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Mistakes in Scientific Studies Surge

By
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It was the kind of study that made doctors around the world sit up and take notice: Two popular high-blood-pressure drugs were found to be much better in combination than either alone.

"There was a 'wow' reaction," recalls Franz Messerli, a New York doctor who, like many others, changed his prescription habits after the 2003 report.

Unfortunately, it wasn't true. Six and a half years later, the prestigious medical journal the Lancet retracted the paper, citing "serious concerns" about the findings.

The damage was done. Doctors by then had given the drug combination to well over 100,000 patients. Instead of protecting them from kidney problems, as the study said the drug combo could do, it left them more vulnerable to potentially life-threatening side effects, later studies showed. Today, "tens of thousands" of patients are still on the dual therapy, according to research firm SDI.

When a study is retracted, "it can be hard to make its effects go away," says Sheldon Tobe, a kidney-disease specialist at the University of Toronto.

And that's more important today than ever because retractions of scientific studies are surging.

Since 2001, while the number of papers published in research journals has risen 44%, the number retracted has leapt more than 15-fold, data compiled for The Wall Street Journal by Thomson Reuters reveal.

Just 22 retraction notices appeared in 2001, but 139 in 2006 and 339 last year. Through seven months of this year, there have been 210, according to Thomson Reuters Web of Science, an index of 11,600 peer-reviewed journals world-wide.

In a sign of the times, a blog called "Retraction Watch" has popped up to monitor the flow.

Science is based on trust, and most researchers accept findings published in peer-reviewed journals. The studies spur others to embark on related avenues of research, so if one paper is later found to be tainted, an entire edifice of work comes into doubt. Millions of dollars' worth of private and government funding may go to waste, and, in the case of medical science, patients can be put at risk.

At the Mayo Clinic, a decade of cancer research, partly taxpayer-funded, went down the drain when the prestigious Minnesota institution concluded that intriguing data about harnessing the immune system to fight cancer had been fabricated. Seventeen scholarly papers published in nine research journals had to be retracted. A researcher, who protests his innocence, was fired.

In another major flameout, 18 research journals have said they are planning to retract a total of 89 published studies by a German anesthesiologist, many concerning a drug used for maintaining blood pressure during surgery. Authorities in Britain now are reviewing their usage guidelines as a result, and a prosecutor in Germany is conducting a criminal probe, which he says includes the possibility that data were fabricated. The anesthesiologist couldn't be reached for comment.

Why the backpedaling on more and more scientific research? Some scientific journals argue that the increase could indicate the journals have become better at detecting errors. They point to how software has made it easier to uncover plagiarism.

Others claim to find the cause in a more competitive landscape, both for the growing numbers of working scientific researchers who want to publish to advance their careers, and for research journals themselves.

"The stakes are so high," said the Lancet's editor, Richard Horton. "A single paper in Lancet and you get your chair and you get your money. It's your passport to success."

Retractions related to fraud showed a more than sevenfold increase between 2004 and 2009, exceeding the twofold rise in retractions related to mere error, according to an analysis published in the *Journal of Medical Ethics*. The analyst, Grant Steen, reached that conclusion after studying 742 medicine and biology papers that were withdrawn from 2000 to 2010. He said 73.5% were retracted simply for error but 26.6% were retracted for fraud.

Another researcher, John Budd of the University of Missouri-Columbia, looked at roughly the same set of journals, though over a longer period, and also found the prevalence of scientific misconduct to be on the increase.

The *Lancet*, founded in England in 1823, is among the world's most influential science publications. Just as research published in the *Lancet* can have a significant impact, so can the withdrawal of a *Lancet* paper, especially after it has been in the public domain and influencing scientific thought for years.

In a notorious case, the *Lancet* last year retracted a study claiming a link between autism and the measles-mumps-rubella vaccine—12 years after it was published. In the intervening years, measles cases spiked in the U.K. as some parents refused to let their children be vaccinated. The lead investigator on the now-retracted study, Andrew Wakefield, was stripped of his license to practice medicine in Britain after authorities concluded that he had engaged in "serious professional misconduct."

In an emailed response, Dr. Wakefield says he continues to defend his research, both "the findings and the conclusions."

The *Lancet* issued just a single retraction notice from 2001 through 2005, but five in the next five years, according to Thomson Reuters. They included the one finding great promise in the combined use of two common blood-pressure drugs. The case illustrates both why it can take so long to pull a flawed study and the fallout that can result.

One of the blood-pressure drugs, called an ACE inhibitor, relaxes blood vessels by preventing the body from creating a particular hormone. The other drug, called an ARB, acts on the same hormonal system but in a different way.

High blood pressure can lead to kidney damage, and each of the two common drugs reduces a sign of impending kidney disease—the loss of protein through the urinary system.

A Japanese researcher, Naoyuki Nakao, wondered if using both drugs at once would be even better at reducing this sign of kidney trouble. Sure enough, he reported that the combo was dramatically better than either drug alone.

The *Lancet* published his study, dubbed "Cooperate," in January 2003. It jumped to the No. 2 spot among the most-cited papers published by the *Lancet* that month and created a buzz at medical conferences.

Doctors increasingly prescribed the dual therapy. By 2008, about 140,000 patients in the U.S. were on it, according to SDI, the research firm.

But the report struck some kidney-disease specialists in Switzerland as too good to be true. The report said patients given the drug combo saw a 76% decrease in protein loss, compared with 42% with one drug by itself and 44% with the other one alone. To see such a dramatic difference was unusual, says one of the Swiss doctors, Regina Kunz, who also was dubious of a particular statistical result in the study.

"It was too perfect an effect. You wouldn't expect it with such a small sample size," says Dr. Kunz, director of the Academy of Insurance Medicine in Basel. "I think the peer reviewers should have caught it."

She and three colleagues wrote to the *Lancet* in 2006 urging it to look into the matter. The *Lancet's* editor, Dr. Horton, says the journal passed their concerns on to Dr. Nakao in Japan, who responded with some "recalculations."

The *Lancet* then passed all this material on an independent reviewer, who concluded in December 2006 that "it was impossible to tell whether data in the [original paper] were the result of fraud or incompetence," according to Dr. Horton.

The *Lancet* tried to get Dr. Nakao to respond, "but he seemed to be prevaricating," according to Dr. Horton. Dr. Nakao, now at Isekai Hospital in Osaka, declined to be interviewed.

In May 2008, the *Lancet* published a "letter of concern" by the Swiss doctors who had first written to the journal in 2006. The letter wondered whether certain inconsistencies were "only a case of extremely sloppy reporting or

a hint towards more severe problems with the data."

The Lancet now took the matter to another outside group, a U.K. nonprofit called the Committee on Publication Ethics. According to Dr. Horton, it decided the work was incompetent rather than fraudulent.

The Lancet then wrote to a Japanese hospital where Dr. Nakao worked when he published his study. This hospital said it would do an investigation, but it would take six months.

Pressure mounted. Dr. Messerli in New York, a cardiologist, wrote to the Lancet in mid-2009 arguing that it had a "moral obligation" to withdraw the paper. The Lancet said it would await the results of the hospital investigation.

The hospital investigating committee examined medical records at another Japanese hospital where Dr. Nakao said he and his colleagues had done the research on 336 patients. But committee members "were not able to identify even a single patient who matched the contents of the paper," said Yutuka Sanada, the president of the hospital that investigated, called Showa University Fujigaoka Hospital, in Yokohama.

"Dr. Nakao was not able to explain" this, he added, but "insisted that his paper was not a fabricated one."

The investigation took until the summer of 2009, about a year after the Lancet first contacted the university hospital.

"We should have raised the alarm with the university earlier," Dr. Horton now says.

In October 2009, nearly seven years after the Lancet published the blood-pressure study and three years after questions were raised about it, the Lancet printed a retraction notice.

It said the Japanese hospital investigation had concluded that the researchers hadn't obtained proper patient consent; that they hadn't obtained approval for the study from the ethics committee of the hospital where they said the research was done; and that the involvement of a statistician in the clinical trial couldn't be verified.

The Lancet also pointed to a finding by the investigating committee that the trial wasn't "double-blind," a standard precaution in which neither researchers nor patients know who is getting what drug or placebo. Instead, the committee found that Dr. Nakao knew who was getting the drug combination and who wasn't—a situation many investigators consider tantamount to fraud.

By the time the Lancet retracted the study, concerns were growing about potential harm to patients who got the combination therapy, except in certain rare cases where patients benefited. Data from clinical trials involving high blood pressure involving diabetes, coronary heart disease and advanced age persuasively showed that any small benefits of the combination therapy were easily outweighed by the side effects.

"Even patients with uncomplicated essential hypertension were not entirely able to escape this fashionable trend" in treatment, Dr. Messerli in New York wrote in the European Heart Journal.

As often happens, the original paper had inspired clinical research by others to test the dual therapy—studies that enrolled up to 36,000 patients, according to Dr. Steen, the analyst who did a study of retractions. "If there's a bad trial out there, there will be more flawed secondary trials, which put more patients at risk," he said.

Dr. Kunz in Switzerland said the Lancet and its peer reviewers ought to have been more skeptical about the overly positive results and should have caught the statistical anomaly she noticed. "Journals all want to have spectacular results," she said. "Increasingly, they're willing to publish more risky papers."

The Lancet's Dr. Horton dismisses that notion. He says journals hit by fraud and error are becoming more conservative about publishing provocative research. But he also says journals and research institutions don't have adequate systems in place to properly investigate misconduct.

The apparent rise in scientific fraud, said Dr. Horton "is a scar on the moral body of science."