Doubt has been cast on billions of dollars worth of medical research that used mice to test theories, writes Gina Kolata.

For decades, mice have been the species of choice in the study of human diseases. But now, researchers report stunning evidence that the mouse model has been 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 does not mean that mice are useless models for all human diseases. But, its authors say, it does raise troubling questions about diseases such as those 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," says Dr Shaw Warren, a sepsis researcher at Massachusetts General Hospital and a lead author of the study, published in the Proceedings of the National Academy of Sciences.

The paper helps explain why every one of almost 150 drugs tested at huge expense in patients with sepsis has failed. The drug tests all were based on studies in mice. And mice, it turns out, have a disease that looks like sepsis in humans but is very different from the human disease.

Experts not associated with the study say the findings should change the course of research worldwide for a deadly and frustrating disorder. Sepsis afflicts 750,000 patients a year in the US and kills one quarter to 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," Dr Mitchell Fink, a sepsis expert at the University of California, says.

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

Potentially deadly immune responses occur when a person's immune system responds to what it perceives as danger signals, including toxic molecules from bacteria, viruses, fungi, or proteins released from cells damaged by trauma or burns, Dr Clifford Deutschman, who directs sepsis research at the University of Pennsylvania, says.

The ramped-up immune system releases its own proteins in such overwhelming amounts that it makes capillaries 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 are 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, says Ronald 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, Davis says, 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 says. "They are so ingrained in trying to cure mice that they forget we are trying to cure humans. That started us thinking, is it the same in the mouse or not?"

The group decided to look, expecting to find some similarities. But when the data were analysed, there were none at all. "We were kind of blown away," Davis says.

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 works in mice by disabling that gene could make the response even more deadly in humans.

Even more surprising, Warren says, 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, Warren says, that if researchers can find a drug that works for one of those conditions in people, the same drug might work for all three. The study's investigators tried for more than a year to publish their paper showing 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 by 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 says the journal accepts only about 7 per cent of the almost 13,000 papers submitted each year, so it is not uncommon for a paper to make the rounds.

Still, Davis says, reviewers did not point out scientific errors. Instead, he says, "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 the Proceedings of the National Academy of Sciences. As a member of the academy, Davis could suggest reviewers for his paper, and he proposed researchers he thought would give the work a fair hearing. "If they don't like it, I want to know why,” he says.

They recommended publication, and the editorial board of the journal, which independently assesses papers, agreed.

Some researchers say they were 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," Fink says. "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 says, "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 1 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," Davis says. "Humans can't do that. We are too sensitive.”

Researchers say 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, too.

Dr Richard Hotchkiss, a sepsis researcher at Washington University in St Louis, says the paper makes the case for testing with human tissue.

"To understand sepsis you need to go to the patients. Get their cells. Get their tissues whenever you can. Get cells from airways,” he says.

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