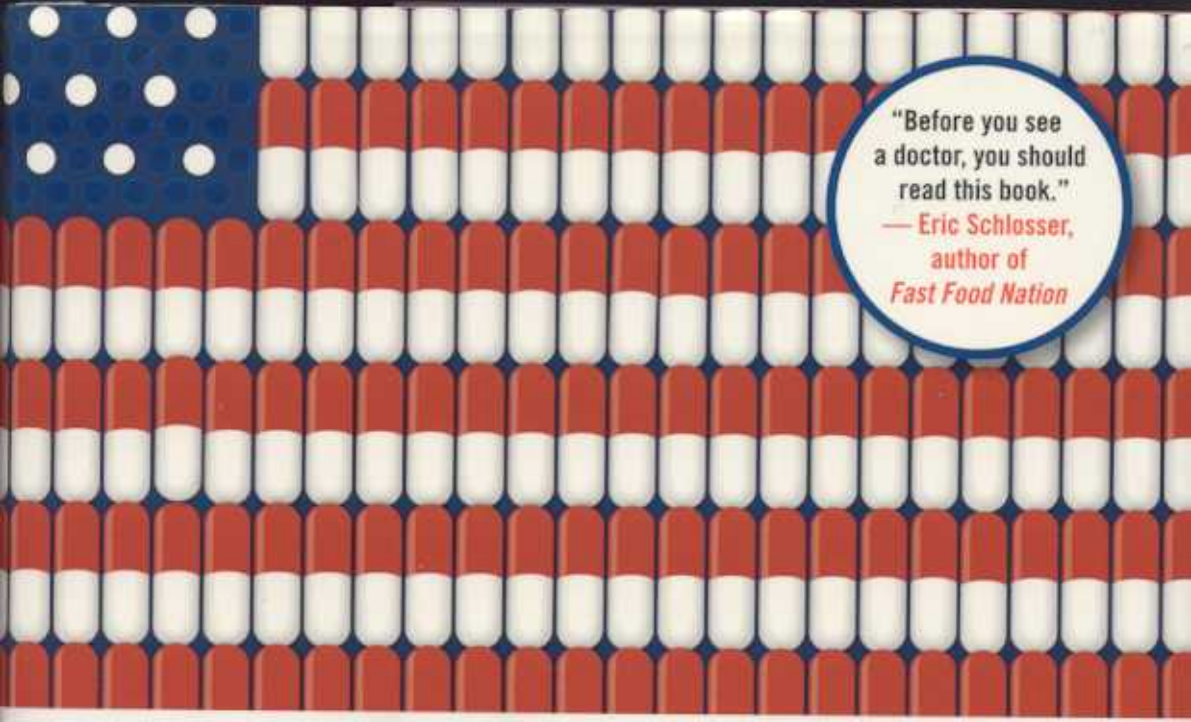

OVERDO$ED AMERICA

THE BROKEN PROMISE OF AMERICAN MEDICINE

How the Pharmaceutical Companies Distort Medical Knowledge, Mislead Doctors, and Compromise Your Health

JOHN ABRAMSON, M.D.

CHAPTER 2

SPINNING THE EVIDENCE

EVEN THE MOST RESPECTED MEDICAL JOURNALS ARE NOT IMMUNE

By the time all the morning patients had been seen, phone calls returned, nurses' questions about patient care answered, and administrative issues addressed, I would be ready for some time alone to eat lunch and relax. I enjoyed reading through the current medical journals during my short break, looking for articles that might be relevant to my practice.

In August 2000, I was reading the *New England Journal of Medicine* (NEJM) over a typical lunch in my office when I noticed an article titled "Pravastatin Therapy and the Risk of Stroke." This caught my attention because stroke is a fairly common problem among my elderly patients, and though most strokes are minor, some are tragic, leaving patients trapped in a permanent state of severe disability. I remembered one patient in particular, Mrs. Rose, who had spent the last year and a half of her life in a nursing home, wheelchair-bound, unable to feed herself or take care of her basic needs independently. Even though the stroke had left Mrs. Rose with garbled, almost incomprehensible speech, she managed to make it painfully clear to me each time I went to see her in the nursing home that she would much rather have died from her stroke than be stuck living that way.

I was certainly interested in decreasing other patients' risk of suffering

the same fate. But as I started to read the abstract (a brief summary of the study's design, findings, and conclusions that precedes most articles in medical journals), I became a bit suspicious when I realized that the title itself was misleading. The study did indeed examine the effect of pravastatin, a cholesterol-lowering statin drug (more commonly known by its brand name Pravachol), in decreasing the risk of stroke, but it only included people who had already suffered a heart attack or unstable angina (chest pain that may precede a heart attack). The reduction in the risk of stroke reported in the study did not apply to Mrs. Rose or to other patients who did not already have heart disease, as might be reasonably assumed from the article's title. Still, the abstract went on to report a statistically significant reduction in the risk of strokes among post–heart attack patients given Pravachol compared with those given a placebo, and concluded that "pravastatin has a moderate effect in reducing the risk of stroke."

THE DEVIL IS IN THE (STATISTICAL) DETAILS

In the few minutes I had left before it was time to see my afternoon patients, I noticed that when the pre-study differences in conditions that predisposed a person to stroke (such as diabetes, high blood pressure, smoking, atrial fibrillation, and previous strokes) were taken into account, the reduction of stroke in the people who took Pravachol was not even large enough to be statistically significant.* This was the first time I had seen an article published in a major journal that reported

*The standard way to determine whether a treatment has a significant effect is to calculate the probability that the observed difference in outcome (improvement or side effect) between the patients in the group that received the new treatment and the group that received the old treatment (or placebo) would have happened by chance if, in fact, the treatment really had no effect whatsoever. The conventional cutoff for determining statistical significance is a probability (p) of the observed difference between the groups occurring purely by chance less than 5 times out of 100 trials, or $p < .05$. This translates to: "the probability that this difference will occur at random is less than 5 chances in 100 trials." The smaller the p value, the less likely it is that the difference between the groups happened by chance, and therefore the stronger—i.e., the more statistically significant—the finding.

results that did not reach statistical significance. I paused for a moment to register this fact and then read on.

The NEJM article reported an impressive-sounding 19 percent reduction in the risk of stroke in people who had taken Pravachol compared with those who had been given the placebo. This came down to 16 percent when the results were corrected for pre-study differences in factors that predispose to stroke. This way of expressing the effect of taking Pravachol is called the "relative risk reduction." But *relative* risk tells only part of the story and often conveys an exaggerated impression of the benefit of the new drug or therapy. The far more important result is the amount of disease that is prevented by a given drug or therapy, called the "*absolute* risk reduction."

The research skills I had learned as a Robert Wood Johnson Fellow served me well in critically reading articles in medical journals. Occasionally I would take out a pencil and calculator to do the arithmetic when the findings were confusing or their importance was not clear. And that is what I did with this study.

Over the course of this six-year study, 4.5 percent of the patients who took the placebo had strokes, compared with 3.7 percent of the patients who took Pravachol. The ratio between 4.5 percent and 3.7 percent provides the relative risk reduction of 19 percent. However, the actual number of strokes prevented by taking Pravachol, or the absolute risk reduction, is calculated by subtracting 3.7 percent from 4.5 percent. So over the six years of the study there were 0.8 percent fewer strokes among the people who took Pravachol. In other words, if 1000 post–heart attack patients took Pravachol for a year, there would be about one less stroke. This didn't sound to me like a major finding. I called the local pharmacy to find out the cost of Pravachol 40 mg per day (the dose used in the study) and calculated that the cost of each stroke thus prevented was $1.2 million, not even including the cost of the extra blood tests and doctor visits to monitor for potentially dangerous side effects of the medication.

My curiosity about the rest of this article was now piqued, but it was time to start the afternoon clinic session. I took the article home to continue the time-consuming process of careful analysis. One of the benefits of a faculty appointment at Harvard Medical School is access to the school's digital library, which provides access to virtually all the impor-

tant medical journals. I wanted to dig around a little to see if I could find more information about statins and strokes

STUDYING THE WRONG PEOPLE

The better I understood the details of this article, the more misleading its conclusion appeared to be. The biggest problem was the disparity between the people included in the study and the people most at risk of stroke. The people in the study averaged 62 years of age, but the age at which most strokes occur in the general population is much older: half of the men who have strokes are 71 or older, and half of the women who have strokes, like Mrs. Rose, are 79 or older. This is important because the patients in the study age 70 and older who had been treated with Pravachol actually had 21 percent *more* strokes than the patients given a placebo.

I kept going.

Eighty-three percent of the people included in the study were men, but three out of five stroke victims in the general population are women. The fact that fewer than one out of eight people in the Pravachol study were women turns out to be important because the women in the study who were given Pravachol experienced 26 percent *more* strokes than the women who were given a placebo.

And five out of six patients in the study were taking aspirin routinely to decrease their risk of having more heart trouble. But in the general population, the vast majority of people, like Mrs. Rose, do not take aspirin routinely. This is important because among the people in the study who were not taking aspirin, those taking Pravachol had 20 percent *more* strokes than those taking placebos.

My patient, Mrs. Rose, was a typical stroke victim: female, in her early eighties, and not taking aspirin. According to the results of the study, her risk of stroke would have been increased, not decreased, by treating her with Pravachol. It seemed to me that the only conclusion that could be reasonably drawn from the data presented was that men under the age of 70 who had suffered a heart attack and were taking aspirin might lower their risk of stroke by taking Pravachol.

When I finished analyzing the article and understood that the title didn't tell the whole story, that the findings were not statistically significant, and that Pravachol appeared to cause *more* strokes in the population at greater risk, it felt like a violation of the trust that doctors (including me) place in the research published in respected medical journals. More than anything else in medical training, doctors are taught that good medical care is based upon a foundation of scientific evidence. I can remember well as a medical student, intern, and resident the daily exchange of photocopied journal articles as we went from patient to patient on hospital rounds. The latest articles from respected journals were accepted as the undisputed authority, defining good medicine and defending the decisions that had been made. A big part of becoming a doctor is learning to trust this scientific evidence enough to let it guide decisions that can have profound effects on vulnerable patients.

The Pravachol article seemed likely to have the effect of exploiting this deeply ingrained trust. Had the purpose of the study truly been to assist doctors in reducing their patients' risk of stroke, it certainly would have mentioned other proven approaches to achieve that goal. Even taking at face value the article's claimed 19 percent reduction in the risk of stroke—just to make this point—other more effective ways to decrease the risk of stroke had been well documented at the time the article was published. For example, simply eating fish once a week reduces the risk of stroke by 22 percent. Controlling high blood pressure reduces the risk of stroke by 35 to 45 percent. And even moderate exercise for less than two hours a week reduces the risk of stroke in an elderly population by about 60 percent.

The purpose of this article seemed incontrovertible: to establish "scientific evidence," legitimized by the prestige of the *New England Journal of Medicine,* that would lead doctors to believe that they were reducing their patients' risk of stroke by prescribing Pravachol. The collateral damage in establishing this belief is the diversion of doctors' and patients' attention away from far more effective ways to prevent stroke and achieve better health. But there is no profit to be made from these nondrug approaches, and therefore they receive much less attention than profitable and expensive drugs.

COLLABORATION IN THE ACADEMY

My instinct was to write an article for a medical journal explaining to doctors how to avoid being misled by the pro-drug spin in the pravastatin article and others like it that might appear in the future. I was confident of my analysis but thought that teaming up with an academic expert would make an even more powerful paper. I went over the problems I had identified in the article with a recognized authority. He found no fault with my analysis. I asked if he would be interested in writing the article with me, assuming that a university-based expert would welcome the opportunity to help correct the commercial bias that was creeping into the medical literature. He politely declined, explaining that he did "some consulting for the drug companies." Stunned by his response, I quickly realized how naive I had been about the growing commercial influence in academic medicine. Nonetheless, this expert had generously taken the time to go over the article with me, so I did my best not to show my dismay.

I came away with a whole new understanding of how behind-the-scenes financial relationships between the drug companies and the academic experts (who write the articles in medical journals that are then received as "scientific evidence") can neutralize potential criticism. I was starting to understand that these issues were all of a piece: the changes in my own practice, the disordered priorities, and the growing commercial influence in clinical research and medicine. I went back to my day-to-day practice with the sense of having lost my innocence and with a new wariness about the research findings presented in the medical journals.

STATINS AND STROKE REDUX

In June 2001 another article reporting the results of a study about stroke prevention appeared, this time in the *Journal of the American Medical Association* (JAMA). The stated purpose of the study was to examine the association between ischemic strokes and the three commonly measured forms of cholesterol—HDL (good), LDL (bad), and total cholesterol.

(Ischemic strokes, the most common kind, are caused by loss of blood supply to an area of the brain, resulting in cell death and irreversible brain injury.) By examining hospital records, the study identified cases of ischemic stroke among racially and ethnically diverse residents of Harlem. Each case was then matched with two similar control patients from the same community who had not suffered a stroke.

The cases and controls were then compared for significant differences in cholesterol levels, as well as other lifestyle, medical, and demographic factors, to identify risk factors associated with ischemic stroke. The study found that the people with low levels of HDL (good) cholesterol were at increased risk of suffering a stroke. On the basis of this finding, the authors recommended checking HDL cholesterol levels routinely and suggested that people with low levels consider treatment with a statin drug to increase their "good" cholesterol. From a quick read of the abstract, this recommendation made sense, but as with the Pravachol and stroke article, as I carefully went through the details I realized that the data led to a very different conclusion. And as in the case of the Pravachol article, the direction of the spin would lead doctors to prescribe more statins. I took out my pencil again.

Not mentioned in the article's abstract, and mentioned only once in passing in the text, were the unexpected findings that the lower (that is, what we think of as healthier) the total and LDL (bad) cholesterol, the *greater* was the risk of stroke. (More on cholesterol later, but generally total cholesterol and more specifically LDL cholesterol play a role in blocking arteries, and HDL cholesterol partially counteracts this effect.) Buried within the tables included in this article were statistics showing that lower levels of total cholesterol and lower levels of LDL cholesterol were both significantly correlated with a *higher* risk of stroke ($p < .001$ and $p = .04$, respectively). As I read on, I was completely baffled by the authors' statement that "we found no relation between total cholesterol levels and stroke risk." How could they say there was no relationship between total cholesterol and stroke when their own data showed that the odds were greater than 1000 to 1 that lower total cholesterol levels were associated with a higher risk of stroke? A follow-up letter to the editor of JAMA from a doctor employed by the U.S. Department of Health and Human Services (expressing his own views) pointed out that the authors

had "neglected to discuss these findings," but once the cows are out of the barn such a letter has very little effect in correcting the misperception created by the original article.

The article got even stranger when it argued that its data supported the use of statins to prevent strokes in patients with low HDL cholesterol levels. Statins raise HDL cholesterol only half as much as the article found would be necessary to significantly reduce the risk of stroke. But statins lower total and LDL cholesterol at least three times more on a percentage basis, far more than enough to significantly *increase* the risk of stroke, according to the data from the study. Nevertheless, the article concluded that treatment of low HDL cholesterol with statin drugs could significantly decrease the risk of stroke—ignoring its own findings that the overall effect on cholesterol would be associated with increased risk of stroke.

I started to wonder why the article focused on cholesterol at all. The study found that other factors were just as significant as low HDL cholesterol in increasing the risk of stroke: untreated blood pressure, lack of exercise, cigarette smoking, heavy drinking, not graduating from high school, and being uninsured or on Medicaid. In fact, the authors of this article had used data from the same case-control study in an article published in 1998 to show that even light to moderate physical activity reduced the risk of stroke in the same people by 61 percent and that heavy exercise reduced the risk of stroke by 77 percent. The benefit of exercise documented by these authors certainly overshadows the 19 percent reduction in stroke associated with an increase in HDL of 5 mg/dL*—almost twice as much as is achievable with statins. Curiously, the authors' earlier findings about the important role of exercise were not even mentioned in the current article. And, though the authors did cite the earlier NEJM article about Pravachol and stroke, they failed to mention that that article found no relationship between low HDL levels and increased risk of stroke.

*The blood levels of all three kinds of cholesterol (total, LDL, and HDL) are expressed as "mg/dL," meaning the number of milligrams of cholesterol present in one-tenth of a liter of serum (the clear liquid that remains after the cells have been removed from a blood sample).

It was hard for me to believe that the *Journal of the American Medical Association* would have published an article that had strayed so far from its own data and the medical literature, and so far from recommending what seemed like the best approach to helping patients avoid strokes. Thinking that it would probably not be a good idea to go back to the same research expert to review the article, I asked a well-respected cardiologist who had published more than 50 papers to look over my critique and make sure I had it right. He saw no problems with my analysis.

COMMERCIAL GOALS OR HEALTH GOALS?

The JAMA study focusing on the increased risk of stroke in people with low HDL cholesterol levels was done in a community with many more risk factors and health problems than most. The life expectancy of a black man in Harlem is only 60 years, less than the life expectancy of a man in Bangladesh. So why did this article ignore the much more powerful anti-stroke effects of positive lifestyle changes and blood pressure control? And why did it focus on raising HDL cholesterol with statins, while ignoring its own findings that the more powerful effect of statins on total and LDL cholesterol would increase, not decrease, the risk of stroke?

At the time the study was published, there were two potential changes coming that could have provided commercial incentive to do so. Pfizer had a new "HDL-elevator" drug that was well along in the pipeline of drug approval, and already being tested in clinical trials. It was also becoming clear that senior citizens would soon get some kind of assistance with prescription drug coverage from the federal government. Lower-income minority communities like Harlem represent relatively unpenetrated markets for expensive drugs with purported widespread benefits. A generous prescription drug benefit would make statin drugs affordable to many residents in this community who could not previously afford them. It seemed sinful to me to be recommending that more than $1000 per patient be spent each year—in a community with a 34 percent poverty rate—on treating people with statins with at best shaky scientific justification, while ignoring proven interventions such as

increasing participation in exercise, smoking cessation programs, nutritional counseling, blood pressure control, and other medical outreach. These could have a much stronger impact not only on stroke reduction but on overall health and quality of life.

These two articles about using statins to prevent strokes, appearing in the two most influential American medical journals, seemed to approach stroke not as a human tragedy but as a commercial opportunity. Both appeared to spin research results to provide "scientific evidence" that justified more use of expensive drugs. The article in the NEJM presented findings from a study done on an unrepresentative group of patients, findings that were not even statistically significant. The article in JAMA ignored its own data showing that treatment with a statin drug was more likely to increase the risk of stroke. Both articles focused almost exclusively on drug therapy rather than inexpensive lifestyle changes that have been shown to be far more effective.

Why was all of this so important to me? For the elderly, a debilitating stroke is one of the worst possible fates. Both of these articles seemed off-key, particularly as I reflected back on Mrs. Rose's suffering and what I hoped to accomplish as a doctor. Remembering my own medical training and watching the medical students whom I was teaching struggle to learn how to base their care on the scientific evidence in the medical journals, I could see that doctors' trust in the literature was being skillfully exploited by commercial interests. But my colleagues and students were skeptical when I tried to show them that the material they were trying so hard to keep up with could not always be trusted.

I had always thought of myself as a disciplined mainstream practitioner grounded in medical science, caring, and common sense. But I was losing my faith in the knowledge that guides medical practice, and there was no going back.

In retrospect I can see that these two articles on stroke reduction, for all their flaws, had at least presented enough data to allow the commercial sleight of hand to be uncovered by careful analysis. I was soon to learn that this is not always the case.