but as the case of the HeLa cells suggests, contaminated research materials are a prime culprit. The International Cell Line Authentication Committee, a volunteer group of about 20 scientists, has been keeping tabs on the number of misidentified cell lines. Their count is now over 450. HeLa is the contaminant in 113 of those cases, but it is hardly alone.



A colored scanning electron micrograph of a HeLa cell growing in culture. *PHOTO: GETTY IMAGES*

For many years, a cell line called MDA-MB-425—isolated in 1976 at Houston's MD Anderson Cancer Hospital and Tumor Institute (as it was known at the time) from a woman with breast cancer—was considered one of the most important tools for studying breast tumors. In 2000, scientists ran a genetic fingerprint of this cell and discovered that it was, in fact, a melanoma. That information has been widely disseminated, but even so, scientists have since published more than 900 "breast cancer" reports involving this cell line.

Another key source of error is bad research design: Too many scientists conduct poorly conceived experiments or fail to analyze them properly. They often use too few animals and don't take all the steps necessary to reduce the risk of bias.

Consider the trail of failures in the search for drugs to treat amyotrophic lateral sclerosis, or ALS, better known as Lou Gehrig's disease. Scientists have spent millions of taxpayer dollars over the past few decades to test out seemingly promising drugs to treat this unstoppable neuromuscular disease, which gradually robs people of the ability to move and breathe.

But no effective treatments have been developed. Scientists at the ALS Therapy Development Institute in Cambridge, Mass., set out to discover why. As they reported in 2008 in the journal Amyotrophic Lateral Sclerosis, they found serious defects in almost all of the underlying research. The studies often used fewer than a dozen mice per experiment and didn't take care to avoid significant sources of bias, such as genetic variability in the animals. The ALS institute redid the studies with proper controls and found that none of the dozen or so drugs, despite the initial findings, showed any real promise.

The ALS institute now conducts its own lab studies on promising therapies, typically with 32 mice in the testing group and 32 in a control group. Doing it right costs more than $100,000 per experiment, a sum that most academic researchers are unable to raise for a single study.

'Researchers often don't have the training to design rigorous studies in the first place.'

But the issue isn't just money. Researchers often don't have the training to design rigorous studies in the first place. Young scientists may take a statistics class or two, but they tend to learn about experimental design in a very ad hoc way, primarily by working as cheap labor in their mentors' labs. In 2014, in an attempt to improve training, Jon Lorsch, who directs the National Institute of General Medical Sciences at the NIH, sought to replicate the best methodology classes he could find. He put out a call to universities asking for suggestions but found essentially nothing. The NIH has since funded efforts to develop methodology courses.

Exacerbating the problem of poor training is the professional pressure to get splashy results. Biomedical research is a hypercompetitive environment, driven in large measure by the competition for funding. The federal government now supports 58% of biomedical research at universities, according to 2014 data from the National Science Foundation, with just 4% from state and local governments and the remainder from university endowments, companies and nonprofits.

Funding by the NIH declined by 22% between 2003 and 2015. *PHOTO: GETTY IMAGES*

Public support for biomedical research, however, has been in sharp decline for some time now. According to the federal government, funding by the NIH declined by 22% between 2003 and 2015, as measured in real dollars. The Trump administration's budget plan would immediately reduce the NIH budget by another 18.3%, though Congress is unlikely to accept such a steep cut.

Funding is so tight these days, according to the NIH, that someone running a lab must write, on average, five grant proposals to get funding for one project. The pressure is intense. Scientists who lose their grants may eventually lose their employees, labs and careers.

"Most people who work in science are working as hard as they can," says Brian Martinson, a sociologist at HealthPartners Institute, a nonprofit research agency in Minnesota. So what's left, he asks, "to get an edge, to get ahead, to be the person who crosses the finish line first? All you can do is cut corners. That's the only option left you."

Scientists hoping to land good jobs or university tenure also need to have their studies published in one of a handful of top journals. No paper in the prestigious journal Nature? No job interview. That provides further incentive to pretty up one's work by leaving out inconvenient findings, enhancing images or even avoiding experiments that could undercut a surprising conclusion.

Scientists and science administrators have come to realize that they can no longer afford to ignore this complicated set of interlocking problems. A few researchers, including Dr. Ioannidis and his colleague Steven Goodman, are focusing their work on efforts to improve the practice of biomedical research. At Stanford, they have created the Meta-Research Innovation Center, which aims to find ways to transform work in the field.

"I would be the last to say we've solved all the problems of clinical research," Dr. Goodman says. "But at least we have a decent template of what needs to be done." A crucial first step, he argues, would be to increase transparency throughout the research process.

Brian Nosek, executive director of the Center for Open Science and a psychology professor at the University of Virginia, also believes that researchers should make all of their methods and data freely available. This would allow the more rapid correction of faulty work—and would also encourage researchers to be more careful in the first place. Dr. Nosek has created a free online resource called the Open Science Framework that is designed to allow scientists to make their hypotheses, methods, computer code and data freely available. For its part, Johns Hopkins University is pioneering a program that verifies exciting results from lab studies before those findings get passed along to biopharma companies.

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Some companies also have stepped into the gap. Protocols.io, in Berkeley, Calif., is a repository of research methods, so scientists can record exactly what they've done and use the same formula the next time that they run a study, or share those detailed methods with someone else. Ryffin in Oakland, Calif., is another specialized firm in this niche, with software that helps scientists to map out their experiments, manage scattered data sets, pull it all together for analysis and share it with colleagues.

University deans and departments also could change the perverse incentive system that distorts so much research. Instead of asking professors up for promotion to hand in a stack of all their published work, they could tell scientists at the outset that they will be judged on only two or three important findings. That would encourage them to strive for quality over quantity.

Some simple technological fixes also can help. As of January 2016, the NIH requires scientists getting federal grants to check the cell lines for their studies to make sure that they aren't inadvertently using HeLa or other impostors. An inexpensive test is readily

available and could solve the problem of contamination. Researchers have to include the test in their research plan, but it isn't yet clear how the NIH will verify compliance or penalize infractions.

There is no easy solution for the mismatch between funds available for research and the number of scientific mouths to feed. The ecosystem is fundamentally out of balance. Slashing funding wouldn't simply cut out the waste. Peer review already weeds out 80% of grant proposals before research has even begun, including those with weak methods.

There's no formula, of course, for predicting which research program will yield the next wonder drug. If we knew that, there would be no need to run the experiments. But standards and rules, more rigorously applied, can at least eliminate many needless errors. And transparency can help to bring the inevitable errors to light more quickly.

Reforming the professional habits and culture of biomedical research won't be easy, and it's still smart to cast a wary eye on sensational results from the latest study. But real change is starting to take shape. It has the potential to accelerate progress toward the new drugs and improved treatments that everyone wants but that science, over the past several decades, has been struggling to deliver.

Mr. Harris is a longtime science correspondent at NPR News. This piece is adapted from his new book, "Rigor Mortis: How Sloppy Science Creates Worthless Cures, Crushes Hope and Wastes Billions," published by Basic Books.

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