MEDICINE AND SOCIETY

CONFLICTS OF INTEREST — PART 1
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Reconnecting the Dots — Reinterpreting Industry–Physician Relations

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In November 2013, shortly after the release of controversial new cholesterol guidelines that expanded the target population for preventive statin therapy, I ran into a man known for his work on eliminating unnecessary medical care. "Can you believe the guidelines?" he asked. Then he added, shaking his head, "The authors are all in bed with the pharmaceutical industry. It's a marketing scheme to get more people on statins."

He was not alone in that perception. In a *New York Times* op-ed, for example, a cardiologist and another physician and industry critic argued that making more patients eligible for statin therapy would "benefit the pharmaceutical industry more than anyone else."[1] Objecting to using statins for primary prevention, they drew from a medical journal article that one of them had coauthored emphasizing the frequency of side effects.[2] This frequency turned out to be exaggerated, necessitating an erratum in the journal.[2] Yet no one was questioning the editorialists' credibility in the public press; rather, the editorialists challenged the credibility of the guideline writers: "The American people deserve to have important medical guidelines developed by doctors and scientists on whom they can confidently rely to make judgments free from influence, conscious or unconscious, by the industries that stand to gain or lose."

One could argue that people also deserve to know that statins are, in many cases, the best drugs we have to prevent cardiovascular disease and that the committee had spent 5 years reviewing the evidence to identify the patients who would benefit most. True, 7 of the 15 committee members had current or previous ties to industry, mostly in the form of research support or consulting fees.[3] Nevertheless, it does not seem reasonable to conclude that their recommendations were motivated by a desire for financial gain.

First, the members with current industry ties were not allowed to vote on the quality of the evidence statements or the recommendations, and none of the members without industry ties have developed ties since the guidelines were published. Second, because of past concerns about conflicts, the committee used an independent contractor, appointed by the National Heart, Lung, and Blood Institute, to choose the studies on which the recommendations were based. Third, though the controversy centered on primary prevention for people whose 10-year risk of a cardiovascular event exceeds 7.5%, the guidelines make clear that this cut point is merely a threshold for initiating discussion about statins, rather than a mandate to start treatment with one. Finally, the resulting guidelines are actually no boon to companies selling patent-protected drugs: most statins are available in generic versions, and the guidelines recommend against using (patent-protected) drugs that improve lipid levels but that hadn't, at the time of guideline writing, been proven to improve outcomes.

So why the rush to conclude that the guidelines were part of an industry plot? Have stories about industry greed so permeated our collective consciousness that we have forgotten that industry and physicians often share a mission — to fight disease?

TOWARD A REASONED APPROACH

Physician–industry interactions are common and diverse, ranging from the $10 bagel sandwich to the $1 million research grant.[4] Although most

observers agree that we must mitigate the risk of bias introduced by these relationships, the benefits wrought by interactions between physician-scientists and industry at the basic or translational research level are equally clear. The question, then, is how to best manage conflicts of interest while preserving the collaborations on which medical advances depend.

Though we have grappled with this question for decades, the answer still largely eludes us. Some difficulty arises from overwhelming complexity. Not only does each type of interaction have a unique set of risks and benefits, but within each category are nuances altering this calculus — consulting for one statin manufacturer, for instance, may engender a different allegiance than consulting for many companies making similar products. Moreover, some of our intuitions about these interactions, such as the assumption that greater financial stakes pose greater risk of bias, are not borne out empirically. Though considerable social science research suggests that even small gifts may influence physicians,[5] it doesn't necessarily follow that greater financial stakes are more influential. Not only do one's preexisting financial state and nonfinancial motivations interact with new financial incentives, but even seemingly straightforward aspects, such as dollar amounts, cannot be understood without context. A guideline-panel member's receipt of thousands of dollars in research support, for example, may raise a red flag, unless we also know that most of the payment went to institutional overhead costs and none found its way into the principal investigator's pocket.

But the greater difficulty is that whereas a rational approach to regulating industry interactions requires careful parsing of such nuances, our general feelings about industry interactions, as the easy dismissal of the statin guidelines illustrates, can be impervious to relevant detail. I think we therefore need to begin by exploring our general impressions of industry interactions, the role these impressions have played in shaping our regulatory approach, and the implications for our ability to strike an ideal balance.

Though I believe outrage over industry behavior has made reasoned regulation difficult, I don't think we should excuse past wrongdoings or eliminate oversight. Rather, I think we need to shift the conversation away from one driven by indignation toward one that better accounts for the diversity of interactions, the attendant trade-offs, and our dependence on industry in advancing patient care. Before a reasoned approach can be developed, however, it's helpful to consider the roots of the enduring emotions, some of which lie in canonical conflict-of-interest stories and pharmaceutical marketing scandals.

THE GELSINGER TRAGEDY

When 18-year-old Jesse Gelsinger volunteered for a 1999 trial of gene therapy for ornithine transcarbamylase deficiency, of which he had a relatively mild phenotype, he knew he was unlikely to benefit personally. Before flying to the trial site at the University of Pennsylvania, he reportedly said to a friend, "What's the worst that can happen to me? I die, and it's for the babies."[6] As everyone knows, Gelsinger did die in that study, without any immediate benefit to babies.

What went wrong? Gene therapy had been overhyped, the excitement about its potential efficacy far outpacing the science needed to establish its safety. Animal studies conducted by some of the clinical trial investigators had revealed a systemic inflammatory response — but it had not been immediately reported to the Food and Drug Administration (FDA). And there were questions about research ethics: the investigators had been advised that it was unethical to test the therapy in babies who might actually benefit because parents were so desperate for a treatment that soliciting their participation was akin to coercion. But was it ethical for someone like Gelsinger, who would not benefit, to assume such risk?

These complexities were soon obscured, however, when a more galvanizing explanation for the tragic outcome surfaced: the lead investigator, James Wilson, held substantial equity in Genovo, a gene-therapy company. Suddenly, the general understanding of a terrible outcome resulting from many potential missteps worth exploring was reduced to a simple explanation: Gelsinger's death was attributable to financial greed. It soon "came to signify the corrosive influence of financial interests in human subject research."[7]

But was Wilson's financial stake the reason

for the tragedy? And if so, would more stringent conflict-of-interest policies have prevented it?

Answering these questions is difficult. For one thing, it remains unclear what the financial stakes actually were. Wilson had founded the biotechnology company Genovo, which focused on gene therapy, but Genovo did not sponsor the trial, nor were any of its licensed technologies being investigated. In addition, the university had recognized the potential for conflict-induced bias: concerned that Wilson, having invented some gene-therapy technology, would be overly invested in its success, the university allowed him to participate in trial design but barred him from patient enrollment or interaction — restrictions that were quite rigorous at the time. Finally, whatever the financial stake and however effectively it's managed, the role of bias is impossible to prove; it's as easy to attribute a bad outcome to a financial motive as it is to suggest that a financial relationship is irrelevant.

Wilson was not naive about the potential for bias to compromise scientific integrity; he had just worried about the wrong bias. Concerned that his belief in gene therapy's potential for curing disease threatened his objectivity, he'd asked a colleague to be principal investigator. "Physician scientists have to believe in what they do with religious zeal," he told me. "We want a biased commitment to making things happen. If you don't stay with it, progress won't be made."

VIOXX AND OTHER DEBACLES

Wilson may not in fact have been driven by a profit motive, but other well-publicized disasters — though similarly multifactorial — have certainly involved bad behavior by people who were. The Vioxx story is a case in point.

Merck touted the potential of Vioxx (rofecoxib), its selective cyclooxygenase-2 inhibitor, to relieve inflammation without the gastrointestinal side effects of nonselective nonsteroidal antiinflammatory drugs.[8] Though it turned out that Vioxx also probably created a more thrombogenic environment, Merck did not acknowledge that possibility until months after the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial had been published in the *Journal*, when it sent the FDA more data that included three cardiovascular events not reported in the article. The article's authors had attributed the (smaller acknowledged) discrepancy in cardiovascular risk not to a harmful effect of Vioxx but to a cardioprotective effect of naproxen.

This theory had little empirical basis, but the *Journal*'s publication of it was seen as a tacit endorsement, and the article became an invaluable marketing tool for Merck. David Anstice, Merck's head of marketing, advised salespeople to handle physician concerns about risks by suggesting that people were confused about the data: "To understand VIGOR, you must understand that Naproxen is cardio-protective, like aspirin. In VIGOR, Vioxx did not increase the number of MIs; rather Naproxen decreased the number of MIs."[9]

This tactic apparently worked. More than 20 million Americans took Vioxx, and though it's unclear how many deaths it caused, some of the tragic consequences could certainly have been avoided. All drugs pose risks, but it is unconscionable to deny physicians and patients information about those risks.

The academic researchers involved in VIGOR, however, may have had nothing to do with concealing cardiovascular events or devising marketing tactics. Yet inevitably, everyone from the chair of VIGOR's data and safety monitoring committee to the FDA was accused of being motivated by conflicting interests, even when their actions actually threatened Vioxx's success. Egregious behavior by a company tarnishes the reputations of everyone associated with it. Vioxx's continued relevance to our management of physician–industry interactions lies in the lingering impression that some companies will do anything to profit, even if it means suppressing evidence to patients' detriment — an impression reinforced by subsequent Big Pharma scandals.

GlaxoSmithKline (GSK), for example, recently had to pay the Chinese government $500 million to settle a case over its practice of bribing Chinese hospitals and doctors to prescribe its products. That settlement was small, however, relative to the $3 billion that GSK had to pay the United States in 2013 for promoting drugs for off-label uses and not reporting safety data for its diabetes drug.[10] And in the past decade, other pharmaceutical giants, including Pfizer, Eli Lilly, Abbott Laboratories, and AztraZeneca, have also been accused of illegal behavior such as off-label promotion and paying kickbacks. One might imagine that the large settlements in these cases would deter continued fraud, but many compa-

nies continue to profit despite, or perhaps because of, these behaviors. As one spokesman for the whistle-blower group Taxpayers Against Fraud commented after GSK's settlement, "A $3 billion settlement for half a dozen drugs over 10 years can be rationalized as the cost of doing business."[10]

For the many physicians whose primary interactions with industry are of the marketing variety, the beneficial nature of other industry relationships may lack emotional traction. We see the attractive pharmaceutical reps in our offices. We eat the lunches (or walk away hungry). Our patients, heeding the "Ask your doctor" mantra of drug ads, request medications we may not believe should be prescribed. We hear that our prescription habits are being monitored so that we can be targeted for better sales. And we observe colleagues, their suits sharp, their skin tanned from a free Hawaiian vacation, their children's college education covered, and though we may take some satisfaction in eschewing pharmaceutical largesse, still, for some, the resentment burns.

By contrast, how visible to us are physician-scientists whose National Institutes of Health grant applications go unfunded, and who therefore increasingly rely on industry support for their laboratories? Does it cross our minds, when we prescribe statins after a myocardial infarction, how much collaboration between industry and physician-scientists was required to develop them? When we read an editorial by someone who is "conflict-free," do we wonder whether someone else whose industry ties prevented authorship might have had unique expertise to share? Of course, the fact that the benefits of industry interactions are often imperceptible does not excuse the more easily imagined offenses. But the visibility imbalance helps explain why our aversion to certain industry behaviors deeply colors our overall impressions of industry.

QUESTIONING AFFECTIVE IMPRESSIONS

As the work of social psychologist Robert Zajonc helped establish, feeling precedes cognition, rather than vice versa. Even when we think we are thinking, almost nothing we perceive is emotionally neutral. "We do not just see a 'a house,'" Zajonc wrote. "We see 'a *handsome* house,' 'an *ugly* house,' or 'a *pretentious* house.'"[11]

I think Zajonc's insight offers a framework to guide our learning from "conflict-of-interest" stories and examples of industry fraud. On one level, each scandal offers "cognitive" lessons, which often have nothing to do with conflicts. The Vioxx case, for instance, clarified the need for a better postmarketing-surveillance system, particularly for drugs with risks that are otherwise common, such as cardiovascular disease.

But the enduring influence of these stories may be emotional rather than cognitive. No one worries about industry interacting with physicians: we worry about "*corrupt* industry" interacting with "*corruptible* physicians." And as Zajonc argued, our confidence in affective impressions trumps any evidence calling them into question. Can we, as we manage industry interactions moving forward, better separate the cognitive lessons from the emotional?

For James Wilson, the gene-therapy investigator, the distinction is in some ways irrelevant. In 2009, after a period of restricted involvement in human subjects research, Wilson published an essay entitled, "Lessons Learned." Wilson, who initially denied the influence of financial conflicts in the Gelsinger case, now regrets this stance: the actual details of his involvement with the gene-therapy company, he now understands, mattered far less than public perceptions. In these situations, he argues, "perception can quickly become reality." Wilson urges young investigators to avoid situations in which three factors converge: a bad outcome, suspicion of error, and the appearance of financial conflict. "If those things happen, and it rises to the attention of the press," he told me, "the dots will be connected. No matter what you do, the mistakes will be perceived as having been made on purpose."

Wilson believes, and I agree, that scientists who develop novel treatments should not be the ones testing them in humans. Financial conflicts aside, the desire for the treatment to succeed, as Wilson articulated, can cloud judgment. Moreover, since the ingenuity required to develop a novel treatment tends to differ from the skills needed to run clinical trials, separating the roles should not threaten innovation.

But by deferring to the primacy of appearance over reality, are we locking ourselves into

an "ugly house" understanding of the world? Our feelings about greed and corruption drive our interpretations of physician–industry interactions, the resultant stories intensify our impressions of such evil's pervasiveness, and when the next bad outcome occurs, we are quicker to blame financial motives. As the gap between evidence and impressions grows, reasoned approaches to managing financial conflicts are eclipsed by cries of corruption even when none exists.

What are we striving to achieve in our management of conflicts, and are we succeeding?

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article is Part 1 in a three-part series.
Next week: "Understanding Bias — The Case for Careful Study."