



## **Publication Bias, Data Ownership, and the Funding Effect in Science: Threats to the Integrity of Biomedical Research**

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### **The Social Context of Science**

The noun *science* and all of its adjectival forms confers a sense of authority to its associated activities. Nearly everyone wants to be on the side of “good science.” Environmental agencies speak of “science-based” policy, while the Food and Drug Administration (FDA) and many professional societies identify themselves with “evidence-based” medicine. Strong disagreements among scientists can create a cognitive dissonance within the popular culture. Yet, despite its authoritative position, the system of science – consisting of research and educational institutions, certified practitioners, journals and funding agencies – is embedded in a social context. The elements that make up this context can influence the questions that get asked, the studies that get funded, the results that get published, and the biases that enter into scientific practice and impair its quality.

The normative structure of science has evolved over centuries, beginning with the Enlightenment, continuing through the development of nation-states and the rise of international scientific societies, and during the current era of globalization. That structure includes a shared set of goals for uncovering the truths about the natural world, the recognition that science is a social activity that demands openness and transparency of claims and evidence, and the commitment to an epistemology that embodies a standard of empirical verifiability for certifying knowledge claims.

The pursuit of objective and verifiable knowledge can be derailed by social determinants and ideology that view science as a means to an end,

rather than as an end in itself. For this reason, when science serves more than one master or when the pursuit of truth is only one of several motivations, deviance from the normative standards can be observed.

This chapter examines some of the essential requirements for the healthy functioning of science and draws attention to the deviance from those conditions, with special consideration given to the biomedical sciences. The chapter applies the overarching principles of scientific independence that are a major element of the framework for this book: To produce “healthy science,” scientists must be able to conduct research without unjustified restrictions from private sponsors or government, including unwarranted influence in the research protocols, the data analysis, and the interpretation or publication of results. This means that research must never be suppressed because it produces results that are adverse to a sponsor or other interested party. Scientists should remain free to time the disclosure of data or the results of ongoing research unless the research could help address pressing public health problems or is otherwise submitted to the government as a basis for regulatory decisions. Clinical investigators must be free to report adverse effects of experimental drugs or to withdraw human subjects from a trial without fear of being sued. Sponsors must never place restrictions or otherwise influence the design or conduct of a study in an attempt to obtain results favorable to their interests. No publication or summary of research should ever be influenced – in tone or content – by the sponsoring entity. And finally, vested interests, who use the legal system to harass scientists whose research or expert testimony calls into question the safety of their practices or products, must be held accountable with sanctions and, in some cases, must compensate injured scientists for the resulting interference with their research and damage to their reputations.

This chapter begins by establishing the foundation for these principles of healthy science with a review of what philosophers and sociologists of science have contributed to our understanding of the nature of scientific knowledge and its normative structure. Second, the chapter discusses some recent trends that intrude on the integrity of science, such as the loss of disinterestedness, the lack of openness, and the commingling of science with the production of wealth. Third, it explores the “funding effect” in science and discusses its implications in the social enterprise of knowledge production. The funding effect provides empirical evidence of some adverse consequences that flow from recent intrusions on healthy science. Finally,

the chapter suggests some remedies to restore integrity to the biomedical sciences.

## Normative Underpinnings of Science

### Community of Inquirers

Science is a way of knowing and generating reliable knowledge about the physical universe, including both natural and social phenomena. It is one of several ways of fixing belief about the empirical world, as noted by philosopher Charles Pierce in his famous essay, "The Fixation of Belief."<sup>1</sup> Pierce contrasted science with authoritarianism, intuition, and folk knowledge. We can add to that list sacred texts or knowledge by plebiscites.

Science has several features that distinguish it from the other forms of fixing belief. Unlike the fixation of belief by appeal to authority, scientific claims must be certified through a community of inquirers. For each subfield of science, the community of inquirers shares a methodology that might include measuring instruments, theoretical frameworks, nomenclature, quantitative methods of analysis, and canonical principles for interpreting data.

In contrast to intuitive ways of knowing or the appeal to sacred texts, scientific methodology must be transparent and available to anyone familiar with the art of inquiry for that subdiscipline. The democracy of science demands a transparency of methods and data. This transparency is the premise behind open publication. Where possible, those properly trained in the art of scientific inquiry should be able to replicate the outcome of an experiment, which implies a sharing of techniques and materials.

In science there is no room for "unquestionable authority." No one in science can claim infallibility. Biologist Howard Temin underscored this point in an interview with historian Horace Freeland Judson. "When an experiment is challenged no matter who it is challenged by, it's your responsibility to check. That is an ironclad rule of science, that when you publish something you are responsible for it... even the most senior professor if challenged by the lowliest technician or graduate student, is required to treat them seriously and to consider their criticisms."<sup>2</sup>

<sup>1</sup> Charles Pierce, "The Fixation of Belief," *Popular Science Monthly* 12 (Nov. 1877): 1-15.

<sup>2</sup> Horace Freeland Judson, *The Great Betrayal* (New York: Harcourt, 2004), 242.

### The Private Use of Science

The methods or discoveries of science should not be restricted to private use. That outcome is inconsistent with its communitarian enterprise. The commercialization of some areas of science can occur more readily under the newly liberalized intellectual property rules. For example, when Stanley Cohen of Stanford and Herbert Boyer of the University of California at San Francisco discovered a method of recombining and transferring DNA (recombinant DNA molecule technology), their respective institutions took out a patent for the technique. The institutions decided against restrictive licensing of the technique, which made it available to all users at a modest fee. Had they decided to offer restrictive licenses for the genetic engineering technique to a few companies, the progress of science would have suffered severely.

In her book *University, Inc.*, Jennifer Washburn reminds us of the work of Richard Nelson and Kenneth Arrow regarding the economic benefits of treating scientific methods and discovery as a nonrivalrous good that should be part of the knowledge commons. Nelson and Arrow reasoned that the public interest would be best served if most of this nonrival, basic science remained in the public domain, because any policies restricting access to that knowledge (such as exclusive licenses or secrecy provisions) would only impose substantial costs on the excluded parties, and on the economy as a whole, by stifling open competition and invention activity.<sup>3</sup> When scientific methods or seminal discoveries are patented, academic scientists, wishing to use the results, are not protected by a legislated research exemption, as they are in other countries. The concept of a free and open scientific inquiry has been hampered by patenting of genes and other techniques, particularly when exclusive licenses are issued.

### Freedom to Advance Theories

Science must be open to alternative hypotheses, interpretations of data, and theories that account for similar observations or facts. In a healthy scientific environment, even the marginalized and unpopular theories should have access to publications because those theories and explanations may

<sup>3</sup> Jennifer Washburn, *University, Inc.* (New York: Basic Books, 2005), 62.

someday become the orthodoxy. This access was the case when two relatively unknown Australian physicians, Barry Marshall and Robin Warren, formulated the hypothesis that gastritis and peptic ulcers were caused by the colonization of *H. pylori* bacteria in the intestinal tract.

The physicians met enormous opposition to their theory. To test his belief, Marshall had infected himself with the bacteria to demonstrate the cause. His published account of his self-induced ulcers and their successful treatment with antibiotics was not sufficient in itself to change the entrenched beliefs among gastroenterologists that ulcers were a stress-related disease. Skepticism toward the bacterial theory persisted until a controlled study comparing acid blockers and a placebo clearly demonstrated the success of antibiotics in the treatment, corroborating the bacterial theory of ulcers.<sup>4</sup> Marshall and Warren were awarded the 2005 Nobel Prize in Physiology or Medicine.

### Self-Correction

Science must be able to correct itself. It is thus unlike religion or political ideology, which are static, doctrinaire belief systems that are immutable to new information, and refractory to contradictory evidence. Science must be self-reflecting of its own biases and limitations and of its own errors. Unlike political institutions, scientific culture must have a systematic process of admitting mistakes and reporting them.

Science must strive for logical consistency. The fundamental rules of logic tell us that from a contradiction, you can derive any proposition. We cannot have a reliable system of beliefs where everything holds, where both *P* and not-*P* are true at the same time. Just as nature abhors a vacuum, science abhors a contradiction.

### Universal Truths

In healthy science, the results must stand as universal rather than as supporting distinct truths about natural phenomena according to different cultures. The physical and toxicological properties of benzene are not

<sup>4</sup> Terrence Monmaney, "Marshall's Hunch: Annals of Medicine," *New Yorker* (Sept. 20, 1993): 64-72.

culture-specific. Although the effects of benzene may be genotype-specific, there is no male science and female science, or Japanese science and American science as regards the knowledge of the physical world. However, there may be different cultural paths of inquiry or alternative means (models and metaphors) to describe the physical world.

Healthy science distinguishes the path to truth claims from the validation of those claims. According to the philosopher Karl Popper, the source of the origin of a hypothesis is distinct from the conditions of its validity. He wrote in *The Logic of Scientific Discovery*, "I shall distinguish sharply between the process of conceiving a new idea, and the methods and results of examining it logically."<sup>5</sup> Revelation or divine inspiration may be a means to discover scientific truths, but it is not a satisfactory test of their soundness. "So long as a theory [or hypothesis] stands up to the severest tests we can design, it is accepted; if it does not, it is rejected."<sup>6</sup>

Trust plays an essential role in the healthy functioning of science. We trust that researchers will record their data accurately and that they will not fabricate data or fudge results. Replication of studies is costly and rarely done. In his book *Real Science*, Dr. John Ziman notes: "Amongst working scientists, this trustworthiness is part of the moral order of each research community. The complex interplay of originality and skepticism that operates in such groups requires absolute impersonal trust on matters of empirical 'fact.'"<sup>7</sup> Trust can be undermined when scientists are working in an environment replete with incentives for secrecy or misconduct. Any confounding interests that can compromise the penultimate goal of getting at the truth will begin to diminish the integrity of and public confidence in the scientific enterprise.

### Tendencies Toward Deviant Science

The social system of science and the society in which it is embedded must be concordant with the general principles behind healthy science. An authoritarian and undemocratic society will not be compatible with open,

<sup>5</sup> Karl R. Popper, *The Logic of Scientific Discovery* (New York: Harper, 1959), 3.

<sup>6</sup> Karl R. Popper, *Conjectures and Refutations: The Growth of Scientific Knowledge*, 54.

<sup>7</sup> John Ziman, *Real Science* (Cambridge, UK: Cambridge University Press, 2000), 98.

unfettered science. More than likely, such societies will impose false beliefs such as “abortions result in higher rates of breast cancer,” or “small doses of dioxins are actually good for our health,” regardless of what the data show. The factors that foster deviance within science are complex. In different historical periods, ideology, the exigencies of war, the lust for power and prestige, and the pursuit of wealth have all contributed to aberrant behavior with respect to the normative structure of science. This section explores how commercial interests in the biomedical sciences have preempted the traditional norms of scientific practice.

### Withholding Scientific Data and Discoveries

Withholding of information violates the communitarian norm of science. It also limits the possibilities for self-correction. Among the major tributaries of biomedical science are drug companies that sponsor clinical trials. Withholding of clinical trial data that would be financially harmful to a company seems to be commonplace. It has added to publication bias in certain fields of clinical medicine. In March 2004, the *Canadian Medical Association Journal* reported that one of the world's largest drug companies withheld clinical trial findings in 1998 that indicated the antidepressant paroxetine (known as Paxil in North America) had no beneficial effect on treating adolescents. A company memorandum (revealed from discovery documents in litigation) stated: “It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.”<sup>8</sup>

Drug manufacturers also withheld trial results of antipsychotic drugs that showed increases in suicidal behavior and other adverse side effects. It is well documented that there is a preponderance of positive company-sponsored studies, with no clear explanation—only the plausible hypothesis that companies suppress results that are not in their financial interests. Occasionally, companies have used legal threats to prevent publication of negative data in studies they had sponsored.

<sup>8</sup> Wayne Kondro and Barbara Sibbald, “Drug Company Experts Advised Staff to Withhold Data about SSRI Use in Children,” *Canadian Medical Association Journal* 170, no. 5 (2004): 783.

Because drug companies sponsor many multistage clinical trials, these companies can restrict scientific communication between sites. This practice can sometimes lead to missed opportunities to protect human subjects from dangerous drug side effects. One company stated publicly that it adopted guidelines in which it would commit to publish the results of certain clinical trials involved in hypothesis testing – which excludes testing the safety of the drug.<sup>9</sup>

The new guidelines issued by the pharmaceutical industry organization PhRMA states that

Individual investigators in multi-site clinical trials will have their own research participants' data...any investigator who participated in the conduct of a multi-site clinical trial will be able to review relevant statistical tables...for the entire study at the sponsor's facilities...Sponsors have the right to review any manuscripts, presentations, or abstracts that originate from our studies or that utilize our data before they are submitted for publication or other means of communication.<sup>10</sup>

These are supposedly the “best” guidelines in the industry – and they are purely voluntary.

Data ownership and control by sponsors of clinical trials circumvent the authority and responsibility of the investigator and may compromise the care given to human subjects involved in the trial. Many institutions continue to permit contracts that allow sponsors to review research before it is published, to edit the prepublication manuscript, and to decide when the study should be released for publication. One survey of biomedical scientists found that those who received funding from industry were “significantly more likely to delay publication of their research results by more than 6 months to allow for the commercialization of their research.”<sup>11</sup>

<sup>9</sup> Laurence Hirsch, “Randomized Clinical Trials: What Gets Published, and When?” *Canadian Medical Association Journal* 170, no. 4 (2004): 493.

<sup>10</sup> Pharmaceutical Research and Manufacturers of America, “Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results,” 22–3 (June 30, 2004) (available at <http://www.phrma.org/publications/publications/h2004-06-30.1035.pdf>).

<sup>11</sup> Eric G. Campbell et al., “Managing the Triple Helix in the Life Sciences,” *Issues in Science and Technology* 21, no. 2 (2005): 50; Richard A. Knox, “Biomedical Results Often Are Withheld: Study Examines Researchers’ Financial Links to Corporations,” *Boston Globe*, April 16, 1997, sec. A.



Betty Dong and Nancy Olivieri are two scientists who signed “gag-clauses” in clinical trial agreements<sup>12</sup> but refused to compromise their right to communicate research results while they were under contract with a for-profit sponsor. Dong, a pharmacologist at the University of California, San Francisco (UCSF), investigated the bioequivalency of a trade and generic drug for hypothyroidism, expecting to find the trade drug superior. When her investigation revealed that the drugs were bioequivalent but substantially different in price, her sponsoring company threatened to sue her for publishing her results.<sup>13</sup>

Dr. Olivieri, a hematologist and specialist in the treatment of rare blood diseases at the University of Toronto Medical School, participated in a clinical trial to test an oral drug that seemed like a promising therapy to reduce tissue iron loading in transfusion-dependent thalassemia patients. During the trial, Dr. Olivieri identified an unexpected risk and a loss of sustained efficacy of the drug. When she was about to report those results to her colleagues and to inform patients of the risk, her sponsoring company stopped the trial and threatened to take legal action against her.<sup>14</sup> Both Dr. Dong and Dr. Olivieri were eventually recognized by their respective institutions for acting properly in not permitting the contractual language of their clinical trial agreement to preempt their fiduciary responsibilities as scientists and, in Dr. Olivieri’s case, as a physician. How can scientists be epistemologically disinterested in the research and yet be sponsored by a for-profit entity? The next section explores the concept of “disinterestedness” in sponsored research.

Fortunately, there is a growing interest in establishing researchers’ rights to communicate and publish scientific and clinical data collected under their supervision. A dozen journals associated with the International Committee of Medical Journal Editors have set a new standard for medical publications that requires authors to disclose whether or not they had full responsibility for the conduct of the trial, had access to the data, and controlled the decision to publish. Individual scientists are also resisting pressure to withhold data and results.

<sup>12</sup> Robert Steinbrook, “Gag Clauses in Clinical-Trial Agreements,” *New England Journal of Medicine* 352, no. 21 (2005): 2160-2.

<sup>13</sup> Drummond Rennie, “Thyroid Storm,” *Journal of the American Medical Association* 277, no. 15 (1997): 1238-43.

<sup>14</sup> Jon Thompson et al., *The Olivieri Report* (Toronto: James Lorimer, 2001).

### Scientific Bias

Columbia University sociologist Robert K. Merton cited “disinterestedness” along with “universalism,” “communalism,” and “organized skepticism” as comprising norms of scientific inquiry. He might have added “trust,” “openness,” and “honesty” to his list.<sup>15</sup> By “disinterestedness,” Merton did not mean that scientists are neutral with respect to their choice of hypotheses or that they are impartial to one theory or another. The preference for scientists to exhibit, either overtly or tacitly, support for a hypothesis that explains a physical effect is part of the lifeblood of scientific investigation. A hunch turns into an obsession. Scientific passions are what drive discovery. So where does “disinterestedness” enter?

“Disinterestedness” implies that scientists apply their methods of inquiry, make observations, take readings, perform their analysis, and execute the interpretation of results without consideration of personal gain, ideology, or fidelity to any cause other than the pursuit of truth. Scientists may not be disinterested in learning that their empirical findings do not corroborate their hypothesis. They must, however, behave *as if* they were disinterested by allowing the data to determine the fate of their hunch.

Typically, scientists possess an intellectual standpoint in their work. They may be centrists who support a generally accepted theory or they may be renegades who back a new and controversial theory. The affinities of scientists toward one theoretical approach or another are obvious to anyone familiar with the literature of a field. For example, during the development of Quantum Theory in physics in the early part of the twentieth century, some physicists were opposed to an interpretation of the data that embodied indeterminism as a core principle.

A scientist who allows nonintellectual factors, such as religion or commerce, to influence his or her science is not disinterested in the sense I have described. Some observers have concluded that the new entrepreneurial revolution in academic science has eliminated disinterestedness as an operating norm. Ziman, a Fellow of the Royal Society, physicist, and sociologist of science, has written about the demise of “disinterestedness” as a core norm in science.

<sup>15</sup> Robert K. Merton, “Science and the Social Order,” *Philosophy of Science* 5 (1938): 321–37.

What cannot be denied is that the academic norm of disinterestedness no longer operates. Even the genteel pages of the official scientific literature, where feigned humility is still the rule, are being bypassed by self-promoting press releases. In any case, scientific authors indicate by the "affiliations" and "acknowledgments" in their papers that interests other than their own personal advancement have had a hand in the research.<sup>16</sup>

The question then arises: does the loss of disinterestedness affect the objectivity of science "which is usually attributed to the detached, impartial, unbiased, dispassionate (etc., etc.) attitude with which scientists undertake their research?"<sup>17</sup> Can science still remain healthy despite the loss of "disinterestedness"? Dr. Ziman argues that the demise of "disinterestedness" will affect the public's confidence in science, or what he calls "social objectivity." But he claims that science will continue to produce reliable knowledge. The production of objective knowledge thus depends less on genuine personal disinterestedness than on the effective operation of other norms, especially the norms of communalism, universalism, and skepticism. So long as post-academic science abides by these norms, its long-term cognitive objectivity is not in serious doubt.<sup>18</sup> Dr. Ziman's conclusions about the loss of disinterestedness presupposes one or both of the following premises: (1) Skepticism in science will cancel out any short-term effects on objectivity brought about by the loss of disinterestedness; (2) the self-correcting power of science will, over time, identify and correct error and bias.

In the biomedical sciences, the time it might take to correct errors or to discover bias resulting from covert commercial interests has a cost in morbidity and mortality. Even if it were the case that science would eventually correct itself, the human toll could be considerable until the time that false knowledge is discovered. The central question is whether commercial interests in science and the growth in academic-industry partnerships have an effect on the objectivity of outcome and eventually on human well-being. We shall return to this question in the section on the "funding effect" in science. Meanwhile, scientific journals, the gatekeepers of certifiable knowledge, are also tied to the commercial world by the advertising

<sup>16</sup> Ziman. *Real Science*, 174.

<sup>17</sup> *Ibid.*

<sup>18</sup> *Ibid.*

they receive. Can journals be immunized against the influence of their advertisers?

### The Negative Influence of Marketing

It is generally recognized that drug company advertisements support the existence of many specialized journals and contribute to the financial viability of the leading general medical journals. David Orentlicher and Michael K. Hehir II have outlined the conflicts of interest that arise for journal editors and professional societies from advertising.<sup>19</sup> The prestigious, high-impact journals claim to have erected a firewall between their business and editorial divisions. The less prosperous journals are vulnerable both to potential litigation and withdrawal of lucrative advertisers. A survey of 350 journal editors who are members of the Committee on Publication Ethics found that 40 percent of biomedical journals have no declared policy on separating editorial and commercial matters.<sup>20</sup>

Consider the following case. In January 2004, the *British Medical Journal* reported that the California-based nephrology journal *Transplantation and Dialysis* rejected a peer-reviewed editorial – reviewed favorably by three experts – on the grounds that the marketing department rejected the article. The article questioned the survival benefits of a drug treatment on end-stage renal disease. The author of the editorial received a letter from the editor indicating that he had been overruled by his marketing department.<sup>21</sup>

This is an unusual case because the editor of the journal disclosed the influence of the marketing department to the author. There is no indication of how commonly or infrequently marketing plays a role in editorial decisions. But what we do know is that in the biomedical field, where new therapeutics can be worth billions of dollars in revenue, companies will make great efforts to bias the outcome of the results in their favor either

<sup>19</sup> David Orentlicher and Michael K. Hehir II, "Advertising Policies of Medical Journals: Conflicts of Interest for Journal Editors and Professional Societies," *Journal of Law, Medicine and Ethics* 27, no. 2 (1999): 113–21.

<sup>20</sup> Jim Giles, "Journals Lack Explicit Policies for Separating Eds from Ads," *Nature* 434, no. 7033 (2005): 549.

<sup>21</sup> Owen Dyer, "Journal Rejects Article after Objections from Marketing Department," *British Medical Journal* 328, no. 7434 (2004): 244.

by adding “spin” to an article, not reporting negative results, or keeping a drug on the market despite information about adverse effects.

Some observers have noted the impact that advertisements have on medical journals and have called for more stringent ethical guidelines on publishing drug advertisements, which in some cases make up 30–40 percent of the pages devoted to the journal. In a letter to the *British Medical Journal*, a writer noted:

Drug companies' advertisements in medical journals may pose an even greater threat to medical practice and education than pharmaceutical funding of medical research because of the industry's use of the latest “technology” in advertising methods. Surely another mechanism to fund medical journals should be investigated.<sup>22</sup>

Some new experiments in funding journal publication have been introduced by public access electronic journals such as *Public Library of Science* (PLOS), which have no advertisements. But what about the numerous investigators who receive funding from for-profit companies? Can they remain disinterested in the outcome of their studies? Can we get objective science through private sponsorship of research?

### The Funding Effect in Science

As I explained in the preceding section, an increasing number of studies show that deviations from the principles of healthy science take their toll on the results of scientific research. Specifically, this empirical research reveals that privately funded research biases the results toward the financial interests of the sponsors.<sup>23</sup> The poster child of advocacy science is the tobacco industry as revealed in a thoroughly researched report issued by the World Health Organization.<sup>24</sup> But the funding effect on science is also showing up in the pharmaceutical, chemical, and oil/energy industries.

<sup>22</sup> S. Sussman, “Conflicts of Interest Drug Advertising Corrupts Journals,” *British Medical Journal* 308, no. 6939 (1994): 1301.

<sup>23</sup> Justin E. Bekelman et al., “Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review,” *Journal of the American Medical Association* 289, no. 4 (2003): 454–65.

<sup>24</sup> World Health Organization, Committee of Experts on Tobacco Industry Documents, *Tobacco Company Strategies to Undermine Tobacco Control Activities at the World Health Organization* (July 2000) (available at <http://www.who.int/genevahearings/inquiry.html>).

Frederick vom Saal and Claude Hughes report a striking pattern of bias in research findings on the toxicology of the chemical bisphenol A, which is ubiquitously used in plastics. They found that, of 115 relevant studies published, none of the 11 funded by for-profit companies reported adverse effects at low-level exposures, whereas 94 of 104 government-funded studies reported such effects at extremely low doses.<sup>25</sup> In a metastudy of conflict-of-interest papers in biomedicine, Bekelman et al. concluded: "evidence suggests that the financial ties that intertwine industry, investigators, and academic institutions can influence the research process. Strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions."<sup>26</sup>

Because real science does not selectively publish data skewed only toward one hypothesis, it must address the issue that researchers supported by private sponsors or who have financial interests in the subject matter of their study are subject to a subtle form of bias. Healthy science requires that this potential biasing effect be made known to reviewers, editors, and readers of the article. The *Washington Monthly* quoted Drummond Rennie, deputy editor of the *Journal of the American Medical Association (JAMA)*, responding to the conflicts of interest in the life science: "This is all about bypassing science. Medicine is becoming a sort of Cloud Cuckoo Land, where doctors don't know what papers they can trust in the journals, and the public doesn't know what to believe."<sup>27</sup>

Conflicts of interest in producing research are exacerbated by the fact that the pharmaceutical industry is in control of vast amounts of information, much of which remains secret or is shared as privileged business information with regulatory agencies. The practice of suppressing data unfavorable to industry's bottom line is not *prima facie* illegal, but it delays the science and can cost lives. Science is self-correcting, but it may take years for that correction. The cost in lives that may result from sequestered data must be weighed against the rights of companies to their confidential business information.

<sup>25</sup> Frederick S. vom Saal and Claude Hughes, "An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment," *Environmental Health Perspectives Online* (April 13, 2005).

<sup>26</sup> Bekelman et al., 463.

<sup>27</sup> Shannon Brownlee, "Doctors without Borders: Why You Can't Trust Medical Journals Anymore," *Washington Monthly* 36, no. 4 (2004): 38.

easy as it sounds since the science applied to drug safety and efficacy trials has its own idiosyncratic structure. Most of the studies are contracted out to academic centers or the burgeoning for-profit clinical research organizations (CROs) by the drug industry.<sup>29</sup> Clinical trials are not designed to contribute to basic knowledge but rather to supply data that pharmaceutical companies can use to bring drugs to market. Privately funded drug studies stop short of pursuing scientifically interesting questions that have no commercial value. Most drugs tested in clinical trials never reach the market. Yet, positive results in drug testing are more likely than negative outcomes to get published.

Several reasons might explain this result. First, journals have a strong preference for publishing positive rather than negative studies. Second, companies undertake in-house studies to screen out drugs that would prove ineffective in humans, weighting the drugs they contract out for external trials toward positive outcomes. Third, many corporations that fund drug studies exhibit a bias toward publishing only those results that elevate the potential market of their products. Sponsor bias has been confirmed by the appearance of secret covenants in research contracts that give the private funder of the study control over the data and/or publication of the results. Richard Friedman noted in a *New York Times* guest column that "a drug company can cherry-pick favorable studies for publication and file away studies that show its drug in a negative light."<sup>30</sup> In another example, Eli Lilly allegedly withheld clinical trial data on the drug fluoxetine (aka Prozac) that linked it to suicide attempts and violence.<sup>31</sup>

### *Two Case Studies*

Two cases illustrate how companies with a vested interest in certain findings seek to suppress negative outcomes. As mentioned earlier, a pharmacologist at the University of California named Betty Dong signed a contract with Flint Laboratories to undertake a six-month clinical trial comparing the company's popular thyroid drug against a generic competitor. The

<sup>29</sup> It has been estimated that industry funds 70 percent of the clinical trials in the United States. *Ibid.*, 2202.

<sup>30</sup> Richard Friedman, "What You Do Know Can't Hurt You," *New York Times*, Aug. 12, 2003, Op-Ed sect.

<sup>31</sup> Jeanne Lenzer, "FDA to Review 'Missing' Drug Company Documents," *British Medical Journal* 330, no. 7481 (2005): 7.

### **Redeeming Biomedical Science**

The redemption of drug science will be a challenging task given the structure of the industry – which is all but vertically integrated. Companies pay for most of the drug testing; they control the data; they contract out with academic scientists and in some cases with for-profit clinical trial companies. Sometimes these contracts permit sponsor control over publications and statistical analysis of results.<sup>25</sup>

The drug industry is also in control of much of the market for its products. The industry uses several methods to exert such control. Drug companies support journals through ads and pay high premiums for journal supplements, provide the main financial support for the continuing education of doctors, market directly to consumers, lobby Congress and state legislators in setting drug prescription guidelines, pay generous speaker fees to scientists who promote their drugs, provide all sorts of gifts to physicians, and serve as the primary source of drug information for clinicians. In addition, they sponsor panels to develop clinical guidelines and choose panelists with company affiliations.

Getting healthy science from a system replete with conflicts of interest is truly a challenge, especially where the sector boundaries between drug development and drug evaluation have become blurred. Yet reform must begin somewhere. Four important changes are required to improve the integrity of drug science: (1) guaranteeing the openness of all clinical trial data; (2) developing a firewall between the drug manufacturers and the drug testers; (3) establishing a national, comprehensive system of postmarketing drug evaluation; and (4) mandating comprehensive and transparent disclosure policy for drug journals, clinical guidelines, and federal advisory committees.

### **Openness of Clinical Trial Data**

#### *Obstacles to Disclosure*

Perhaps the most obvious reform is to require that clinical trial data be shared openly with the scientific community and the public. This is not as

<sup>25</sup> Michelle M. Mello et al., "Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry," *New England Journal of Medicine* 352, no. 21 (2005): 2202–10.



contract contained the following clause: "Data obtained by the investigator while carrying out this study is also considered confidential and is not to be published or otherwise released without written consent from Flint Laboratories."<sup>32</sup> Unaware of the clause, Dr. Dong submitted the results for publication in the *Journal of the American Medical Association*, where her paper was refereed and accepted for publication. When the paper appeared in galleys, Dr. Dong requested that it be withdrawn in the wake of threatened legal action by Knoll Pharmaceuticals, a company that had taken over the rights to the drug and which declared Dong's results in error.<sup>33</sup>

In a second case, Attorney General Eliot Spitzer of New York State charged the pharmaceutical company GlaxoSmithKline (GSK) with concealing information about the safety and effectiveness of an antidepressant. The company conducted at least five studies with children and adolescents as subjects on its antidepressant Paxil (also known as paroxetine). The lawsuit alleged that GSK suppressed the negative studies that showed Paxil was no more effective than placebo and that it increased the risk of suicidal ideation. These cases, among others, have created a ground swell of interest in public databases for registering clinical trials. Currently, there are hundreds of online registers that provide different information formats, and together do not account for all the trials.<sup>34</sup>

### *Centralized Registry*

In June 2004, the American Medical Association called upon the Department of Health and Human Services to establish a centralized clinical trials registry. The International Committee of Medical Journal Editors (ICMJE), representing a dozen prestigious medical journals, issued a statement in September 2004 that their journals would not publish clinical trial results if the trials were not posted on a public database. A House bill (HR 5252) introduced by Edward Markey (D-MA) and Henry Waxman (D-CA), titled "Fair Access to Clinical Trials Act," would require any recipient of a federal grant, contract, or cooperative agreement for the conduct of a

<sup>32</sup> Rennie, 1239.

<sup>33</sup> Dorothy S. Zinberg, "Cautionary Tale," *Science* 273, no. 5274 (1996): 411.

<sup>34</sup> Eric Manheimer and Diana Anderson, "Survey of Public Information about Ongoing Clinical Trials Funded by Industry: Evaluation of Completeness and Accessibility," *British Medical Journal* 325, no. 7363 (2002): 528–31.

clinical trial to register the trial on a database to be established by the secretary of Health and Human Services.<sup>35</sup>

Pharmaceutical Research and Manufacturers of America (PhRMA), the trade organization for major pharmaceutical companies, recently came out in support of a voluntary system of posting, in a standardized industry-approved format, "timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing, regardless of outcome."<sup>36</sup>

These proposals differ in many important details, especially the following: which trials would be posted (hypothesis-driven, exploratory, inconclusive, aborted); when they would be posted (at inception; at conclusion); which databases would be acceptable (single or multiple databases); what type of information should be included (protocols, raw data, analyzed data, interpretation of data); in what format should the information be posted; and within what time period after a trial has begun and/or ended should a posting be required.

The ICMJE proposal requires posting the protocols of all clinical studies designed to determine the cause-effect relationship between a medical intervention and a health outcome. It excludes phase I trials that focus exclusively on drug pharmacokinetics and toxicity. The congressional bills and American Medical Association (AMA) proposal include a requirement that a summary of results of all completed trials should be posted as well. The central rationale behind the public databases was stated by the ICMJE: "If all trials are registered in a public repository at their inception, every trial's existence is part of the public record and the many stakeholders in clinical research can explore the full range of clinical evidence."<sup>37</sup>

For the postings to have value to the clinical community and the public, a summary of results should be a part of the mandatory registration. The raw data by itself would not be useful to those who cannot undertake the statistical analysis indicated in the protocol. Under the New York State-GSK settlement, GSK is required to post a *clinical study report*, a type of detailed abstract, defined as "a description of the protocol, all the data,

<sup>35</sup> Senator Christopher Dodd (D-CT) introduced a companion bill to the Senate (S. 2933).

<sup>36</sup> Pharmaceutical Researchers and Manufacturers of America, 19.

<sup>37</sup> Catherine DeAngelis et al., "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors," *New England Journal of Medicine* 351, no. 12 (2004): 1250-1.

and the clinically relevant conclusions drawn from the data, including the answers to the questions posed in the protocol.<sup>38</sup>

Posting every trial report on a database presents problems, however. How do readers of the posted study know whether the study was well conceived, and whether the statistics were executed correctly? One well-designed negative study may be more valuable than two poorly designed positive studies. If the statistics for a particular study are standardized and stipulated by the protocol, concerns about post-trial selection of statistics to get the “best” outcome will be minimized.

Some studies posted on the registry will be published; others will not. Will the unpublished trials be included in review articles, given that unrefereed studies are rarely included? Could the pharmaceutical industry gain some market power from poorly designed studies merely by being posted on the registry? Would they be unfairly penalized from studies that are inconclusive and would ordinarily not get published even if well executed? This raises the question of whether all studies appearing on the database, but especially those that are unpublished, should receive a rating. Without some rating system, weaker studies may have an undue influence on readers untrained in biostatistics and research methodology.

The mandatory registration of all clinical trial protocols in a standardized format will be of unequivocal benefit to the medical community. But a consensus must be reached about the form in which the results of clinical trials (raw and analyzed data) should be presented in a registry that will be recalcitrant to the sponsor’s interpretive bias and transparent to the power and the quality of the science.

### A National Institute of Drug Testing

In *Science and the Private Interest*, I identified three ethical norms that should serve as the standards for the integrity of clinical and environmental research.<sup>39</sup> These norms are that: (i) the roles of those who produce knowledge in academia and those stakeholders who have a financial

<sup>38</sup> Press Release, Department of Law, State of New York, “Settlement Sets New Standard for Release of Drug Information” (Aug. 26, 2004) (available at <http://www.oag.state.ny.us/press/2004/aug/aug26a.04.html>).

<sup>39</sup> Sheldon Krinsky, *Science and the Private Interest* (Lanham, MD: Rowman and Littlefield, 2003), 227.

interest in that knowledge should be kept separate and distinct; (2) the roles of those who have a fiduciary responsibility to care for patients while enlisting them as research subjects, and those who have a financial stake in the specific pharmaceuticals, therapies, products, clinical trials, or facilities contributing to patient care, should be kept separate and distinct; and (3) the roles of those who assess therapies, drugs, toxic substances, or consumer products and those who have a financial stake in the success or failure of those products should be kept separate and distinct.

In the case of drug testing, it is difficult to fulfill these norms without a structural change of the system currently in place. To establish a firewall between the drug manufacturers and the drug testers, an intermediary agency is needed to distance the sponsors of drugs tests from the scientists who undertake the testing and who are paid directly by the drug manufacturers. The "funding effect" shows us that without such a firewall, scientists will likely internalize the values of their private funders, resulting in biased outcome. This is a population effect and is not observed for each scientist. But the effect demonstrates that privately funded studies are skewed toward the sponsor's interests. My proposal is to establish a National Institute of Drug Testing (NIDT).<sup>40</sup>

The function of the NIDT would be to serve as the firewall between the drug companies and the researchers who study the safety and efficacy of their products. Using fees from drug companies that are based on the real costs of carrying out a clinical trial, the NIDT would screen and select qualified scientists to undertake the study. In addition, the NIDT would ensure that drug testing met high ethical standards while protecting confidential business information.

The data from such tests, whether favorable or unfavorable to the manufacturer, would be fully accessible to the drug company, other researchers, health care providers, and the general public once the investigators publish the results. It is also expected that the trial results would be posted on a public database. The NIDT would reinstitute the concept of independent and disinterested science in drug testing by establishing a separation between drug manufacturers and testers that would prevent even the appearance of conflict of interest. This proposal will respond to recent criticisms and lawsuits directed at drug companies.

<sup>40</sup> *Ibid.*, 229.

A year after I published the concept of the NIDT, a similar idea was proposed by Marcia Angell in her book *The Truth about the Drug Companies*.<sup>41</sup> Angell wrote:

I propose that an Institute for Prescription Drug Trials be established within the National Institutes of Health (NIH) to administer clinical trails of prescription drugs. Drug companies would be required to contribute a percentage of revenues to this institute, but their contributions would not be related to particular drugs (as in the case with FDA user fees). The institute would then contract with independent researchers in academic medical centers to conduct drug trials. The researchers would design the trials, analyze the data, write the papers, and decide about the publications. The data would become the joint property of the NIH and the researchers, not be controlled by the sponsoring company.<sup>42</sup>

One of the benefits of an agency like the NIDT is that it can set parameters on what data are necessary to evaluate a drug fully for efficacy and safety. There is a great difference in the effort taken to gather pre-marketing as contrasted with post-marketing data for drug studies. In the next subsection, I discuss how the science can be skewed by this difference of effort and what can be done about it.

### Comprehensive System of Post-Marketing Drug Evaluation

Post-marketing drug evaluations have not caught up with the information age, and this is thus another important area for reform. It is generally acknowledged that drug testing is never complete until a product is evaluated when it is used in large populations. Clinical trials that involve several hundred to a few thousand subjects cannot assess the drug's effect over the range of diversity that is manifest in the human genome. Therefore, clinical trial data can be considered preliminary only until the drug is tested over a sizable human population of drug users. The science of drug testing demands post-marketing data, both for evidence of efficacy and safety. If that data are not forthcoming, then there is a serious limitation to the science.

<sup>41</sup> Marcia Angell, *The Truth about the Drug Companies* (New York: Random House, 2004), 245.

<sup>42</sup> *Ibid.*

The current system of reporting adverse drug reactions in the United States is decentralized, haphazard, and purely voluntary. Physicians typically do not take the time to investigate and report adverse drug reactions to the FDA or a drug company. Therefore, valuable data necessary for self-correcting science are lost.

With current information technology, it would be possible to establish a central data bank managed by a federal agency for all drugs approved by the FDA. Physicians would have to be given an incentive or a mandate to report adverse drug incidents. Only then would we be able to realize fully the benefits of the data possibilities in drug evaluations.

Several years ago, the Japanese Ministry of Health and Welfare (MHW) revised its Good Post-Marketing Surveillance Practice with a new reporting system for adverse drug reactions. Immediately following drug approval, medical representatives are responsible for visiting each institution using the new drug periodically for six months to remind health care professionals of their obligation to report adverse events. Under the new regulations, physicians, dentists, and pharmacists as well as pharmaceutical companies are all required to submit adverse drug reports to the MHW.<sup>43</sup>

### Mandating Disclosure

The recognition and acknowledgment of potential bias in scientific studies are essential parts of healthy science, and requiring conflict disclosures is another obvious area for reform. Increasingly, we are learning that having a financial interest in the subject matter of one's research can bias the outcome. Catherine D. DeAngelis, editor of *JAMA*, noted that: "when an investigator has a financial interest in or funding by a company with activities related to his or her research the research is: lower in quality, more likely to favor the sponsor's products, less likely to be published, and more likely to have delayed publication."<sup>44</sup> Thus, the disclosure of potential conflicts of interest must be transparent.

<sup>43</sup> Ames Cross, "Regulatory Changes in Japan's Pharmaceutical Industry," *Pacific Bridge Medical* (Nov. 1998) (available at <http://www.pacificbridgemedical.com/publications/html/JapanNov98.htm>).

<sup>44</sup> Catherine D. DeAngelis, "Conflict of Interest and the Public Trust," *Journal of the American Medical Association* 284, no. 17 (2000): 2237-8.

The journal *Nature* was the last of the prestige science journals to adopt an author disclosure policy. In explaining the reasons for adopting the policy, the editor of the journal wrote, "There is suggestive evidence in the literature that publication practices in biomedical research have been influenced by the commercial interests of authors."<sup>45</sup> It is estimated that at least 60 percent of the English-language medical journals have a conflict of interest policy for contributors of original research.<sup>46</sup> Using *Ulrich's Periodicals Director*, I conducted a survey of English-language psychiatry journals that published drug studies and found 42 percent had conflict-of-interest (COI) policies.<sup>47</sup>

In addition to influencing authors, financial ties might also bias the decisions of reviewers and editors. Some journals, therefore, extend their COI policies to others involved in journal publications.

Two other areas where disclosure is deemed important in revealing potential biases in medical science are in clinical guidelines and in recommendations of federal advisory committees. Many journals neglect to disclose the financial interests of biomedical scientists whose names are listed on an expert panel signing off on the recommendations cited in the guidelines.

Only in the past few years, however, has any attention been given to the transparency of financial interests of those participating in the development of clinical guidelines for preventative and therapeutic interventions. In one study of 191 clinical guidelines published in six major medical journals between 1979 and 1999, only 7 published guidelines disclosed the potential COIs of the expert panel members.<sup>48</sup>

<sup>45</sup> Philip Campbell, "Declaration of Financial Interests: Introducing a New Policy for Authors of Research Papers in *Nature* and *Nature Journals*," *Nature* 412, no. 6849 (2001): 751.

<sup>46</sup> Richard M. Glass and Mindy Schneiderman, "A Survey of Journal Conflict of Interest Policies," talk given at the International Congress on Biomedical Peer Review and Scientific Publication, Prague, Czech Republic (Sept. 18–20, 1997).

<sup>47</sup> Using the search terms "psychiatry and drugs," "psychopharmacology," "drugs and mental illness," and "psychiatry and medication" in *Ulrich's Periodicals Directory* when restricted to descriptors "active," "academic/scholarly," "English language," and "refereed journals," the search yielded forty-five journals of psychiatry. Of those, nineteen had conflict-of-interest policies.

<sup>48</sup> George N. Papanikolaou et al., "Reporting of Conflicts of Interest in Guidelines of Preventive and Therapeutic Interventions," *BMC Medical Research Methodology* 1, no. 3 (2001) (available at <http://www.biomedcentral.com/1471-2288/1/3>).

Clinical guidelines are most often published under the auspices of professional medical associations, government agencies, or health promotion organizations such as the American Heart Association. These guidelines play an integral role in the practice of medicine. Most physicians do not have the time to undertake the type of comprehensive and critical review of medical evidence that is expected of panels of experts. If a financial conflict of interest among medical researchers can bias the outcome of a study (as recent research shows),<sup>49</sup> there is as much reason to believe it can also bias the recommendations in a clinical guideline. In one study, University of Toronto researchers surveyed 192 medical experts who participated in writing forty-four sets of guidelines for the treatment of asthma, coronary artery disease, depression, high cholesterol, and pneumonia. One hundred respondents indicated that nine out of ten had some type of relationship with a drug manufacturer. About six out of ten had financial ties to companies whose drugs were either considered or recommended in the guidelines they wrote. Of the forty-four guidelines, just one reported a potential COI.

A 2001 study examined six influential medical journals that published clinical guidelines from 1979–99. The journals were *Annals of Internal Medicine*, *British Medical Journal*, *NEJM*, *JAMA*, *Pediatric*, and the *Lancet*. Of the 115 guidelines that were published when the journal disclosure policies were in effect, only seven guidelines disclosed potential COIs.

The importance of protecting the integrity and public trust in scientific and medical advisory committees has been widely discussed.<sup>50</sup> Yet, there remains a lack of transparency of advisers with financial COIs, despite the fact that such disclosures have become standard procedure in the major medical publications.<sup>51</sup>

## Conclusion

It is impossible to remove science from its social context. Healthy science depends on the funding it receives from the government, other nonprofit

<sup>49</sup> Bekelman, 454.

<sup>50</sup> Sara Schroter et al., "Does the Type of Competing Interest Statement Affect Readers' Perceptions of the Credibility of Research? Randomised Trial," *British Medical Journal* 328, no. 7442 (2004): 742–3.

<sup>51</sup> Sheryl Gay Stolberg, "Study Says Clinical Guides Often Hide Ties of Doctors," *New York Times*, Feb. 6, 2002, sec. A.



institutions, and for-profit institutions. But the health and integrity of science must be protected from its capture by private interests. The independence of academic science from its for-profit sponsors must be a national goal shared by all professional societies, journals, academic institutions, and government agencies. This chapter has discussed some of the challenges facing that goal and made recommendations designed to insulate science from those tendencies of society that seek to exploit it for personal gain or for interests other than those that support its role as a generator of trustworthy and reliable knowledge.