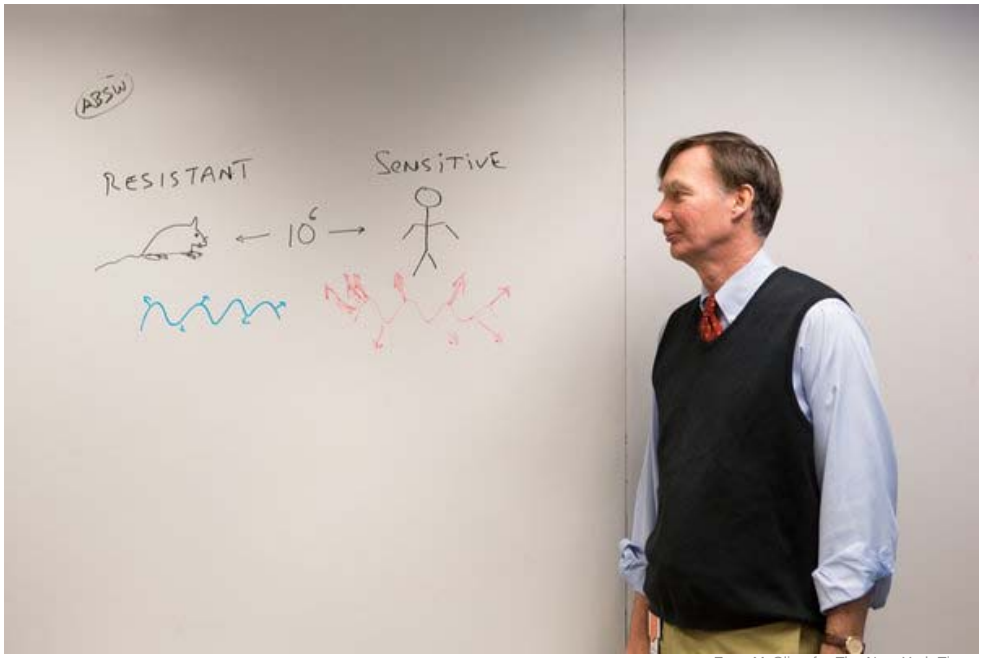
Mice Fall Short as Test Subjects for Humans' Deadly Ills



Evan McGlinn for The New York Times

Dr. H. Shaw Warren is one of the authors of a new study that questions the use of laboratory mice as models for all human diseases.

By GINA KOLATA
Published: February 11, 2013 | 285 Comments

For decades, mice have been the species of choice in the study of human diseases. But now, researchers report evidence that the mouse model has been totally misleading for at least three major killers — sepsis, burns and trauma. As a result, years and billions of dollars have been wasted following false leads, they say.

The study's findings do not mean that mice are useless models for all human diseases. But, its authors said, they do raise troubling questions about diseases like the ones in the study that involve the immune system, including cancer and heart disease.

"Our article raises at least the possibility that a parallel situation may be present," said Dr. H. Shaw Warren, a sepsis researcher at Massachusetts General Hospital and a lead author of the new study.

The paper, published Monday in Proceedings of the National Academy of Sciences, helps explain why every one of nearly 150 drugs tested at a huge expense in patients with sepsis has failed. The drug tests all were based on studies in mice. And mice, it turns out, can have something that looks like sepsis in humans, but is very different from the condition in humans.

Medical experts not associated with the study said that the findings should change the course of research worldwide for a deadly and frustrating condition. Sepsis, a potentially deadly reaction that occurs as the body tries to fight an infection, afflicts 750,000

patients a year in the United States, kills one-fourth to one-half of them, and costs the nation $17 billion a year. It is the leading cause of death in intensive-care units.

“This is a game changer,” said Dr. Mitchell Fink, a sepsis expert at the University of California, Los Angeles, of the new study.

“It’s amazing,” said Dr. Richard Wenzel, a former chairman at the department of internal medicine at Virginia Commonwealth University and a former editor of The New England Journal of Medicine. “They are absolutely right on.”

Potentially deadly immune responses occur when a person’s immune system overreacts to what it perceives as danger signals, including toxic molecules from bacteria, viruses, fungi, or proteins released from cells damaged by trauma or burns, said Dr. Clifford S. Deutschman, who directs sepsis research at the University of Pennsylvania and was not part of the study.

The ramped-up immune system releases its own proteins in such overwhelming amounts that capillaries begin to leak. The leak becomes excessive, and serum seeps out of the tiny blood vessels. Blood pressure falls, and vital organs do not get enough blood. Despite efforts, doctors and nurses in an intensive-care unit or an emergency room may be unable to keep up with the leaks, stop the infection or halt the tissue damage. Vital organs eventually fail.

The new study, which took 10 years and involved 39 researchers from across the country, began by studying white blood cells from hundreds of patients with severe burns, trauma or sepsis to see what genes were being used by white blood cells when responding to these danger signals.

The researchers found some interesting patterns and accumulated a large, rigorously collected data set that should help move the field forward, said Ronald W. Davis, a genomics expert at Stanford University and a lead author of the new paper. Some patterns seemed to predict who would survive and who would end up in intensive care, clinging to life and, often, dying.

The group had tried to publish its findings in several papers. One objection, Dr. Davis said, was that the researchers had not shown the same gene response had happened in mice.

“They were so used to doing mouse studies that they thought that was how you validate things,” he said. “They are so ingrained in trying to cure mice that they forget we are trying to cure humans.”

“That started us thinking,” he continued. “Is it the same in the mouse or not?”

The group decided to look, expecting to find some similarities. But when the data were analyzed, there were none at all.

“We were kind of blown away,” Dr. Davis said.

The drug failures became clear. For example, often in mice, a gene would be used, while in humans, the comparable gene would be suppressed. A drug that worked in mice by disabling that gene could make the response even more deadly in humans.

Even more surprising, Dr. Warren said, was that different conditions in mice — burns, trauma, sepsis — did not fit the same pattern. Each condition used different groups of genes. In humans, though, similar genes were used in all three conditions. That means, Dr. Warren said, that if researchers can find a drug that works for one of those conditions in people, it might work for all three.

The study's investigators tried for more than a year to publish their paper, which showed that there was no relationship between the genetic responses of mice and those of humans. They submitted it to the publications Science and Nature, hoping to reach a wide audience. It was rejected from both.

Science and Nature said it was their policy not to comment on the fate of a rejected paper, or whether it had even been submitted to them. But, Ginger Pinholster of Science said, the journal accepts only about 7 percent of the nearly 13,000 papers submitted each year, so it is not uncommon for a paper to make the rounds.

Still, Dr. Davis said, reviewers did not point out scientific errors. Instead, he said, "the most common response was, 'It has to be wrong. I don't know why it is wrong, but it has to be wrong.' "

The investigators turned to Proceedings of the National Academy of Sciences. As a member of the academy, Dr. Davis could suggest reviewers for his paper, and he proposed researchers who he thought would give the work a fair hearing. "If they don't like it, I want to know why," he said. They recommended publication, and the editorial board of the journal, which independently assesses papers, agreed.

Some researchers, reading the paper now, say they are as astonished as the researchers were when they saw the data.

"When I read the paper, I was stunned by just how bad the mouse data are," Dr. Fink said. "It's really amazing — no correlation at all. These data are so persuasive and so robust that I think funding agencies are going to take note." Until now, he said, "to get funding, you had to propose experiments using the mouse model."

Yet there was always one major clue that mice might not really mimic humans in this regard: it is very hard to kill a mouse with a bacterial infection. Mice need a million times more bacteria in their blood than what would kill a person.

"Mice can eat garbage and food that is lying around and is rotten," Dr. Davis said. "Humans can't do that. We are too sensitive."

Researchers said that if they could figure out why mice were so resistant, they might be able to use that discovery to find something to make people resistant.

"This is a very important paper," said Dr. Richard Hotchkiss, a sepsis researcher at Washington University who was not involved in the study. "It argues strongly — go to the patients. Get their cells. Get their tissues whenever you can. Get cells from airways."

"To understand sepsis, you have to go to the patients," he said.