Scrutinizing Industry-Funded Science: The Crusade Against Conflicts of Interest

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Executive Summary

For approximately a century, industry has been a powerful motivating force in the creation of new technology and the underwriting of scientific research. Yet the last two decades have seen the development of a sweeping conflicts of interest movement aimed squarely at curtailing academic/industry biomedical research collaborations and restricting membership on government scientific advisory boards to researchers associated with industry.

Conflicts of interest activists assert that ties between researchers and industry are harming patients and consumers, undermining public trust in research, food safety and environmental regulation and boosting the costs of medicine and other products. As evidence, they repeatedly point to the same handful of research "scandals" and have produced a number of studies correlating industry sponsorship with favorable results in clinical research. In addition, the anti-industry activist groups are trying to exclude academic researchers who have any ties whatsoever to industry from government scientific advisory boards. However, even the activists' own flawed studies can't demonstrate that industry "influence" is distorting the decisions made by those boards. The campaign to purge any experts with industry ties—no matter how slender—from advisory panels is chilling scientific debate and depriving regulators and the public of valuable insights.

These conflicts of interest activists focus almost entirely on the alleged baleful effects of financial conflicts of interest while ignoring how other conflicts can bias scientific research and advice to government agencies. People are influenced by all sorts of interests besides money. Why should having once consulted with Pfizer or DuPont disqualify a scientist from serving on a government advisory board or writing a review article in a scientific journal, while being a lifelong member of Greenpeace does not? And if owning $10,000 in Dow stock represents a potential conflict of interest, surely $10,000 in funding from the Union of Concerned Scientists does too.

Contrary to the claims of conflicts of interest activists, the overwhelming majority of patients and research subjects are not being harmed, public trust in scientists and scientific research remains extremely high, and new drugs not only save lives but money. CenterWatch, which tracks 59,000 clinical trials in the United States, found that industry-sponsored drug trials are in fact safer than those at academic institutions funded by government. Polls regularly show that physicians and scientists are two of the most trusted professions. In fact, a recent poll found that three-quarters of cancer patients would have no qualms about enrolling in a study of a treatment sponsored by a company in which a researcher owns stock or from which he/she receives royalties. And finally, econometric research shows that newer drugs, rather than increasing overall medical costs (and thus arguably being foisted in a fraudulent fashion on a cash-strapped public), reduce other medical expenses by a factor of five.[1]

The current obsession with conflicts of interest is not harmless. The activists have provoked the development of unnecessary and complex academic regulations and restrictions that are interfering with the speedy translation of scientific discoveries into effective treatments and new products and technologies. Instead of improving public health or making our environment safer and cleaner, the activities of conflict of interest activists are harming them. Researchers are abandoning universities and some are even leaving the country for locales in which academic-industry collaboration is encouraged rather than denigrated and penalized. Government agencies are being denied access to sound scientific advice, which distorts regulatory priorities, risks lives and raises costs.

When abuses have been uncovered, private entities including journals, universities and scientific professional societies have adequately addressed them. Such private solutions include the advent of permanent online peer-review of scientific studies and the requirement by scientific journals that all clinical trials be registered. These private efforts are undercutting the campaign by activists to have Congress enact onerous conflicts of interest regulations.

The plain fact of the matter is that there is very little evidence that alleged conflicts of interests are significantly distorting scientific research, harming consumers and patients or misleading public policy. Most conflicts of interest activists clearly have prior strong ideological commitments against markets and corporations. They view the conflicts of interest campaign as another tool to attack an enterprise which they already despise on other grounds.

Introduction

History clearly shows that industry and academic science have long been productive partners. The desire for profit has driven the subsidizing of much valuable research. Nonetheless, an influential movement to prevent conflicts of interest is sweeping through the U.S. biomedical research and regulatory communities, and its arguments are routinely based on the assumption that all ties between scientists and industry are likely corrupting. This conflicts of interest (COI) controversy has been built on a few high-profile research scandals and a series of ambiguous reports and studies on alleged undue industry influence on clinical trials and government advisory boards. COI activists claim that growing ties between researchers and industry are harming consumers and patients, undermining public trust and boosting the costs of medicines and other products. This report reviews the evidence and finds that these claims are overstated and mostly without merit.

The public, patients and research subjects are not being subjected to undue risks, public trust in scientists and scientific research remains extremely high, and new drugs save lives, while new products provide greater convenience and save money. When abuses

have been uncovered, private entities including journals, universities and scientific professional societies have effectively addressed them. Despite prodigious efforts, critics of government scientific advisory boards have not been able to demonstrate that industry unduly influences advice given by those boards.

The COI activists seek to demonize researchers whose work receives support from commercial sponsors, especially drug companies and the makers of synthetic chemicals used in agriculture, industry and everyday life. At most, COI activists can show a correlation between sponsorship and results that are often favorable to sponsors. However, correlation does not necessarily imply causation, and even COI activists acknowledge that there are plausible non-threatening explanations for why this might be so but nevertheless hint darkly of undue influence. Far more importantly, the activists have failed to show any correlation between sponsorship and harm to patients, consumers or degradation of the environment.

In fact, given the dramatic reduction in morbidity and mortality in treating illnesses such as cardiovascular disease, increases in crop yields, ever more convenient products, declining levels of air and water pollution, it is clear that patients and consumers have gained enormously from the commercial sponsorship of research.

Far from harming patients, commercial support for biomedical research is vital for speeding new effective therapies from the lab bench to patients' bedsides. In the biomedical area, there is some evidence that the push to tighten COI rules may well already be slowing down the process of getting vital new drugs and other treatments to patients. In 2007, the FDA approved just 19 new medications, a decrease from 22 in 2006 and the lowest number since 1983, when the agency approved 14 new treatments.[2] The activist-generated fear of litigation has also been an obstacle to the development and marketing of newer, cheaper and safer consumer products and technologies.

COI activists are also targeting the scientific advisory committees that counsel government regulatory agencies such the Food and Drug Administration and the Environmental Protection Agency. They are campaigning to require that scientists who receive commercial support for their research be excluded from government advisory committees. The problem here is that industry also seeks out the most qualified and experienced researchers for their advice and research acumen. Systematically excluding such scientists would deny government agencies the expertise that world class scientists can offer. Instead, the goal of COI activists appears to be packing government scientific advisory boards with researchers with an anti-industry ideology, or ones not qualified to work in the private sector. Skepticism toward the motives of any research sponsors is certainly appropriate, but COI activists have intimidated editors at scientific journals and leading universities into adopting draconian policies that appear on balance to be causing more harm and than good.[3]

Adopting proposals such as having the federal government fund all clinical trials would likely yield as many new therapies as Soviet scientific research did.[4] As health economists Joseph A. DiMasi of Tufts University and Henry G. Grabowsky of Duke University note, the Soviet "record of innovation was not impressive."[5] Government bureaucrats and university administrators simply do not have the vision, expertise or incentive to nurture a proposed new treatment from brainchild to cure.

The conflicts of interest campaign is not harmless. The COI campaign has provoked the development of unnecessary and over-elaborate academic regulations and restrictions that are interfering with the speedy translation of scientific discoveries into new effective treatments. Instead of helping patients or improving public health, the activities of conflict of interest activists are harming them. And government agencies are being denied access to sound scientific advice, which distorts regulatory priorities, risks lives and raises costs.

Just as the Bush Administration's restrictions on human embryonic stem cell research have driven some of that research abroad, the COI campaign is driving biomedical research abroad too. Chafed by unreasonable conflicts of interest strictures, some researchers have left the country for locales in which academic-industry collaboration is encouraged rather than denigrated and penalized. For example, Dr. Ashley Bush, while he was a medical professor at Harvard University, discovered novel compounds that reversed Alzheimer's-like disease in mice. Because of what Dr. Bush describes as Harvard's "extremely harsh conflict of interest rules," he decided to leave the university and move to Australia. Harvard's COI rules did not allow him (and any other similarly situated researchers) to have any commercial interest in his work, nor was he allowed to do any research related to his new compounds that might be associated with their commercial development.[6]

"The rules are forced down your throat," Dr. Bush said. "They have a conflict of interest police force. If they hear any whispers about conflicts of interests, they basically threaten your job."[7] As a consequence, Dr. Bush has joined the faculty at the University of Melbourne in Australia. Australian COI rules have allowed him to found a company, Prana Biotechnology, which has just launched clinical trials using compounds he developed to treat Alzheimer's disease. "In the last ten years, I have seen a lot of talent leave academia over university conflicts of interest rules," added Bush. Because of its harsh COI rules, Bush noted, "Harvard has one of the worst records of spin-offs, not like MIT." In fact, Harvard ranks first in terms of biotech research, as measured by papers and citations, but is only eighteenth on the Milken Institute's University Technology Transfer and Commercialization Index. MIT is number 1 on that index.[8]

This report concludes that the conflicts of interest campaign against industry/academic collaboration research has shown:

(1) no evidence of patient harm
(2) no evidence of loss of faith in scientific research
(3) no evidence that integrity of science is being threatened by commercial influences
(4) no evidence that collaboration boosts the overall costs of medical care or of consumer products
(5) little evidence that industry unduly influences decisions of government agencies
(6) no evidence that environmental regulations routinely err on the side of industry

This report will also show that government conflicts of interest regulation has not been necessary. Private initiatives are already taking care of any perceived problems including:

(1) relevant disclosures—though such disclosure should be expanded to include ideological commitments, such as anti-chemical and anti-corporate activism and relevant organizational affiliations
(2) peer-review, which is becoming a permanent and transparent activity
(3) clinical trials being registered so that they can be monitored publicly—before legislation pre-empted these private initiatives

Ultimately, the COI crusade is anti-industry ideology masquerading as a patient safety and consumer advocacy campaign. What the critics really attack isn't conflicts of interest per se. Rather, their target is the presence of private industry in every aspect of scientific research, and "conflicts of interest" is code for this detested intrusion. Entities such as universities and scientific journals must realize this and begin to reform and rein in their unnecessarily restrictive COI rules.

Finally, science has shown itself capable of effectively addressing concerns about conflicts of interest and the validity of research results without government intervention.

Scenes from the Conflicts of Interest Campaign

"Drug profits infect medical studies," reads the headline on a commentary in the January 6, 2006 *Los Angeles Times*. "Industry ties cloud research," reports the *San Jose Mercury News* in August 2005. "The drive for profits may be putting consumers in danger. Are drugs safe?" wondered an op-ed in the *Denver Post* on June 5, 2005. Activist attorneys with the Center for Progressive Reform, Wendy Wagner and Rena Steinzor, claim that the Bush Administration was "stacking government agencies' various scientific advisory committees with pro-industry scientists or with candidates with scant scientific experience but impeccable ideological credentials."[9] The Nader-inspired anti-business think tank, Center for Science in the Public Interest (CSPI) established its Integrity in Science Project that aims to raise awareness about the role that corporate funding and other cor-

porate interests play in scientific research and government regulatory oversight. The CSPI project investigates and publicizes alleged conflicts of interest and the influence of industry-sponsored science on policymaking. Not to be outdone, the Union of Concerned Scientists has also launched its own Scientific Integrity Program to "push for reforms that will protect our health, safety and environment."

These worries over the dangers of industry-funded clinical and toxicological research are being fueled by stories about drug company chicanery over the painkiller Vioxx and alleged industry misinformation about public exposure to "carcinogens." Activists, politicians and other commentators claim that conflicts of interest are rife in industry-funded clinical and epidemiological research. The concerns have been that conflicts of interest (almost solely financial ones) risk harm to research subjects and patients; will tarnish the integrity of scientific research; and risk undermining public trust and support for scientific research. In addition, biased reporting of scientific results could boost overall medical costs by misleading physicians and patients to select treatments that are no better than cheaper medicines. To counter these alleged harms, some activists and politicians want to impose more stringent government regulations on private clinical research or even eliminate industry-funded research entirely. In addition, some activists want to ban government agencies from obtaining advice from scientists who have had any prior relationship with private industry. Far from banishing conflicts of interest on government advisory panels, activist groups evidently want to stack such panels with scientists whose political and policy perspectives mirror their own.

Their efforts are not by any means limited to pharmaceutical controversies, either:

• The October-December issue of the *International Journal of Occupational Environmental Health* (IJOEH) was a Special Issue entitled "Corporate Corruption of Science." The synopsis of the special edition claims that corporate funding of research has a "substantial tradition of manipulation of evidence, data and analysis, ultimately designed to maintain favorable conditions for industry, at both the material and ideological levels." The special edition includes some 14 articles largely written by researchers associated with activist organizations such as Earthjustice, Center for Science in the Public Interest, Natural Resources Defense Council (NRDC) and Pesticide Action Network of North America (PANNA) to name a few.[10] The guest editors of the issue work for the Massachusetts-based Never Again Consulting which regularly supplies expert witnesses for plaintiff attorneys.[11]

• The World Health Organization (WHO) has barred a life sciences industry association from participating in setting global standards protecting food and water supplies because its members have a financial stake in the outcome. Under pressure from activist organizations, the UN health agency's Executive Board decided that the International Life Sciences Institute (ILSI), an association of food, chemical and pharmaceutical companies based in Washington, DC, can no longer participate in WHO health standard-setting

activities.[12] Yet, activist groups such as Consumers International and Corporate Accountability International remain in good standing at WHO.[13]

The COI charge is being used as a political tool to silence opposition (whether in academia, at the EPA or elsewhere) by people with an anti-industry agenda—and it is a highly effective means of delegitimizing experts and the conclusions of the panels on which they sit, creating a broader chilling effect on scientific dialogue.

Despite the headlines and activist claims, history shows that "conflicts of interest" pose few risks. For example, few consumers or research subjects have been harmed, public trust of scientific research remains high, pharmaceutical innovation lowers rather than raises health care costs and charges that industrial products are imperiling public health are overblown. In any case, private initiatives aimed at thwarting rare possible abuses of research are already being implemented by medical journals, universities and companies.

Brief History of Funding of Scientific Research

After World War II, research took off in the United States, and economic growth duly followed in its wake, increasing gross domestic product (GDP) in real terms more than sixfold from $1.7 trillion to over $11 trillion between 1950 and 2005 while population only doubled.[14] Discoveries in the material sciences enabled the creation of a plethora of new cheap-and-convenient products such as plastics, pesticides and fabrics throughout the 1950s, 60s and 70s. Among the more crucial products were electronic devices such as semiconductors and integrated circuits. The new electronic revolution was centered around Stanford University which established an industrial park next door to its campus in 1951 as "a center of high technology close to a cooperative university." Stanford produced and encouraged its scientists and engineers such as William Hewlett, David Packard, Russell Varian and William Shockley to found and staff now legendary Silicon Valley companies such as Fairchild Semiconductors, Intel and Apple Computers. By 2000, Silicon Valley's high-tech electronics and computing firms employed more than half a million engineers, scientists, managers and operators.[15] The electronic revolution was fueled by close ties between academic researchers in physical, computer and engineering sciences and in business enterprises. This process of translating academic research into commercial products continues. For example, 31 percent of the Massachusetts Institute of Technology's science and engineering faculty has outside income.[16]

In 1980, the industry journal *Chemical Week* noted that ties between industry and universities had been much closer in the 1950s. For example in 1953, 11 percent of university basic research funds came from industry. However as federal R&D funding from National Science Foundation and the Defense Department grew, industrial support for basic research on campuses dropped to just 2.7 percent by 1978.[17] That soon began to change.

By 1983, 43 percent of faculty members in departments of chemistry and engineering at major research universities received support from private industry for their research. In contrast, only 17 percent of life sciences faculty members were receiving industry support for their research.[18] That also was about to change. By the late 1990s, studies found that 90 percent of life sciences firms had some relationship with a university and that 25 percent of life sciences faculty had received some research support from industry. In addition, over 50 percent of life sciences faculty had consulted with industry and 7 percent owned equity in companies doing work related to their research.[19]

In the last couple of decades, industry support of biomedical research has surged. Between 1980 and 2000, industry's share of spending on biomedical research rose from 32 percent to 62 percent. By one estimate, 70 percent of the money for clinical drug trials in the United States comes from pharmaceutical companies. The result of this commercial funding surge is that scientists have discovered and developed more than 300 new medicines, vaccines and biologics to treat more than 150 illnesses since 1990. However, as commercial enterprises have become more involved in funding scientific research, a cadre of COI activists have begun arguing that the concern for the bottom line is distorting scientific findings. COI activists consequently assert that "industry-funded science" cannot be trusted.

In 2005, the *Journal of the American Medical Association* (JAMA) published a report on the financial anatomy of biomedical research that found that the United States spends 5.6 percent of its total health expenditures on biomedical research, more than any other country. Furthermore, funding for biomedical research in the U.S. nearly tripled to $94.3 billion in 2003 from $37.1 billion in 1994,which is roughly a doubling when adjusted for inflation. Industry funded 57 percent and the National Institutes of Health (NIH) provided 28 percent of the total in 2003.[20]

The NIH is by far the Federal government's largest funder of biomedical research. Adjusted for inflation, NIH obligations nearly doubled (in 2003 dollars) from $13.4 billion in 1994 to $26.4 billion in 2003. Private support for biomedical research, adjusted for inflation, increased 36 percent from $1.8 billion in 1994 to $2.5 billion in 2003 (in 2003 dollars). Private support for biomedical research comes primarily from foundations, voluntary health organizations, and the free-standing research institutes. Interestingly, a 2006 Congressional Research Service report notes that only four of the 47 FDA approved drugs generating $500 million a year were developed in part with National Institutes of Health-funded technologies.[21]

Research spending by pharmaceutical firms rose (in 2003 dollars) from $13.5 billion in 1994 to over $30 billion in 2003. Biotech companies boosted research spending in real dollars from $8.5 billion in 1994 to nearly $20 billion in 2003. Research spending by medical device firms rose from $3.5 billion in 1994 to nearly $11 billion in 2003. Industry sponsorship of clinical trials increased from $4 to $14.2 billion in real dollars.

From an economic perspective, biotechnology and medical device companies were most productive, as measured by new diagnostic and therapeutic devices per dollar of research and development cost. Productivity declined for new pharmaceuticals. Might the COI campaign be responsible for part of the decline in pharmaceutical productivity?

Biomedical firms seek advice from academic scientists who are on the cutting edge of research. Their advice is crucial in helping firms to identify fruitful avenues for research and avoid dead ends. "Outside consulting is often key to prudent decision-making, whereas dampening or abolishing this activity would be a disservice to society," argues John Calfee, a scholar at the American Enterprise Institute.[22]

It is a truism among academic researchers that Federal funding is necessary for fundamental research and that such funding is perpetually inadequate. However, a 2001 study by Organization for Economic Co-operation and Development (OECD) researchers found, in fact, higher spending by industry on R&D correlates well with higher economic growth rates. In contrast to the academic truisms about the need for Federal funding, the study found that "business-performed R&D…drives the positive association between total R&D intensity and output growth." [23] The OECD researchers noted that publicly funded defense research crowded out private research, "while civilian public research is neutral with respect to business-performed R&D."[24] In other words, government funded civilian research didn't hurt the private sector but there was not much evidence that it helped, at least in the short term. The report concluded, "Research and development (R&D) activities undertaken by the business sector seem to have high social returns, while no clear-cut relationship could be established between non-business-oriented R&D activities and growth."[25] That means economic growth associated with R&D was linked almost entirely to private sector research funding. The OECD report did allow that perhaps publicly funded research might eventually result in long-term technology spillovers, but that contention was hard to evaluate. Whatever the effects of publicly versus privately funded R&D, it is clear that rigidly segregating them would delay, if not deny, the benefits to the public of innovative new products and services.

The huge expansion of commercial funding of scientific research over the past 40 years has greatly strengthened the ties between academic and industrial science. This cooperation between academia and industry has been essential to speeding new treatments from lab bench to hospital bedside. Even some critics recognize that "the relationship between academic institutions and industry [has] flourished, spawning medical advances, creating new biotechnology markets and providing needed support for further discovery."[26]

The Conflict of Interest Campaign Begins

Despite the fact that industry-funded science has fueled remarkable economic growth and improvements in every aspect of our society: health care, agricultural productivity, food safety, modern consumer products and technologies, COI activists are now claim-

ing that industry-funded research is distorting scientific objectivity. They focus particularly on biomedical research. As evidence they point to a few widely reported research "scandals." Furthermore, drugs being taken off the market for safety reasons by the FDA also get wider attention than they used to from the media, activists and public. In addition, FDA drug withdrawals receive exaggerated press attention because aggressive trial lawyers file more high profile lawsuits against pharmaceutical companies. And science and health stories are garnering more news coverage. The number of newspaper front-page stories involving science tripled from 1 to 3 percent between 1977 and 2004 and in news magazines the number of pages devoted to health and science has quadrupled since 1980.[27] Along with the rise in reporting has come a huge increase in direct-to-consumer pharmaceutical advertising, which has greatly boosted consumer awareness of the availability of new treatments.

One of the hoariest maxims of journalism is "follow the money" and COI activists are now applying it with a vengeance to scientific findings with which they disagree or which they dislike. Another version is encapsulated by the Latin tag "cui bono" meaning "to whose advantage." We all instinctively understand muckraker Upton Sinclair's point: "It is difficult to get a man to understand something when his salary depends upon his not understanding it." Relying on our natural suspicion of the temptations of cash, anti-industry ideologues who are engaged in a scientific controversy now commonly (and often illegitimately) seek broadly to dismiss "industry-funded science" and aim to discredit researchers by describing them as "industry-funded."

As a result of the COI campaign, several leading scientific journals in the 1990s began requiring that investigators disclose the funding sources for their work described in papers that they submitted for publication. In 1993, epidemiologist Kenneth Rothman worried that such mandatory disclosures would "thwart the principle that a work should be judged solely on its merits." He astutely added, "The label of conflict of interest is so commonly used with the intent to discredit a person or work that it is disingenuous for anyone to claim that no accusation is intended when describing conflicts of interest. Part of the problem with the current conflict-of-interest disclosures is that those who are innocent of fraud or of any slanting of their work are tarnished along with the guilty, without any real knowledge of who has in fact been influenced by a financial lure or some other factor."[28]

Conflict of Interest Defined

The scientific ideal is that researchers are disinterested pursuers of objective truth. But science is a human activity and like all human activities it has flawed practitioners who fall short of the ideal. "Science is a contact sport," says Dr. Jeffrey Drazen, editor of the *New England Journal of Medicine*, "People think about it being genteel, but it's a tough game."[29] Harvard hematologist Dr. Thomas P. Stossel concurs: "The idea that money is evil and academia is made up of saints is nonsense. Some of my vaunted academic colleagues would run their grandmothers over."[30]

The issue of financial conflicts of interest in academic research rarely came up until the 1990s. Academic researchers on engineering, chemistry, geology, and physics faculties worked together with software, chemical, oil and electronics companies without much objection. Such ties are still generally applauded as examples of virtuous synergy that spurs innovation and economic growth and consulting fees, stock ownership, and patents are considered normal and beneficial to both academia and the public.

So why the current furor over ties between academic biomedical researchers and commercial biomedicine companies? In a word, patients. Or in the clinical research context, voluntary experimental subjects. Few objections are made when biomedical research—either academic or commercial—is conducted using cells or animal models. But when it comes to injecting pioneering medications or inserting novel devices into the bodies of people, the ethical stakes are appropriately raised.

The concept that physicians owe essentially a fiduciary duty to patients was introduced in the 18th century by Dr. John Gregory and Dr. Thomas Percival.[31] They argued that physicians were professionals who are required to place their patients' interests equal to or ahead of their own in all dealings involving them. A special position of trust between patients and physicians is created when patients engage physicians to use their special skills and knowledge, for the benefit of the patients albeit for a fee. Gregory and Percival pushed this line of ethical thinking in part because in the 18th century there were many paths to becoming a medical practitioner. Individual practitioners developed and sold secret nostrums and other treatments, and physicians endured economic insecurity as a result of fierce competition in the medical marketplace. By stressing the fiduciary relationship, Gregory and Percival were trying to distinguish physicians from other medical practitioners and improve their relative standing in the marketplace.

In the context of biomedical research, one must add to the strand of ethical thinking about the duties owed by physicians to patients another that encompasses the Enlightenment ideal of academic freedom. In 2005, the First Global Colloquium of University Presidents defined academic freedom as "the freedom to conduct research, teach, speak and publish, subject to the norms and standards of scholarly inquiry, without interference or penalty, wherever the search for truth and understanding may lead."[32] While noting the global nature of political interference with the exercise of academic freedom, the report also expressed concern about commercial interference with research: "The increasing commercialization of universities and the expanded role of private industry in university research threaten to compromise the academic mission. Increased corporate funding for university research means that universities have yielded some control over research findings. Corporate financiers of research often demand exclusive licensing agreements and/or publication freezes to protect corporate commercial interests while patents are obtained. This marks a potential shift away from the pure and open pursuit of knowledge. One participant noted that this particular challenge presents university leaders with an especially gray area, where they are forced to deal with a devil that is not just a devil."[33]

As vital as the concept of academic freedom has been in protecting scholars in the humanities and social sciences, the fact is that scientific researchers must generally seek outside funding for their work. Tenure with financial guarantees for academic scientists is becoming less common even at prestigious universities. In addition, the peer review committees of governmental agencies and private charitable foundations often have agendas of their own, which researchers must accept when seeking their support for research. "University and governmental rules that prevent wide-ranging interactions between academic researchers and industry limit creative and economic opportunities and are a far greater violation of academic freedom than any documented interference by industry," asserted Harvard University hematologist Thomas Stossel in the *New England Journal of Medicine*.[34]

The concern over academic freedom is in part valid, but no matter how daring the thinking of individual academicians may be, universities are notoriously conservative institutions that are inherently uncomfortable with the dynamism that characterizes institutions that act in markets. Henry Etzkowitz, director of the Science Policy Institute at SUNY Purchase and his collaborator Italian sociologist Riccardo Viale suggest that a creative institutional "triple helix" is emerging as universities, industry and government work out new ways to cooperate to foster innovation. Meanwhile, they suggest the "persistence of pre-modern social structures may explain resistance to change in academia just as feudal relations impeded the transfer of modern technology to southern Europe in the 19th century." As the new cooperative framework emerges, "new tasks are often defined as conflicts of interest and obligation when viewed in relation to old. For example, when research was introduced as an academic task in the late 19th century, some said it diverted teachers' attention from students. A process of normative change takes place as controversies are resolved and new and old tasks are reinterpreted as complementary."[35] So too Etzkowitz and Viale predict that a fruitful accommodation between university and commercial research will be reached and be seen as complementary as current "conflicts of interest" come to be seen more properly as mutually supportive activities.

Given the institutional traditions and cultural issues that surround medicine and medical research, it is not surprising that some current players in academia are suspicious of and resistant to the growing ties between university life sciences researchers and pharmaceutical and biotech companies. Thus it is easy for COI activists to stampede timid university administrators and non-scientist academicians into adopting highly restrictive conflict of interest regulations.

Traditionally, the notion of a conflict of interest applied to a situation in which a public official's private interests stood to benefit from his or her public actions. For example, self-dealing in which, say, a city's mayor orders civil servants to purchase goods and services at a mark up from a company owned by the mayor or the mayor's relatives. One of the simpler definitions is "a conflict between the private interests and the official responsibilities of a person in a position of trust."[36] The concept of conflict of interest

has been expanded to encompass a variety of competing private interests. By one definition, a conflict of interest refers to "any situation in which an individual with responsibility to others (which includes professional responsibilities) might be influenced, consciously or unconsciously, by financial and personal factors that involve self-interest."[37] Another commentator defines conflict of interest as "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."[38]

But surely there are many other ways in which individuals are conflicted. People are influenced by all sorts of interests besides money. Why should having once consulted with Pfizer or DuPont disqualify a scientist from serving on a government advisory board or writing a review article in a scientific journal, while being a lifelong member of Greenpeace does not? And if owning $10,000 in Dow stock represents a potential conflict of interest, surely $5,000 in funding from the Union of Concerned Scientists does too. Why not seek complete transparency and make ideological and political disclosures mandatory as well? If someone is a member of or contributes to groups like Greenpeace, the Christian Coalition, the Pesticide Action Network, Physicians for Social Responsibility, GMWatch, Environmental Defense, or the Cato Institute, that may be of interest to anyone trying to evaluate their work. As SUNY Downstate College of Medicine cardiologist Michael Weber notes, "Major medical journals are increasing the number of articles they publish on social, political and economic issues. This focus can be perfectly legitimate, particularly when health-related issues are involved. Still, wouldn't it be more important than ever—in our new spirit of disclosure—for writers to acknowledge conflicts that could influence their opinions on sensitive or contentious public issues? Clearly there are situations where it would be relevant—far more so than financial disclosures—for readers to know where the writers live; what political parties they support; what their religious preferences might be; and even their sexual orientation."[39]

For example, consider the case of Michael Oppenheimer, who is a professor of Geosciences and International Affairs at Princeton University. Oppenheimer is the co-author of a study in the *Proceedings of the National Academy of Sciences* assessing the effects of human-induced climate change on coral reefs.[40] As part of PNAS disclosure policy, the researchers append the statement: "The authors declare no conflict of interest." Really? Oppenheimer does not disclose that for twenty years he worked as the chief scientist for the green lobby group, Environmental Defense. It is surely arguable that this past affiliation could be reasonably construed as a conflict of interest meriting disclosure. And just as accepting an industry grant to evaluate the toxicology of a pesticide may be relevant, so too should receiving a research grant from a foundation committed to organic farming techniques. How objective can Sheldon Krimsky, a professor of urban and environmental policy and planning at Tufts University and a fierce critic of commercial biotechnology, be as an advisory board member of the anti-biotech crop activist group the Center for Food Safety?

And make no mistake: such groups do have an impact on mainstream science journals, without, it seems, causing any uproar comparable to that which now ensues if, say, a government panel member has consulted with the food industry. For example, much of the current unscientific fear of vaccines having severe side effects such as autism was fueled by one man, Britain's Dr. Andrew Wakefield, who failed to disclose that he was working for plaintiff's attorneys who were seeking evidence that vaccines had injured their clients' children—the medical journal *The Lancet* eventually stated that it was distancing itself from Wakefield's 1998 report.[41] Another esteemed journal, *Science*, similarly announced that a Tulane University graduate student, Steven Arnold, had committed scientific fraud that contributed to dire conclusions reported by Dr. John McLachlan in 1996 about synergistic effects of manmade estrogenic compounds in the environment.[42] Despite these and other instances, the idea nonetheless persists that corporations are a unique source of bias and anti-chemical activists motivated solely by altruism and objectivity.

In any case, conflicts are not at all unusual. An editorial in the *British Medical Journal* noted that conflicts of interest are "a condition not a behaviour, and there is nothing wrong with having a conflict of interest. It is common."[43] Senior Vice President in the Division of Biomedical and Health Sciences Research at the Association of American Medical Colleges David Korn has noted, "Conflicts of interest and commitment are ubiquitous in academic life (and indeed, in all professional life), and conflicting pressures inherent in the academic milieu, e.g., for faculty advancement, obtaining sponsored research funding, winning the acclaim of one's professional peers, competing for prestigious research prizes, and yes, desiring to alleviate human pain and suffering, *all* may be more powerful in influencing faculty behavior than the prospect of material enrichment."[44] However, Korn stresses that the existence of conflicts of interest does not imply wrongdoing. Korn added, "Since these conflicts can never be eradicated from professional life, their existence must be accepted and *not* equated with professional misconduct." In 1993, Kenneth Rothman made the same point: "A conflict of interest by itself does not indicate wrongdoing—it merely refers to a setting in which factors exist that might influence one's conduct."[45]

It is important to remember, further, that even something that clearly falls afoul of current or proposed COI rules does not by any means necessarily demonstrate bias. One could have a strong personal attachment to disinterestedly researching a subject (or, for example, even slight bias in favor of reaching an anti-industry conclusion) even while undeniably having, say, possessed stock in the parent company of an organization likely to take an interest in the outcome of that research. The COI criteria can be defined, enforced and rewritten in countless ways without changing the actual attitudes of the human beings governed by them.

Industry Bias

To bolster their claims that industry funding taints scientific research, COI activists have generated reams of studies comparing the results of clinical trials sponsored by industry to those sponsored by government and non-profit entities. One of the canonical articles in the COI literature was a review of studies looking at the effectiveness of calcium channel blockers in 1998.

1998 Calcium Channel Blocker COI Study

In 1998, the *New England Journal of Medicine* published an article that claimed to demonstrate that commercial interests interfered with dispassionate scientific evaluation of data with regard to the relative safety and effectiveness of calcium-channel blockers for controlling high blood pressure.[46] The study found that "authors who supported the use of calcium-channel antagonists were significantly more likely than neutral or critical authors to have financial relationships with manufacturers of calcium-channel antagonists (96 percent vs. 60 percent and 37 percent, respectively)." The study went on to conclude that this "strong association" meant that the "medical profession needs to develop a more effective policy on conflict of interest." But did the study actually demonstrate that researchers had been unduly influenced by their ties to industry? Not exactly. The study itself noted that an "equally plausible" interpretation of the data was that "pharmaceutical companies sought relationships with clinicians and researchers who had already expressed favorable opinions of their products." In fact, the study authors added, "We believe that the authors we surveyed expressed their own opinions and were not influenced by financial relationships with pharmaceutical manufacturers."

So if it were the case that financial relationships had no clearly discernible influence on the clinicians, what were the study authors concerned about? The public's perception, according to the authors. "We wonder how the public would interpret the debate over calcium-channel antagonists if it knew that most of the authors participating in the debate had undisclosed financial ties with pharmaceutical manufacturers," they mused.

As Harvard hematologist Dr. Thomas Stossel has pointed out, reviewing the data in that study revealed that consultants working for competing companies, which were not performing calcium-channel research, were as likely to favor the drugs as those consulting for companies that did produce these drugs. Stossel suggests that this would unreasonably imply that scientists who consult promote every drug ever produced. Stossel argues that the more logical conclusion is that the researchers who consult with drug companies were better informed, as the drugs have not been found to present an unusual hazard for their users.[47]

In fact, a 2002 meta-analysis of three substantial, randomized outcome trials found that calcium channel blockers have turned out to be at least as safe and effective as alterna-

tive drugs.[48] Calcium-channel blockers are still widely used to control blood pressure. A 2005 study published in *The Lancet* found that a modern combination therapy of calcium channel blockers and ACE inhibitors was safer than a more conventional treatment using diuretics combined with beta blockers.[49] In addition, people with high blood pressure treated with calcium channel blockers are significantly less likely to develop diabetes than those treated with diuretics.[50] Activists fueled the controversy over calcium channel blockers by prematurely claiming that research proved that drug companies were duping physicians and patients into using more expensive treatments that were no more effective than earlier, cheaper medicines. Ten years later, further research shows that the situation is more complicated—there is no one-size-fits-all treatment for hypertension. Based on what we know now, the more benign interpretation—that companies consulted with the most knowledgeable experts rather than that researchers were unduly influenced by their ties to companies—is more likely correct.

The 2003 JAMA Review

Over the years, a number of other COI studies have concluded that industry funding does bias research results in the direction favorable to the sponsoring company. A lot of that conflict of interest research is summed up in a review article by Yale Medical School researchers published in JAMA in January 2003.[51] The review was essentially a meta-analysis of 37 previous studies assessing the extent, impact, or management of financial relationships among industry investigators or academic institutions. The review found that "industry-sponsored studies were significantly more likely to reach conclusions that were favorable to the sponsor than were non-industry studies."

However, this was not because industry-funded studies were of lower quality than non-industry studies. The review noted that "several studies found that industry-sponsored research appears to be of similar quality to other research." This conclusion is supported by a 2002 study that failed to document any association between funding source, trial outcome and reporting quality among a sample of randomized control trials that were recently published in the top five general medical journals.[52] An American Medical Association review of the relevant literature in 2004 found "most authors have concluded that industry-funded studies published in peer-reviewed journals are of equivalent or higher quality than non-industry funded clinical trials."[53]

So in the Yale review of COI studies, why were the reported results favorable to the sponsors? "There are several possible reasons for this finding," report the researchers. "It is possible that, given limited resources, industry only funds potentially winning therapies." However, the Yale researchers further noted, "We found four studies that empirically demonstrated that industry preferentially supports trial designs that favor positive results, such as the use of placebo as the comparison therapy in controlled trials. Comparisons of new therapies to placebo may be appropriate in some cases, although such comparisons are likely to favor the new therapy." The researchers observe that the

FDA only requires that new therapies be tested against placebo. This is, however, a minimal standard because therapies could be compared against one another to determine relative safety and effectiveness. Since the regulatory requirement is a comparison with placebo (essentially a sugar pill), few companies go to the considerable expense and risk of testing their therapies against other drugs.

Another charge launched against academic/industry research collaboration is that companies force academic researchers to withhold data from publication. The Dong and Olivieri cases gives this charge some plausibility (see Appendix: The Canonical Conflict of Interest Cases). In fact, contracts between academic researchers and industry sponsors often do require them to allow sponsoring firms time to assess the commercial potential of a study before publication—especially if the findings of the study might lead to patentable technologies. Three to six months is a typical waiting period. However, the Yale researchers noted that the "evidence shows...that industry sponsorship alone is not associated with data withholding. Rather, such behavior appears to arise when investigators are involved in the process of bringing their research results to market." As critical of apparent financial conflicts of interest as the Yale researchers were, they did caution, "the potential hazards of financial conflicts of interest should be assessed in light of the potential benefits of academic-industry collaboration. These include significant advances in scientific knowledge and public health, wellness and productivity."[54] In other words, be careful not to let conflict of interest inquisitions kill the industry goose that lays so many golden eggs in the form of funding and patient health.

In May 2006, a study published in JAMA analyzed outcomes of 324 cardiovascular clinical trials published between 2000 and 2005 in JAMA, *The Lancet*, and the *New England Journal of Medicine*. The study found that for 202 randomized trials evaluating drugs, the proportions favoring newer agents were 39.5 percent for not-for-profit funded trials, 54.4 percent for jointly sponsored trials, and 65.5 percent for for-profit funded trials. What could explain the differences between non-profit and for-profit trial results? The researchers concluded, "We believe there are additional issues that help to explain, in part, the observed results. For example, when the first trial report of a truly novel therapy is null or negative, it becomes less likely that any funding source will support subsequent studies. On the other hand, when the first trial of a truly novel therapy is positive, the likelihood of further trials is increased. These subsequent trials understandably and perhaps appropriately are more likely to be funded by for-profit organizations."[55] In other words, government and foundations are more likely to fund earlier stages of drug development where the risk of failure is higher. Companies jump in to sponsor drug research at later stages of development when success is more likely. Thus it is not at all surprising that industry-funded research is more likely to reach positive conclusions. This is evidence that the process of translating high-risk research into useable therapies is working as it should. In fact, if a drug company's trials regularly turned up negative findings that would signal serious flaws in its drug discovery process.

Skewing the Scientific Literature

The question arises: Does the publication of trials featuring positive results—that is, the therapy under investigation is effective in treating the targeted malady—dangerously skew the medical literature? According to American Medical Association (AMA) trustee Dr. Joseph M. Heyman, "Studies with positive findings are more likely to be published than studies with negative or null results. We are concerned that this pattern of publication distorts the medical literature, affecting the validity and findings of systematic reviews, the decisions of funding agencies, and, ultimately, the best practice of medicine."[56] It is common scientific lore that researchers are more likely to submit studies showing positive results for publication.[57] Why? Researchers often believe that journal editors are more likely to reject articles reporting negative results and so don't want to spend the time and resources on writing up their results. However, whether or not journal editors are really biased toward publishing positive results is less clear.[58] Still, this tendency to put negative results into a file drawer and forget them has the potential to bias reviews of treatments reported in the medical literature, making them look more effective than they really are. One must also keep in mind that no new drugs are produced based on one or a few studies. As technologies advance, practically all research issues have to be revisited.

It is worth noting that in the area of adverse public health effects of consumer products or byproducts, this issue is reversed. Industry is accused of only publishing negative studies (i.e., studies showing no effect). In *Environmental Health Perspectives*, several industry toxicologists argue that scientific journals tend to be biased against negative toxicity studies. It may be more interesting for academic researchers to administer doses of compounds in unnatural ways, e.g., intraperitoneal injection of materials that are generally found in minute quantities in the diet. The toxicologists claim that while results of such unnatural tests are of "dubious value for risk assessment, [such a test] may be more likely to find its way into the literature than a more relevant dietary study showing negative results with the same material." This bias towards positive results could skew the toxicological literature. The industry toxicologists conclude, "Negative findings from realistic studies make a positive contribution to the shape of a dose-response curve and, more importantly, provide context for positive studies; thus, they are vital for unbiased judgment."[59] In addition, many in industry believe that there is a significant publication bias that results both from (a) researchers' needs/desires to demonstrate adverse findings in order to get recognition and further grants from governments and NGOs and (b) from the reluctance on the part of many journals to publish negative findings.

Disclosure

Even Dr. Thomas Stossel, a strong proponent of academic-industry research collaboration, favors disclosure: "To be sure, it is reasonable to require disclosure of corporate sponsorship by investigators and institutional monitoring of collaborations. But academic

administrators and government officials respond to rare incidents of misconduct and to the barrage of criticism that follows by rushing to pile on restrictions."[60] Stampeded by the few high profile canonical cases discussed above and by a growing conflicts of interest literature that has produced at best ambiguous evidence for bias in industry-funded clinical trials, many leading scientific journals have begun requiring financial disclosure from researchers who submit articles for publication.

"There's the myth that if Mother Theresa, the Dalai Lama and Catherine DeAngelis got up and told us what to do, the public's health would be better off. That's not true," says Stossel. Journal editors "have acquired halos and become arbiters of scientific morality."[61] Chief among the halo-wearing publications are JAMA and NEJM.

The *Journal of the American Medical Association* is one of the more draconian, requiring authors to "provide detailed information about all relevant financial interests and relationships or financial conflicts within the past five years and for the foreseeable future (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received or pending), particularly those present at the time the research was conducted and through publication, as well as other financial interests (such as patent applications in preparation) that represent potential future financial gain."[62] It's worth noting that the JAMA requirement that patent applications in preparation be disclosed is particularly problematic because an inventor would risk losing his patent if he made public disclosure before filing for it. In any case, these disclosures must be included with each manuscript before it is submitted to the peer reviewers, and they are published with the article.

The *New England Journal of Medicine* has a similar conflict of interest policy with regard to research studies. The journal discloses the "sponsorship of the studies and relevant financial information about the authors." Relevant information includes consulting fees, service on advisory boards, ownership of equity (or options thereon), patent royalties, honoraria for lectures, fees for expert testimony and research grants from biomedical companies. All financial relationships deemed relevant are reported in statement accompanying the published article.[63] In 1990, NEJM declared that nobody who wrote a review article or editorial could have any financial interest in a company that made a product discussed by the article, or in any of its competitors. In 2002, the Journal relaxed this rule because it could not find enough qualified experts without financial ties to drug companies.[64]

What are the penalties for failure to comply with the journal disclosure guidelines? Some have formal policies. The *Journal of Thoracic and Cardiovascular Surgery* will blacklist for two years authors who fail to disclose financial ties to companies.[65] So far at major journals, penalties remain largely informal. As one editor noted, she has a long memory, implying that authors who violate her disclosure policies will have difficulty publishing again soon in her journal. Another "penalty" suffered by both journals and

authors is the bad publicity that results when enterprising journalists, often abetted by COI activists, report the alleged malfeasance of failing to comply with a journal's disclosure policies. Naturally, some anti-industry activists want to harden penalties. For example, the Center for Science in the Public Interest wants journal editors to adopt a three-year ban from publishing in their journals when authors fail to disclose relevant financial ties.[66]

Industrial Disinformation—The Tobacco Institute

Critics concerned about the validity and integrity of industry-funded science often point to the infamous disinformation campaign of the Tobacco Institute. American cigarette companies established the Council for Tobacco Research in 1954 with the ostensible goal of funding scientific research on the health effects of smoking. The Council was created to counter the research of British epidemiologists Richard Doll and A. Bradford Hill. Doll and Hill had just published a ground-breaking study of the smoking habits of 40,000 doctors in the *British Medical Journal* in which they discovered that smokers were at much greater risk of lung cancer.[67] Before the Council was disbanded in 1997, it had spent more than $302 million in "total financial assistance rendered to biomedical research programs" resulting in "more than 6,400 scientific publications by investigators who received research grants from the CTR." As one Tobacco Institute official put it: "Doubt is our product since it is the best means of competing with the 'body of fact' that exists in the mind of the general public. It is also the means of establishing a controversy."[68] Today, critics eager to discredit industry-funded science that they dislike often allude to the example of the Council for Tobacco Research, implying that all industry-funded research is just as suspect. Not only did the Tobacco Institute lie for decades to smokers about the deleterious health effects of cigarettes, but their distortion of the research and peer-review process handed anti-industry activists a hammer that they have enthusiastically used to attack other industry-funded research. Unfortunately, some unscrupulous corporations have short-sightedly used this Tobacco Institute model of "selling doubt" to defend their products, further increasing public skepticism toward industrial research.[69]

The Problem of Epidemiology

To fully understand why people are so fearful of subtle biasing effects (subtler, to be sure, than the efforts of the Tobacco Institute) in evaluations of chemical or environmental phenomena, it is first important to understand the strengths and weaknesses of the science of epidemiology, since it is so often epidemiological studies (and related, ambiguous statistical assessments of data) that are under scrutiny by governmental advisory panels and activist critics alike. Here, then, is a brief history of epidemiology, with an emphasis on what it does well and what it cannot do well.

Epidemiology is the study of diseases within a human population, their causes and their

means of prevention. The discipline was born out of the great cholera plague in Paris which killed nearly 20,000 Parisians in 1832. Statistics on age, location and time of death were gathered and published for the first time. In 1854, John Snow plotted the occurrence of cholera in central London and discovered that it centered on a well on Broad Street. Snow famously ended the epidemic by removing the pump handle. However, it took another 50 years after the Paris outbreak for the bacterium that causes cholera to be identified by German physician Robert Koch in 1883. Epidemiology can find patterns but rarely identify causes.

Of course, there have been some true epidemiological triumphs, especially in the area of infectious diseases, such as the spread of malaria, cholera, tuberculosis, influenza, HIV and others. Epidemiologists have also been able to identify lifestyle factors that increase the risk of certain diseases. Tobacco smoking increases one's chances of getting lung cancer by about 1,700 percent (relative risk of 17.0). For example, epidemiologists estimate that only 8 in 100,000 American males age 35-69 who never smoked regularly die each year from lung cancer, while 196 in 100,000 smokers will die of the disease each year. Also, epidemiologists have been able to identify the deleterious effects of occupational exposures to industrial compounds such as asbestos and vinyl chloride. Finally, epidemiology in the form of randomized controlled clinical trials has been critical in helping to determine whether or not new pharmaceuticals or other medical interventions are safe and effective.

In 1965, British epidemiologist Austin Bradford Hill set out nine criteria for guiding practitioners in distinguishing between association and causation. Although all of the elements have come up for criticism, the Bradford Hill criteria are still a basically valid and useful tool for assessing causation. Epidemiologist Robert Fletcher offers this slightly modified (shorter) list[70] of the Bradford Hill criteria:

Temporality—cause precedes effect
Strength—large relative risk
Dose-response—larger exposures to cause associated with higher rates of disease
Reversibility—reduction in exposure is followed by lower rates of disease
Consistency—repeatedly observed in different people, places, circumstances and times
Biologic plausibility—makes sense, according to biologic knowledge of the time
Specificity—one cause leads to one effect
Analogy—cause-and-effect relationship already established for similar exposure and disease

Epidemiology is now being asked to identify all kinds of risks in the real world. For example, do cellphones cause cancer? Does drinking coffee cause cancer—or prevent Alzheimer's disease? Do trans fats contribute to cardiovascular disease? Is DDT a risk factor for breast cancer? Reading the newspapers or listening to cable news, one would think that our lives must be devoted to figuring out which activities, foods and drinks

prevent illness or promote health. But can epidemiology really resolve these issues? Generally, epidemiologists agree that a study should be taken seriously only if it shows a strong association between a disease and a risk factor combined with a highly plausible biological mechanism.

To try to tease out the effects of risk factors on public health, epidemiologists turn to case control studies and cohort studies. In cohort studies, epidemiologists enroll a large population and question them about their lifestyles and environment. Researchers then follow them for years trying to figure out what factors are associated with those who fall ill and what factors are associated with those who remain healthy. The influential Framingham Heart Study, which identified cholesterol as a cardiovascular disease risk factor, is a cohort study. In 1948, researchers recruited over 5,000 men in Framingham Massachusetts and have followed them ever since.

In case control studies of a disease, epidemiologists identify a population that suffers from the disease and then attempt to match them with a similar population and then look for differences in lifestyle, diet or the environment that might account for disease. This should work in theory, but the problems with controlling for biases in the data and for confounding factors are well-known to epidemiologists. Confounding factors are variables that have been overlooked by researchers. Confounders can easily generate spurious associations. For example, one study found a link between heavy coffee drinking and pancreatic cancer that disappeared once the smoking habits of coffee drinkers were taken into account. In addition, biases can creep in because it turns out that control population differs in significant but unrecognized ways. For example, a finding that exposure to electromagnetic fields caused leukemia disappeared when differences in the incomes of the case population and the control population were taken into account. There is a well-known epidemiological relationship between poverty and cancer.

It is not easy to sort actual risk factors from the statistical background noise of confounders and biases. “With epidemiology you can tell a little thing from a big thing. What’s very hard to do is to tell a little thing from nothing at all,” said Michael Thun, an American Cancer Society epidemiologist in 1995.[71] Former Boston University epidemiologist Samuel Shapiro agrees: “In adequately designed studies we can be reasonably confident about *big* relative risks, sometimes; we can be only guardedly confident about relative risks estimates of the order of 2.0, occasionally; we can hardly ever be confident about estimates of less than 2.0, and when estimates are much below 2.0, we are simply out of business. Epidemiologists have only primitive tools, which for small relative risks are too crude to enable us to distinguish between bias, confounding and causation.”[72]

What then to make of a cohort study that finds that females exposed to higher levels of fine particulates in the air have relative risk of 1.4 of dying of coronary heart disease? That is, they are 40 percent more likely to die of coronary heart disease than women who breathed cleaner air. Men in the same study experienced no increased relative risk

as pollutants increased.[73] And what are the implications for regulating mercury emissions from power plants of a study that finds that men whose hair contains high levels of mercury, possibly obtained by eating fish, have a relative risk of 1.6 for an acute coronary event?[74] In other words, men who have higher mercury levels are 60 percent more likely to die of cardiovascular diseases than those with lower exposures. A 2003 meta-anlysis found that the consumption of chlorinated drinking water was associated with an increased risk (odds ratio of 1.4) of bladder cancer in men.[75] What does this mean for the vast majority of men in the United States who regularly drink chlorinated municipal water?

As previously noted, most epidemiologists will respond that one study that identifies a small effect means very little. However, if a number of studies consistently find a similar relative risk for a factor, then perhaps the factor is causal. But consistency among studies can only go so far. If all of the studies have the same design, they could all be missing the same biases and confounders and thus produce the same spurious positive results.

"Some may argue that it is of public health importance to identify and evaluate possible causal implications of small relative risks because for common diseases these can translate into large absolute risks," writes Shapiro. But as he cautions his colleagues, "Unfortunately, however, not all questions are answerable even if we desperately want answers, and public health importance does not equate with scientific validity."[76]

To close out this brief analsysis of the strengths and weaknesses of epidemiology for identifying risks, we must briefly mention two other issues. First, it should be noted that some practitioners have identified a tendency among epidemiologists to publish studies with positive results.[77] As we've seen in the biomedical field, this same tendency may skew clinical research findings toward suggesting that treatments are more effective than they are. In epidemiology, reporting only positive results (that is, a finding that some risk factor is associated with disease) will tend to skew the literature toward implying that various risk factors are more dangerous than is really the case. And secondly, there is the public choice dynamic in which researchers may try to please their sponsors, especially government regulatory agencies that fund their research. As one anonymous researcher at the National Institute of Environmental Health told *Science*, "Investigators who find an effect get support, and investigators who don't find an effect don't get support. When times are rough it becomes extremely difficult for investigators be objective."[78] That would seem to imply financial conflicts of interest that have nothing to do with business ties.

Federal Scientific Advice

Now, a look at how the tension between seeking scientific accuracy and seeking politically-acceptable judges of scientific accuracy—not the same thing—plays out in some of the most important scientific institutions.

The Food and Drug Administration

The U.S. Food and Drug Administration regulates over 150,000 drugs and medical devices as well as much of the food supply—products comprising about a quarter of U.S. GDP. At any time, nearly 3,000 investigational new drugs are being developed.[79]

COI activists are now going after federal scientific advisory boards, analyzing their votes and scrutinizing their alleged conflicts of interest. Even as the FDA science advisory panels have been criticized for alleged conflicts of interests, the agency has seen an explosion of new drugs submitted and approved. A study by the National Institute for Health Care Management found that the FDA approved 1,035 drugs in the period 1989 to 2000; 361 (35 percent) were new molecular entities—drugs based on new chemicals acting in new ways to treat disease. The remaining 674 drugs (65 percent) contained active ingredients that were already available in previously approved drugs.

However, recent criticism appears to have made FDA regulators more cautious about approving new drugs. According to a 2005 JAMA report on the financial anatomy of biomedical research, "It does seem indisputable that there have been shifts in the acceptable threshold for risk/benefit for many diseases as the depth of scientific understanding increases and as information about the effects of drugs on large patient populations is more readily available."[80] For drugs approved in the first half of 2005, the average time from application to approval was 29 months, compared with an average of 16 months for drugs approved in the first half of 2004. And the FDA is more often asking that drug makers study the safety of their medicines after they are approved.[81] Why the slowdown? Because, according to Harvard Business School professor Regina Herzlinger, "Officials know they will be punished by the public and politicians more for underregulating—approving a harmful drug, say—than for tightening the approval process, even if so doing delays a useful innovation."[82]

If the COI campaign has led to longer approval times, this is problematic for public health. Why? Because, according to a 2002 study by health economist Frank Lichtenberg, "there is a highly statistically significant relationship between the number of new molecular entities (NMEs) approved by the FDA and increased longevity: the periods during which the most new drugs have been approved by the FDA tend to be the periods in which longevity grew most rapidly. This suggests that the greater the number of drugs that are available to physicians and consumers, the higher longevity will be."[83] If this correlation is, as it appears, more than coincidence, then slowing down the approval of new drugs through over-cautious regulation may well kill more people than it "protects."

Recall one of the chief assertions by COI activists is that those conflicts will result in more harm to patients and research subjects. Fast approval of unsafe drugs kills people. Critics who think that the FDA has been recklessly approving drugs too fast point to the

2004 withdrawal of Merck's pain reliever Vioxx, for boosting the number of heart attacks. In reaction, the *New York Times* reported in September 2006, the agency appears to be slowing its rate of drug approvals. For example, in 2005 the agency had the lowest approval rate in a decade for nonpriority drugs. And as noted above, in 2007, the FDA approved just 19 new medications, a decrease from 22 in 2006 and the lowest number since 1983, when the agency approved 14 new treatments.[84]

Back in 1992, Congress, worried about the slow rate of approvals, passed legislation imposing FDA user fees on pharmaceutical companies. Flush with these new funds, the agency hired 1,000 additional drug reviewers and slashed review time from 30 months to 15 months. But faster approvals do not please everyone. Sen. Chuck Grassley (R-IA), one of the FDA's chief Congressional critics, in a letter to the agency in September declared, "Under the current FDA review system, patient safety takes a back seat to the fast approval of products." Public health activist and long time FDA critic Sidney Wolfe once compared industry's financial support for the agency review system to charging criminals user fees to pay for the police department. Clearly, in Wolfe's mind, the drug companies are already convicted.

Another anti-industry critic of the pharmaceutical companies and the FDA, Sheldon Krimsky, noted, "Between 1997 and 2004, 12 major prescription drugs, with a market value of billions of dollars were recalled by the FDA." Krimsky claims that such dangerous drugs have been allowed to reach the market because "conflicts of interest have become endemic in the system of drug evaluation. This trend has been exacerbated by the rise of for-profit clinical trials, fast-tracking drug approvals, government-industry partnerships, direct consumer advertising and industry-funded salaries for FDA regulators."[85]

Are Wolfe and Krimsky right? Not really. A 2003 study published in *Health Affairs* of the effects of user fees on FDA drug approvals found "no evidence that larger or more politically active pharmaceutical firms fared better in the review process after PDUFA [the Prescription Drug User Fee Act] was enacted."[86] These Harvard and University of Michigan researchers also reported that their study's "findings cast doubt on the argument that the pharmaceutical industry's most powerful firms have benefited disproportionately from PDUFA and that PDUFA-mandated user fees directly promote industry influence."[87] It is hard to avoid the suspicion that Wolfe and Krimsky are motivated by an anti-business ideology rather than devotion to evidence.

And is Krimsky right that the FDA is actually approving more harmful drugs than it has in the past? Again, not really. A 2005 report by the Tufts University Center for the Study of Drug Development found that faster approval times do not correlate with increased drug safety withdrawals. In fact, the percentage of drugs withdrawn for safety reasons in 1980-1989 was 3.2 percent, rising slightly in 1990-1999 to 3.5 percent, and falling in 2000-2004 to 1.6 percent. In addition, approval time for drugs that are withdrawn is not

appreciably shorter than the average approval times for all drugs.[88] The good news is that the FDA snatches dangerous drugs from the market much sooner than it used to. The average time between FDA approval and subsequent safety withdrawal dropped from 3.7 years in the 1980s to 1.4 years in the 1990s and is now 0.7 years.

As for alleged laxity in approving dangerous drugs, the converse must also be emphasize: An overcautious FDA would also kill people. As Sam Kazman, general counsel of the libertarian policy think tank the Competitive Enterprise Institute, asks, "If a drug that has just been approved by the Food and Drug Administration (FDA) will start saving lives tomorrow, then how many people died yesterday waiting for the agency to act?" ("Yesterday" means the two to three years that it generally takes the FDA to improve a New Drug Application.)[89] That's a good question.

Is Krimsky right that FDA decisions about the safety of drugs being distorted by bought and paid for scientists sitting on the agency's thirty advisory committees? No. For example, in 2006 JAMA published a study sponsored by the anti-industry activist group Public Citizen that analyzed votes by participants on FDA advisory panels.[90] That study found "there was no relationship between the conflict rate and voting outcome" on FDA advisory panels. The Public Citizen researchers, including Sidney Wolfe, did find that for each advisor with a conflict, there was a 10 percent greater likelihood that the meeting would favor approving a particular drug. That being said, the researchers also admit that *they found that excluding all panel members with conflicts would not have changed whether the vote result was favorable or unfavorable toward any drug*.

Even more amazingly, a standard conflict of interest interpretation would imply that FDA scientific advisory panel members who have served as consultants or had other ties to a particular drug company would tend to vote against a drug made by a competing company when it was being considered. However, further analysis of the Public Citizen study finds that, in fact, "advisory committee members and consultants with financial ties to pharmaceutical companies tend to vote against the financial interest of those companies."[91] This result strongly undercuts the charge that the financial interests of voters on FDA advisory committees taint committee votes. The bottom line: An FDA adviser's financial connections to the drug companies had no statistically significant effect on the approval of new drugs.

Another new study by the activist group National Research Center for Women and Families finds that that FDA "advisory committees recommended approval for 76 percent of new drugs and 82 percent of new medical devices."[92] Sounds ominous, but a plausible interpretation for the high approval rate might be that FDA in-house reviewers do not submit drugs to advisory panels for evaluation until they are reasonably sure that they are safe and effective.

Evidence that conflicts of interest are skewing the recommendations of FDA scientific advisory boards is scarce. Still, vigorous assaults on FDA scientific advisory panels are

being mounted by a few outside interest groups that do not like the substance of the conclusions reached by the panels. Groups unable to gain traction on the substantive issues raise conflicts of interest concerns in an attempt to skew panel results in directions they prefer. A 1997 editorial in NEJM expressed concern about how special interests try to "intimidate" researchers, warning, "Special-interest groups with money and power want to define acceptable questions and shape the range of acceptable answers."[93] Everyone can easily understand how corporations are motivated by profit and properly cast a skeptical eye toward their claims. However, it is also the case that so-called public interest groups also have something to "sell." If Big Tobacco's product was "doubt," all too often the product of self-proclaimed public interest groups is "fear." After all, foundation, governmental and individual support will dry up if the problems they promote are "solved."

In any case, anti-industry ideologues have found it relatively easy to point to financial conflicts of interest because researchers whose expertise makes them highly qualified to serve on federal advisory panels will also be highly sought after by industry. As one observer put it in the context of choosing advisors for other Federal panels: "The greater his or her expertise, the more likely that the candidate will appear to have at least some financial conflicts and biases, however mild, based on employment, personal wealth, prior publications, public statements, personal insights, and research agendas. No candidate is capable of a pure passion for dispassionate public service."[94]

In July 2006, the FDA announced that it was beginning the process of formulating new conflict of interest guidelines for its scientific advisory panels.[95] In September 2006, a committee from the Institute of Medicine issued a critical report, The Future of Drug Safety, which made recommendations on how the FDA should handle financial conflicts of interest on its scientific advisory panels. Interestingly, the IOM committee cited the Public Citizen study noting that excluding advisory panel members with financial ties to industry would not have changed the outcome any FDA advisory committee vote. The IOM committee also noted that the Public Citizen study treated any vote as "wrong" by an advisory panel member who had what Public Citizen deemed to be a conflict of interest. The IOM committee correctly concluded "there is no evidence to suggest that this is necessarily so."[96] Nevertheless, the IOM committee succumbed to the COI campaign and recommended that 60 percent of each advisory committee be free of any significant financial involvement with companies whose interests may be affected by the committee's deliberations.[97]

So despite the fact that COI activists could point to practically no evidence that conflicts of interest have skewed FDA advisory committee decisions, the FDA finally bowed to their pressure (and the threat of Congressional legislation) and issued new draft guidance on conflicts of interest for advisory committee members in March, 2007. Under the draft guidance individuals with financial conflicts of interest of $50,000 or less could still serve on the committees but they might be limited to non-voting status. Those with con-

flicts exceeding $50,000 generally would not be considered for committee membership.[98]

An October, 2007 study, *Measuring Conflict of Interest and Expertise on FDA Advisory Committees*, done at the request of the FDA by the Eastern Research Group, found that advisory panel members "with waivers tend to have higher levels of general expertise than members without waivers."[99] How big were the conflicts of interest that were waived? According to the study, "the median total dollar value of financial interest for members with waivers was $14,500." In addition, the study reported the results of an exercise in which alternative panel members with similar expertise were sought. The study did identify possible alternative panel members, but found that many of them would also likely require conflicts of interest waivers. The study concluded "that the ability to create a conflict-free panel is speculative, and that, even if possible, recruiting and screening costs would be much higher than current expenditures. Furthermore, the additional time required to screen candidates could significantly delay FDA decisions on major public health issues."[100]

Thanks to Congress, we will soon learn if trying to reduce financial conflicts of interest on FDA advisory committees will cost more and delay decisions. In September, 2007, Congress passed the FDA Amendments Act (FDAAA) which requires the FDA to determine how many advisory committee members needed waivers for financial conflicts of interest in 2007. The agency must then reduce the number of waivers by 5 percent in each year through 2012 for a total 25 percent reduction in the aggregate number of waivers issued over the next 5 years.[101] The FDAAA requirement that a waiver must be disclosed on the FDA's website no later than 15 days prior to a scheduled advisory committee meeting is less problematic. In addition, FDA must disclose the reasons for granting a waiver. In October, 2007, the FDA issued new draft guidance on the process of considering and granting financial conflicts of interest waivers for FDA advisory panel members and how they will be disclosed to the public.[102]

How will this improve the FDA's drug approval process? The new FDAAA regulations essentially impose an empty ritual that solves no real problems. American Enterprise Institute scholar Jack Calfee suggests that while there are a lot of people who know about the science, what is actually needed is people who understand both the science and drug development process. As we have seen, such experts generally already have consulting relationships with pharmaceutical manufacturers, so the new regulations would exclude many of them from serving on FDA advisory committees. "So they would be sacrificing a lot of talent and would gain very little in return," Calfee said. "The danger is the decisions just won't be as good because the members won't do as good a job of balancing all the factors that go into approving a drug."[103] Will these new COI regulations have any positive effect on improving the health of patients? Will they instead end up depriving the FDA of the expertise of some of the smartest and most involved researchers and have the deleterious effect of further slowing down the approval of vital new medical treatments? Time will tell, but the signs are not good.

The National Academies

In July 2006, the activist group CSPI issued a report, *Ensuring Independence and Objectivity at the National Academies*.[104] The National Academies, much like government agencies, routinely recruit outside experts from universities, industry and other organizations to advise them on scientific matters. Just how objective are such experts? The CSPI report found that over a five-year period one out of five scientists on 21 different National Academies scientific panels had "direct conflicts of interest." Famously, CSPI describes itself as the "food police," decrying all manner of fat- and sugar-laced delicacies.

So what about the CSPI's study of financial conflicts at the National Academies? The National Academies is a Congressionally chartered non-profit corporation made up of distinguished scientists who provide free scientific and technical advice to the government. The National Academies operates by creating ad hoc committees of researchers assembled to answer questions posed by Congress and various federal agencies. The CSPI looked at 320 members of 21 National Academies committees over the past 3 years and found at least 18 percent of them had direct conflicts of interest. The CSPI defines direct conflicts of interest as "a financial tie within the last five years to a company or industry that is relevant to the committee topic." The CSPI report does not say if the "tie" is a couple thousand dollars to speak at an industry event or a million dollars in a company's stock.

Unlike scientific advisory panels at agencies like the FDA or the EPA, which often take formal votes on issues, the National Academies committees issue reports generally based on consensus. Since no formal votes are taken at National Academies committee meetings, the CSPI report simply compiled evidence that 66 of the 320 panel members analyzed did "lean to industry" while only 9 did "lean to public interest groups." The CSPI wants future National Academies committees to be "balanced" and recommended that the National Academies expand their definition of "balance" to include "bias and point of view," not just scientific expertise. The CSPI defined balance "as never having more than three [pro-industy] scientists on any committee and always balancing pro-industry scientists with at least an equal number of public health oriented scientists."

Imposing this kind of "balance" would explicitly inject politics into what heretofore has been conceived of as fact-based activity. Would modeling scientific advisory panels on boards like the Federal Elections Commission—which is "balanced" with equal numbers of Democrats and Republicans—really improve their scientific advice? In addition, the CSPI is implying that a "pro-industry" scientist is not public health oriented and that others, including environmental activists are public health oriented. Neither is necessarily the case. Many scientists who work for or with industry have a strong public health focus. Conversely, there are many environmental activists who seem to care much more for the "wellbeing of the planet" than the people who inhabit the planet. For instance,

those who oppose the responsible use of DDT in malaria endemic countries are apparently willing to risk a couple million preventable deaths per year rather than accept a minuscule possibility of environmental harm.[105]

The CSPI recommended that the National Academies adopt rules that would "exclude any scientists with conflicts of interest from committees unless their expertise is crucial to the successful completion of the committee's task." Did the CSPI study uncover egregious behavior by National Academies advisory panels? No. Michael Jacobson, head of CSPI, admitted, "Whether complete avoidance of conflicts of interest on committees would have improved the committees' recommendation is impossible to know." Jacobson also acknowledged that the institutions' reports "invariably earn high marks from the scientific community, and this study, which did not evaluate the quality of any particular...report, makes no effort to question that consensus view." In other words, the CSPI report failed to uncover any specific problem other than the fact that scientists of the sort the CSPI likes are allegedly underrepresented on the National Academies panels.

As one observer notes, "The best antidote to undue influence caused by financial conflict or personal bias is full understanding by copanelists. A confidential discussion among copanelists regarding bias and conflict...serves to alert copanelists to background and perspective that may shape a panelist's contribution to the consensus effort. The [National Academies have] long used such discussions and proven their worth."[106]

He continues: "The best scientists with the most to contribute will have a rich background of professional and public experience, with at least some type of financial stake and a record of expert opinion in the scientific and public literature. In this way, panelists are implicitly burdened to critically evaluate their copanelists' contributions...disclosure rather than disqualification makes very clear that face-to-face 'peer review' and peer pressure are expected to produce consensus on a science-based report."

In 2004, the Government Accountability Office issued a comprehensive report on federal advisory committees that praised the National Academies conflict of interest policies. The GAO commended the National Academies for using a standard form to request potential advisory committee members disclose organizational affiliations, financial interests, research support, government service, public statements and positions. In addition, the GAO applauded the National Academies for posting candidate information on a website for public comment about any real or perceived conflicts of interest. Advisory committee membership is not finalized until National Academies officials have reviewed the disclosure forms and public comments.[107]

The Environmental Protection Agency

Under various statutes including the Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act, the EPA is charged with regulating exposures to

numerous chemicals to protect the public against deleterious health effects such as cancer and endocrine disruption. In setting exposure tolerances, the EPA relies on advice from several scientific advisory boards (SAB) composed of outside experts drawn from the academic, business and activist communities.

The Federal Advisory Committee Act (FACA) applies to the membership of EPA SABs. FACA requires that each committee be "fairly balanced in terms of points of view presented and the functions to be performed by the advisory committee." The GAO notes that "courts have interpreted this requirement as providing agencies with broad discretion in balancing their committees."[108]

The GAO report also commends the EPA for the procedures it uses to select scientific advisory board members. The report noted that the EPA's staff office uses a standardized form to collect information from prospective panel members about legal conflicts of interest and that the form helps the agency in assessing them for impartiality and points of view. In addition, the GAO noted with approval that the EPA "publishes the names and biographical sketches of candidates for its committees on the [scientific advisory] board's website, requesting the public to provide information, analysis or documentation that it should consider in evaluating the candidates."[109] And like the NAS, the EPA does not finalize panel membership until all submitted information is evaluated.

Let's take a brief look at a recent example of how this process works. In 2006, the EPA announced that it was convening a scientific advisory panel to consider the carcinogenicity of ethylene oxide. Ethylene oxide is a sterilant used to treat spices and dried fruits and is used to produce ethylene glycol in antifreeze. The EPA posted a short list of 31 candidates being considered for the advisory board. In June, the activist group, the Natural Resources Defense Council sent a letter (co-signed by representatives from more than 20 other activist groups) to the EPA objecting to 9 candidates based on their ties to industry.[110] These connections included consulting arrangements and research support. After complaining about the biases of other candidates, the NRDC then suggested alternative candidates, including a retired OSHA epidemiologist, a United Autoworkers toxicologist and an EPA-funded toxicologist who once ran the Radical Science Information Service. In October, only one of the nine candidates to which the NRDC objected was appointed to the 14-member panel. None of the NRDC's nominees was accepted. The recently convened panel has not yet rendered a decision about the dangers posed by ethylene oxide.

This report will not attempt a comprehensive evaluation of the EPA's methodologies for determining the risks to human health from exposure to trace amounts of synthetic chemicals and other environmental hazards. Nevertheless, it must be noted that there is a growing scientific consensus that the public health effects of such exposures are minor, if they exist at all. In 2002, three prominent cancer researchers stated this consensus when they found, "There is no convincing evidence that synthetic chemical pollutants are important as a cause of human cancer."[111]

For example, nearly a decade ago, the National Academy of Science issued a definitive report, *Carcinogens and Anti-Carcinogens in the Human Diet*. The NAS concluded that levels of both synthetic and natural carcinogens are "so low that they are unlikely to pose an appreciable cancer risk."[112] Worse yet from the point of view of anti-chemical activists, the NAS added that Mother Nature's own chemicals probably cause more cancer than anything mankind has dreamed up: "Natural components of the diet may prove to be of greater concern than synthetic components with respect to cancer risk."[113] In 1998, the American Institute for Cancer Research, the largest non-profit cancer and diet research advocacy group in the United States, also concluded, "There is no convincing evidence that eating foods containing trace amounts of chemicals such as fertilizers, pesticides, herbicides and drugs used on farm animals changes cancer risk. Exposure to all manufactured chemicals in air, water, soil and food is believed to cause less than 1 percent of all cancers."[114]

The really good news is that according to the Centers for Disease Control, the cancer rate in the United States has been declining by about 0.5 percent per year for the past decade. During that period, the mortality rate has been declining by more than 1 percent per year. In fact, in an amazing reversal of a decades long trend of ever mounting numbers of cancer deaths, researchers announced this year that the absolute numbers of Americans dying of cancer has dropped for the second year in a row. In fact there is no "cancer epidemic." Except for the cancers associated with smoking tobacco, overall cancer mortality has declined by nearly 20 percent since the 1950s.[115] Reported cancer incidence rates briefly bounced up in the 1980s primarily because new diagnostic tests uncovered breast and prostate cancers at earlier stages. The risk of cancer increases exponentially with age and as the average age of Americans rose, the number of people diagnosed with cancer naturally increased.

Despite the fact that there is little evidence that exposure to synthetic chemicals is an important cause of cancer, the EPA still spends a great of time and effort promulgating and enforcing regulations aimed at reducing trace exposures. In 2005, the EPA issued a new set of guidelines for evaluating cancer risk. Although something of an improvement over earlier guidelines, the new ones still allow default options for the agency to rule that a substance may pose a risk of causing cancer. Essentially, the guidelines can be interpreted as declaring every synthetic chemical guilty until proven innocent. This default means that the merest hint of uncertainty about the "safety" of a substance can trigger EPA regulatory action. Once triggered, manufacturers must spend a great deal of time trying to prove that their products are "safe" when EPA scientific advisory panels are convened to consider action on them. Naturally, this dynamic gives companies a strong incentive to nominate panel members whose research suggests that their products are not hazardous.

Companies can never show that their products are absolutely safe. What manufacturers can sometimes show is that "harm" was not detected under certain conditions. Of course,

regulators and anti-industry activists can always insist on answers to more questions about how a substance is absorbed, metabolized or eliminated by the human body. Regulations such as that created by California's Proposition 65 impose immense costs on industry by requiring warning labels on anything "known to the state of California" to be a carcinogen, where "carcinogen" means merely something that in super-high doses can cause tumors in rodents, not necessarily a good predictor of small-dose effects on humans (nor even, as it happens, other rodents).

Just as public choice theory predicts, government bureaucracies are risk-averse because administrators get into a lot more trouble with the public and Congress for approving a substance that is found later to have problems than for delaying or banning a beneficial one that turns out to be nontoxic. The EPA default assumptions on when to rule that a substance might be carcinogenic fully reflect that public choice dynamic. For example, the new EPA guidelines state that "in the absence of sufficiently, scientifically justifiable" information about how a substance might cause cancer, "EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity." Another way to construe the "public health-protective" interpretation of data is that the interpretations are deliberately designed to increase the number of "false positives" produced by toxicological studies. A false positive is a test result that wrongly or inaccurately shows the presence of a disease or other conditions when none actually exist. It is not at all clear that encouraging the creation of false positives is in fact on balance "health-protective." By encouraging the production of false positives, regulators are likely to incorrectly declare a product or substance dangerous. This means that hyper-cautious regulators end up denying consumers access to technologies and products that are healthier, safer and often cheaper than the older ones that are currently available.

This means that the EPA default uses data from experiments in which animals get cancer after receiving very high doses of a substance (generally just below the level of toxicity that would kill the animals outright). The EPA then extrapolates the results of these high dose animal experiments to assume that very low doses of the same substance over a long time are "likely" to cause cancer in humans. The EPA even admits: "Use of health protective risk assessment procedures as described in these cancer guidelines means that estimates, while uncertain, are more likely to overstate than understate hazard and/or risk."

According to many leading toxicologists, this is an understatement—the "health protective assessment procedures" significantly overstates the risks. Researchers have found that "half of all chemicals tested in standard high-dose animal cancer tests, whether occurring naturally or produced synthetically, are 'carcinogens'."[116] Half of all natural pesticides that have been tested cause cancer in rodents. In other words, of those chemicals tested a "natural" pesticide is as likely to cause cancer as a synthetic one. Natural

pesticides are chemicals produced by plants to defend themselves against fungi, insects, and other animal predators. Now consider that of all pesticides that humans eat, 99.99 percent are natural: Researchers point out that the natural chemicals in a single cup of coffee that animal tests say are carcinogenic equal the total amount of synthetic pesticide residues the average person consumes in a year. This does not mean that coffee or natural pesticides are dangerous, but that high dose animal tests are not a good way to detect substances that are likely cause cancer at the low levels of exposure that people experience.[117]

So if trace exposures to synthetic and natural chemicals is not the source of a great deal of cancer risk, what is it that the EPA is so expensively regulating? And EPA regulations do not come cheap. Researchers at the environmental economics think tank, Resources for the Future, estimated that the costs of environmental compliance amounted to $150 billion per year.[118] Are we getting good value for money spent on environmental protection, including reduced risks from contracting cancer? Evidence shows that we are not. In 1995, researchers at the Harvard Center for Risk Analysis evaluated 500 life-saving interventions for cost effectiveness and found that regulations administered by the Federal Aviation Agency and the Consumer Product Safety Commission, the National Highway Traffic Safety Administration and the Occupational Safety and Health Administration cost less than $100,000 per life-year saved. However, EPA regulations cost an average of $7.8 million per life-year saved. By shifting spending from high cost regulations to lower cost ones, the researchers estimated that the lives of an additional 60,000 Americans could be saved.[119]

Effect of Regulatory Agency Support on Research Results

Given the burgeoning number of recent studies by COI activists scrutinizing the effects that corporate funding has on the outcomes of scientific research, it is surprising to find that there is almost a complete absence of studies that look at the effects that government funding may have on the outcomes of scientific research. Why this should be the case is not clear. After all, scientists who work for or receive grants from government agencies are operating in an already politicized environment. Public choice economic theory suggests that agencies fund analyses to support their program objectives.[120]

As economists William N. Butos and Thomas J. McQuade recently pointed out, "Scientists' success in securing funding testifies to their submission of proposals that receive a favorable hearing by the funding agencies. Thus, scientists have an incentive to develop and nurture professional relationships with agency members, advisors, and consultants. Finally, government funding of science, including that associated with military R&D, unavoidably establishes linkages between the funding agencies' preferences (or legislative charge) and the scientific activity that university and industry researchers perform. These linkages relate to the purposes for which funds are made available, thereby affecting the direction and regulation of scientific research as well as specific protocols for military R&D."[121]

Does government funding really influence the outcome of research? Consider the case of Johns Hopkins University researcher George Ricaurte, whose research has long been funded by the National Institute on Drug Abuse. In 2002, Science published a high impact study by Ricaurte that purported to show that monkeys dosed with Ecstasy—the street name for the chemical methylenedioxymethamphetamine (MDMA)—suffered permanent brain damage, exhibiting symptoms similar to Parkinson's disease. Even more alarming, two of his 10 monkeys actually died shortly after being dosed.[122] *Science* published Ricuarte's study just as Congress was considering the draconian Reducing Americans Vulnerability to Ecstasy (RAVE) Act, which notoriously allows the police to shut down clubs and bars and prosecute their owners if any patron is caught using the apparently deadly drug Ecstasy on their premises. In September 2003, Ricaurte was forced to retract his *Science* article because its results could not be reproduced, allegedly due to laboratory error.[123] *The Scientist* called the retraction "an outrageous scandal", noting that many in the scientific community believed that *Science* rushed publication of the article because legislation was pending in Congress.[124]

Ricaurte's first study of Ecstasy appeared in 1985 just as the Drug Enforcement Administration was considering banning Ecstasy by putting it on its Schedule 1 of controlled substances. Subsequently, Ricuarte received more than $10 million in research grants from the National Institute on Drug Abuse which is part of the National Institutes of Health.[125] The charitable interpretation is that NIDA officials decided to fund Ricaurte because they thought that Ricaurte was doing excellent science. Less charitably, Ricaurte was funded because his research dependably found what federal officials wanted it to find.

The National Institutes of Health

Since December 7, 2003, when a *Los Angeles Times* article appeared condemning National Institutes of Health researchers for having a number of consulting arrangements with pharmaceutical and biomedical companies the NIH has been embroiled in an ongoing controversy over financial conflicts of interest. In 1995, then-director of the NIH, Harold Varmus, loosened earlier financial conflicts of interest regulations to allow much more outside consulting by NIH researchers. NIH researchers who consulted with pharmaceutical and biotechnology companies were supposed to clear the arrangements with their superiors ahead of time.[126]

The *Los Angeles Times* identified a number of arrangements that had not been properly reported to the appropriate officials at the NIH. The *Times*' article caught the attention of Congressional leaders who questioned NIH director Elias Zerhouni about the propriety of the arrangements. In the House, Rep. James C. Greenwood (R-PA), chairman of the Oversight and Investigations subcommittee, said NIH policies had led to, not a revolving door, but a "swivel chair" in which agency employees were paid simultaneously by the public and by industry.[127] Zerhouni was initially somewhat dismissive suggesting that

most of the violations were paperwork problems, but eventually he convened a ten member NIH Blue Ribbon Committee on Conflict of Interest Policies to advise him on new conflicts of interest policies. The Blue Ribbon Committee issued recommendations that would forbid NIH researchers from receiving stock options from companies, but would allow consulting to continue.

In May, 2004, the House Subcommittee on Oversight and Investigations held hearings on conflicts of interest at NIH. At the hearing subcommittee chairman James Greenwood declared, "It is clear from the cases we have reviewed that some NIH scientists are either very close to the line or have crossed the line [of ethical conduct]. If we are serious about upholding the highest ethical standards at the NIH, then NIH scientists should not even be close to the line."[128] The subcommittee asked 20 pharmaceutical and biotechnology companies for the names of NIH scientists with whom they had consulting arrangements. The companies supplied the subcommittee with the names of about 100 scientists who were involved in were 130 arrangements that had not appeared on a list that NIH itself had given the subcommittee. Congress cried foul, suggesting NIH was concealing its degree of entanglement with corporations.

So in February, 2005, under considerable pressure from activists and Congress, Zerhouni banned all NIH employees from consulting for drug, biotech or medical-device firms. In addition, they were forbidden to own stock in these companies. In fact, all NIH employees would be required to divest such stocks valued at more than $15,000. And NIH employees were no longer allowed to consult for research institutions, health care providers, trade associations or insurers, nor could they accept awards from institutions that seek or receive grants from the NIH.[129] At the end of February, NIH investigators cleared most of the 100 or so researchers because much as 80 percent of the seeming improprieties were actually the result of errors by government investigators.[130] Two months later, Zerhouni returned to Capitol Hill to complain that his strict limits on stock ownership was causing researchers to defect and would have a deleterious effect on the agency.[131]

In August, 2005, the conflicts of interest furor at the NIH intensified when the inspector general at the Department of Health and Human Services released another report that found that many NIH scientists had not properly disclosed their outside arrangements. The HHS report found that information submitted by the scientists to NIH ethics officials "included insufficient detail regarding the nature of the outside activities, the nature of employees' official job duties, the differences between the outside activities and their official job duties, the outside organizations, and any NIH funding or partnerships with the outside organizations."[132] In September, 2005, Zerhouni issued the final conflicts of interest rules for the NIH. Under the final rules NIH employees are prohibited from owning more than $15,000 worth of stock in any biomedical firm, and not more than $50,000 total in biomedical stock. In addition, NIH researchers are prohibited from consulting with biotechnology, pharmaceutical, medical device companies and may not engage in teaching, speaking, writing or editing for compensation with such firms.[133]

According to an internal NIH survey in October 2006, the result of the conflicts of interest crackdown is that nearly 40 percent of the scientists conducting hands-on research at the agency responded that they are looking for other jobs or are considering doing so to escape new ethics rules that have curtailed their opportunity to earn outside income.[134] In addition, nearly 75 percent of survey respondents believe the ethics rules are too severe, and think they will hinder the government's ability to attract and keep top-notch research talent. One-third of NIH scientists think the new rules are harming NIH's ability to fulfill its mission, and argue the old rules should have been enforced better rather than tightened. In March 2007, NIH became more deeply embroiled in the conflicts of interest issue when the Health and Human Services Department inspector general announced that he is going to re-examine cases against 103 NIH scientists, most of whom were cleared in earlier ethics probes.[135]

The paramount issue to keep in mind is that over the last three years of conflicts of interest hullabaloo at NIH, no one has found that public health or individual patients were harmed by NIH researchers' outside arrangements. Biomedical companies sought the advice of NIH researchers because they are among the best in the world. The agency, which is limited by a government pay scale, was able to retain top researchers because they had opportunities, both intellectual and financial, to collaborate with private sector researchers. As the NIH's own internal survey showed, the new rules have demoralized researchers and many are seeking to leave. This is not to say that potential conflicts of interests do not need to be monitored—they do—and especially so in a government agency that hands out billions of dollars in grants every year. Rules requiring that all outside arrangements be approved by an internal ethics monitoring committee and that all arrangements be publicly disclosed would be adequate.

Not Much Evidence that Industry/Academic Cooperation Has Undermined Biomedical Research

Recall that the COI activists launched their attack on industry-funded scientists and science based on three assertions: Collaborative research is putting patients at risk, undermining public trust and unnecessarily boosting the cost of medical care. It turns out that there is precious little evidence for any of those assertions.

Public Trust

While the COI activists distrust researchers and physicians, there is little evidence that the public shares this feeling. For example, a recent Harris poll shows that both physicians and scientists are at the top of professional groups trusted by Americans. In fact doctors are the most trusted profession, with 85 percent of Americans saying that they can trusted to be truthful. Trust in the truthfulness of scientists is only slightly lower at 77 percent.[136]

A 2006 poll of cancer patients participating in 5 research trials found that the vast majority (more than 90 percent) of them were unconcerned about any financial ties that their doctors may have with drug companies. According to the poll results, published in November 30, 2006 issue of the *New England Journal of Medicine*, most patients said they would have enrolled in the trial even if the drug company had paid the researcher for speaking (82 percent of those interviewed) or consulting (75 percent) or if the researcher had received royalty payments (70 percent) or owned stock in the company (76 percent). In addition, most patients believed it was ethical for researchers to receive speaking fees (81 percent) or consulting fees (82 percent) from the company.[137]

One reasonable interpretation of this poll is that cancer patients prefer to be treated by physician-researchers who passionately believe in what they are doing. Patients are also fully aware that companies make money by finding successful treatments. So it is not at all surprising that most patients said they opposed bans on relationships between researchers and drug companies and some said they would be more likely to participate if a company were involved. Even among the well-educated respondents, less than one-third said they wanted to know about potential conflicts.[138]

Of course, the COI activists might argue that the public is naive. Poll respondents did expect that there were oversight mechanisms in place to manage conflicts of interests. And as we shall see below, there are and more are being developed.

Patient Safety

Another concern is that financial conflicts of interest will undermine research subject and patient safety. It's hard to get firm numbers, but the Boston-based medical publishing firm CenterWatch that tracks clinical trials has estimated more 59,000 clinical trials currently in progress involving more than 20 million subjects. The good news is that there are very few documented examples in which patients or research subjects were unreasonably harmed. In 2001, a CenterWatch study on research risks to clinical trial participants evaluated the studies that led to the approval of one-third all new drugs (new molecular entities) between 1987 and 2001. That study found that one in 30 study subjects will experience a serious side effect during a trial. In addition, the study reported that "each year, an average of 3.6 deaths attributed to study drug effects are reported to the FDA for approved drugs." The CenterWatch report notes that in industry reports to the FDA, "one out of 10,000 study subjects have died as a result of study drug effects while participating in clinical research studies." In comparison, one in 3,000 people die from an accidental injury each year, and one out of every 6,000 people die from a motor vehicle accident annually. Disturbingly, the CenterWatch study also found,"Unlike industry-sponsored clinical trials that are regulated by the FDA, government-funded studies conducted by individual investigators at academic medical centers frequently have risks that go unreported to the [federal Office of Human Research Protection]."[139]

"It is not a patient-beware situation," said Ken Getz, president of CenterWatch. "The vast, vast majority of clinical trial participants have very positive experiences."[140] Given CenterWatch's concerns about government-sponsored research and the inherently risky nature of clinical research it is nothing short of amazing that only 8 patient deaths were reported between 1990 and 2000 to the Office of Human Research Protections at the U.S. Department of Health and Human Services.[141] Even in the conflict of interest cases cited in the Appendix—with the exception of Jesse Gelsinger—patients were not unnecessarily harmed.

One other measure of relative benefit and risk to patients from new drugs comes from a fascinating 2005 study by University of Chicago economists who calculated that the acceleration in FDA drug approvals that occurred after 1992, when new FDA user fees were enacted by Congress, may have been responsible for saving the equivalent of 180,000 to 310,000 life-years.[142] On the other hand, the economists estimated that at worst, about 56,000 life-years were lost to drugs that were eventually withdrawn for safety reasons. Unfortunately, it's much easier to identify people who are harmed by drugs than those who are saved by drugs. In the face of this information asymmetry regulators focus on reducing lives lost to unsafe drugs rather than preventing deaths by speeding effective new therapies to patients.

Cost of Medical Care

It is conventional wisdom that health care costs in the United States are spiraling out of control. In fact, health care as a percent of U.S. GDP has tripled from 5.2 percent in 1960 to 16 percent today. Some analyses project that health care expenditures will rise to 25 percent of America's GDP by 2030.[143] But are pharmaceuticals primarily responsible for an excessive rise in the cost of medical care? Not according to research done by Columbia University economist Frank Lichtenberg. In a 2002 study done for the National Bureau of Economic Research, Lichtenberg estimates that "reducing the mean age of drugs used to treat a given condition from 15 years to 5.5 years will increase prescription drug spending per medical condition by $18 for the entire population, but will lower other medical spending by $129. That yields a $111 net reduction in total health spending per medical condition. Most of the savings are attributable to reductions in hospital expenditures ($80 or 62 percent) and in physician office-visit expenditures ($24)."[144] In other words, using newer drugs reduces non-drug medical expenditures by more than sevenfold the extra amount spent on drugs.

Today, 30 percent of the $2.2 trillion Americans spend on health care goes to hospitals. Physicians get 20 percent and 10 percent pays for dental and other professional services. All of these are labor intensive treatments. In comparison, prescription drugs account for about 10 percent of health care spending.[145] "Within a generation or two," Manhattan Institute fellow Peter Huber has observed, "they will undoubtedly account for most of it-which will be another good thing. Pharma's biochemical cures always end up far cheaper than the people-centered services they replace."[146]

For example, due in part to new cholesterol and blood pressure lowering medicines, deaths from cardiovascular disease have dropped dramatically. In 2003, statisticians at National Heart, Lung and Blood Institute calculated that if death rates were the same as those of 30 years ago, 815,000 more Americans a year would be dying of heart disease and 250,000 more of strokes.[147]

Of course, as profit-making entities, drug companies try to sell as much of their drugs for the highest prices they can get. But computer manufacturers, automakers, grocery stores, restaurants, oil companies, internet service providers, insurers, homebuilders, and yes, even physicians also try to maximize their incomes. Fortunately, the competition that helps keep prices reasonable in the rest of economy is also at work in the pharmaceutical arena. This is where the much disparaged "me-too" drugs come in.

A typical complaint comes from fierce COI activist, pharmaceutical company critic and former *New England Journal of Medicine* editor Marcia Angell who asserted to *Mother Jones* magazine in 2004 that the majority of the new pharmaceuticals are "me-too" drugs. She simplistically characterized "me-too" drugs as being "no better than drugs already on the market to treat the same condition."[148] The implication is that companies are only trying to take market share away from each other without providing any "real" benefits to patients. Of course, "trying to take market share away" is better known as "competition" and results in lower prices to consumers.

In addition, Angell's economically obtuse view disregards the plain fact that companies are likely to be researching similar drugs to begin with and that one firm has to be first to market. But so-called me-too drugs actually benefit patients, not simply by offering different treatments for similar conditions—Tagamet and Zantac, for instance, have different active ingredients—but by driving down prices in a given treatment category. "The period of one-brand dominance for an innovating drug within a breakthrough therapeutic category has unmistakably shortened," writes American Enterprise Institute scholar John Calfee.[149] This faster competition leads to price cuts among rival medicines. Hence, when new anti-depressant medications were introduced in the mid-1990s, they cost only 53 percent as much as Prozac did when it first hit shelves in 1988 and had the field more or less to itself. Similarly, new cholesterol-lowering drugs that came to market in the mid-1990s cost 60 percent less than pioneering effort Mevacor did when it first showed up in 1987.

Even more worryingly, Angell and her COI colleagues ignore the fact that individual patients often respond differently to different drugs. A drug may be approved to treat heart disease, ulcers, cancer, infections, but it may not work well for some portion of the patient population whereas another so-called me-too drug will. "The FDA would like to offer patients a choice of drugs within the same class, since not every patient responds to every drug in the same manner," observed then-Director of the FDA Center for Drug Evaluation and Research, Janet Woodcock, in 2002.[150]

Just to give a couple of humble examples, the antihistamine Zyrtec (cetirizine) really controls my allergies very well whereas it makes my wife sleepy. She prefers Claritin (loratidine). I use Prilosec (omeprazole) to quench my stomach acids whereas my spouse favors Pepcid (famotidine). Consider a more consequential case. Many patients, who suffer from chronic myeloid leukemia (CML), benefit from Gleevec (imatinib mesylate), a first-in-class kinase inhibitor that targets cancer cells, approved by the FDA in 2001. But not all CML patients respond to Gleevec or become resistant to it over time. Fortunately, they can now turn to a new me-too kinase inhibitor, Sprycel (dasatinib), which the FDA approved in 2006. As an October 2006 Congressional Budget Office report notes, "Me-too drugs benefit consumers by competing with incumbent products and providing alternatives for people who do not respond equally well to all drugs. Some of those benefits come at the expense of producers of pioneering drugs, who see their monopoly profits eroded by competition. But total benefits to society increase when consumers have more choices."[151] A vital point that many COI activists strangely miss.

Furthermore, me-too drugs sometimes do not pan out for the original indications for which they were tested. However, later research turns up intriguing alternative uses. Rogaine and Viagra were developed as potential treatments for high blood pressure. Gemzar was developed as anti-viral, but is now used to treat cancer. Eflornithine didn't work out as a potential cancer treatment. Meanwhile researchers found that it was an effective medicine against sleeping sickness which afflicts 36 subSaharan African countries where 60 million people are at risk. However, as a failed cancer drug, its production was about to be discontinued. Fortunately, researchers discovered that it had another use—it inhibits hair growth on women's faces and is now sold as the women's beauty cream Vaniqa. Since the company can now profitably produce eflornithine as a beauty cream, it could justify producing additional amounts to donate to the World Health Organization for use against sleeping sickness.[152] Without me-too drugs, we put all our eggs in one basket, and that is never a good idea.

Angell also rails against the pharmaceutical industry's "obscene profits."[153] But Princeton University health economist, Uwe Reinhardt points out, "I once calculated that if you rebated all the drug company profits to patients, health spending would only go down by 1.2 percent."[154] In other words, seizing all drug company profits would do nothing to address the current health care spending "crisis," but it would shut off the flow of funds to many academic biomedical researchers and drastically slow the discovery and development of new and more effective drugs.

How Ethical Are Researchers Who Have No Commercial Ties?

A disturbing survey of 3,247 early to mid-career scientists funded by the National Institutes of Health found that many admitted to engaging in various questionable research practices.[155] Of those surveyed, 0.3 percent, that is 3 out 1000, or perhaps 10 researchers out of the total number surveyed admitted to "cooking" or falsifying data. In

addition, 0.3 percent owned up to ignoring major aspects of human subjects protections. Interestingly, only 0.3 percent confessed to not properly disclosing involvement in firms whose products are based on one's own research.

However, 15.5 percent admitted to changing the design, methodology or results of a study in response to pressure from a funding source and 13.5 percent acknowledged using inadequate or inappropriate research designs. Keep in mind that the survey was done of NIH-funded scientists. Some critics suggest that the vaguely worded (perhaps even misleading) questions could also refer to actions that aren't improper. For example, a researcher might modify the design of an experiment to improve it, based on a valid suggestion from a funding source. Yet the survey would count such a modification as misconduct.[156]

The researchers reckoned, "Our evidence suggests that mundane 'regular' misbehaviours present greater threats to the scientific enterprise than those caused by high-profile misconduct cases such as fraud." In a later study the researchers suggested that much of the misconduct uncovered by their initial survey could be traced to the "perceived unfairness in peer-review systems for grants and publications." Crucially, *they did not blame the ethical lapses uncovered by the survey on the pressures that arise from modern research collaborations with industry*. In fact, they concluded, "It is important, therefore, for research institutions, journals, and federal agencies to ensure that their decisions and decision processes related to rewards and responsibilities are as transparent, widely disseminated to researchers, and fair as possible."[157]

"Despite the enormous growth in joint projects between universities and industry, the incidence of fabrication or falsification of research results to NIH's Office of Research Integrity has barely changed over the last decade. None of the reported cases have involved researchers' commercial relationships," notes Dr. Thomas Stossel.[158]

Peer Review and Disclosure

One of the arguments heard is: why bother with disclosure? The data are the data and peer review is enough. In fact, the above analysis shows that scientific misconduct is relatively rare, and cases in which patients or research subjects are harmed as a result of conflicts of interest are also thankfully very rare. Nevertheless, media focus on anecdotes of bad research behavior and the pressure from anti-industry ideological groups have raised concerns which have led to the imposition at journals and in universities of ever more elaborate conflict of interest rules on biomedical research. Such elaborate rules almost guarantee that someone will "violate" them, which then produces further stories and moral outrage from self-appointed scientific watchdogs such as Public Citizen and the Center for Science in the Public Interest. When genuine misconduct, that is, scientific fraud or plagiarism occurs, punishment for the offender must be swift and certain. Violating procedural rules such as disclosure is not scientific fraud or misconduct.

Until recently peer review was how the reporting of valid scientific results was governed. Martin Blume, editor-in-chief of the American Physical Society and its nine physics journals, says that peer review can miss honest errors as well as deliberate fraud. "Peer review doesn't necessarily say that a paper is right," he notes. "It says it's worth publishing."[159] As we have seen, in recent years, as the ties between academic and commercial biomedicine have strengthened, concerns (largely overblown) about conflicts of interest have grown and peer review was no longer considered sufficient to assure scientific validity of reported results. By requiring disclosure, journal editors are admitting that their peer review system was a failure. Warning labels needed to be slapped onto industry-funded studies.

Whatever the current concerns over disclosure may be, a new age of robust peer review is dawning which promises to sweep away the journal-dominated era of scientific publication. Already, researchers in the physical sciences have been migrating away from peer-reviewed print journals to the world of electronic preprints of scientific papers. In 1991, physicist Paul Ginsparg launched arXive.org (the X is pronounced as the Greek letter Chi), which is an online system for distributing scientific research results which bypasses the conventional avenues of scientific publication. The arXive offers open access to 462,504 e-prints in physics, mathematics, computer science and quantitative biology. The e-prints are not formally peer-reviewed but readers can decide for themselves how scientifically valuable they are. As Ginsparg noted twelve years ago at a UNESCO conference on the future of electronic publishing, "in some fields of physics, the on-line electronic archives immediately became the primary means of communicating ongoing research information, with conventional journals entirely supplanted in this role."[160]

In 2000, this model of open scientific publication came to biomedical research when three prominent biomedical researchers launched the Public Library of Science (PLoS). PLoS first encouraged other scientific journals to make their articles available for free online. Currently, the online directory of open access journals lists 3141 journals.[161] In 2003, PLoS began launching a series of online peer-reviewed open source electronic journals. Ginsparg foresaw the possibility that segments of the scientific community (he suggested non-profit scientific societies that publish journals) might "continue to organize high-quality peer-reviewed overlays."

In a sense, this is what the PLoS journals are now doing. Since clinical biomedicine depends on the results of randomized control trials, peer review will probably remain an important process for maintaining data quality. In addition, there is the real possibility that desperate patients might be misled by bad or incomplete biomedical information. Harold Sox, editor of *Annals of Internal Medicine* has noted, "If a medical article gets out and it's wrong, the consequences may be greater."[162]

However, peer review is changing from a one time review of a self-contained research article to a continuous online process. PLoS is launching a new comprehensive online

journal, PLoS One, which will feature reports of primary research from all disciplines within science and medicine. The editorial board will make prompt decisions on whether or not any particular paper merits publication and may refer it to outside reviewers. But unlike print journals, publication is not the end of the peer review process. Once an article has been published on the PLoS One site, community-based open post-publication peer review involving online annotation, discussion, and rating begins. Post-publication peer reviewers can briefly annotate the text of the article with corrections, additions, or links to other relevant articles. They may also engage in online debates concerning the content, conclusions, and consequences of a specific paper. And finally, users may assign ratings to papers.[163] Comments and annotations may not be anonymous. According to the PLoS good practice guidelines for commenting post-publication reviewers should confine their criticisms to the demonstrable content of papers and avoid speculation about the motivations or prejudices of authors. It may be good practice now, but it is inevitable that in the future post-publication peer reviewers will disclose any associations (proper and improper) that they believe relevant to the findings reported in a paper.

With regard to disclosure in a research context, a group of public health professors and lawyers just issued in the journal *IRB: Ethics & Human Research*, model language for clinical trial conflicts of interest disclosures. Institutional review boards (IRBs) would evaluate conflicts of interest to make sure that the "possible financial benefit to the person leading the research is not likely to affect your safety and/or the scientific quality of the study."[164] Depending on the details of the conflicts, the model form would let subjects know that the researcher, the university or the company stood to benefit financially if the new treatment turns out to be safe and effective.

Register All Trials

To overcome any bias toward reporting clinical trials with positive results, all trials should be registered and their results—positive or negative—be reported. This enables other researchers, physicians, patients and regulators to see and evaluate all the information available about the efficacy of any particular intervention or the toxicity of any specific compound. Even negative trials provide useful information about the effectiveness of treatments and the likely toxicity of compounds and as such alerts other researchers not to waste their time and resources on pursuing scientific dead ends. Indeed, it is arguable that researchers have a moral obligation to publish their results—positive and negative—since patients and subjects undertook risks that allow researchers to determine the therapeutic value (or lack of any) of the intervention under investigation.

Over the past five years or so, various private initiatives had succeeded in persuading most researchers to publicly register their clinical trials. In 2004, the International Committee of Medical Journal Editors adopted a policy that requires, as a condition of consideration for publication in their journals, that clinical trials be registered in a public registry. The clinical trials must be registered at or before the onset of patient enrollment

beginning with trials commenced after July 1, 2005. The ICMJE set up various criteria that each trial must meet to insure transparency and required that the registry must be accessible to the public free of charge.[165] The ICMJE noted at the time that the only the website that qualifies so far is www.clinicaltrials.gov, run by United States National Library of Medicine. The ICMJE policy had an effect. After the policy was announced the number of clinical trial registrations increased by 73 percent—from 13,153 to 22,714.[166] As of February 2008, the registry contained nearly 51,000 trials, with more than 200 new trial registrations occurring weekly.[167] Four other clinical trials registries meet the ICMJE criteria including the World Health Organization's International Clinical Trial Registry Platform. In addition, scores of journals have now adopted the ICMJE clinical trials registration policy.

Despite the success of this private effort, the Congress passed the FDA Amendments Act (FDAAA) in September, 2007, requiring that within 21 days of the enrollment of the first patient, all phase 2, 3, and 4 drug trials must be registered in a database that is publicly available online. For approved drugs, the FDAAA requires the creation of a clinical trials results database with online links to key FDA documents; summary tables of primary and secondary outcomes; and information about adverse events. Researchers must submit trial results within one year of trial completion or within 30 days after receiving a drug approval. Researchers who fail to submit data will incur an initial fine of $10 000. After 30 days, the fine is $10 000 per day until the data are submitted.[168] Such mandatory databases will undoubtedly prove useful to physicians, patients and other researchers. And they will restrict the ability of pharmaceutical companies to withhold information. However, given the litigious nature of our society, the databases are also likely to be mined by hired gun statisticians employed by trial lawyers seeking lucrative new ways to shake down pharmaceutical companies.[169] This threat of litigation may well make drug companies and regulators even more cautious, thus further delaying the introduction of new effective treatments to the detriment of the public's health.

As of May 2006, researchers no longer have recourse to the excuse that journal editors will not publish negative or inconclusive research results. The open-access Public Library of Science (PLoS) project, which has begun publication of *PLoS Clinical Trials. PLoS Clinical Trials*, pledges to publish the results of randomized trials in healthcare from all medical and public health disciplines. Publication does not depend on the trial's outcome, size or implied importance. The journal explicitly aims to address the problem of publication bias.[170]

Through such private undertakings as requiring financial disclosure, registering clinical trials, and providing a forum for the peer-reviewed publication of all clinical trial results, the science has shown itself fully capable of addressing concerns about the validity of research results without government intervention.

Conclusion

The conflicts of interest campaign led by a cadre of anti-industry ideologues has been built on a few high profile research scandals and a series of equivocal reports and studies on industry influence on clinical trials and government advisory boards. COI activists claim that growing ties between researchers and industry are harming the public, undermining public trust and boosting the costs of consumer goods and medicines. A review of the evidence finds that these claims are largely without merit. The overwhelming majority of consumers, patients, and research subjects are not being harmed; public trust in scientists and scientific research remains extremely high; new drugs not only save lives, but money; and new products are ever more convenient, safer and less expensive. When abuses have been uncovered, private entities including journals, universities, and scientific professional societies have adequately addressed them. Despite strenuous efforts, critics of government scientific advisory boards have not been able to demonstrate that industry unduly influences advice given by those boards.

Moreover, the conflicts of interest campaign is not harmless. The activists have provoked the development of unnecessary and complex academic regulations and restrictions that are interfering with the speedy translation of scientific discoveries into effective treatments and better products and technologies. Instead of helping consumers and patients or improving public health, the activities of conflict of interest activists are harming them. Researchers are abandoning universities and some are even leaving the country for locales in which academic-industry collaboration is encouraged rather than denigrated and penalized. Government agencies are being denied access to good scientific advice which distorts regulatory priorities, risks lives and raises costs.

Back in 1993, Kenneth Rothman worried, "Since there are no official boundaries on what could be the reason for a conflict of interest, whenever we stray from using anything but the substance of a work itself as the basis for judgment, we begin to substitute prejudice for reason; we abridge the rights of others and convert the free interchange of critical views into a shouting match about pedigrees."

Dr. Thomas Stossel, the co-director of the Hematology Division at the Brigham and Women's Hospital, points out in an NEJM sounding board article: "By any measure, the interactions between academic research and industrial research and development, as epitomized by biotechnology, have been overwhelmingly positive. We should celebrate their achievements and protect the process that led to them." Stossel concludes: "In a transparent atmosphere, misconduct can be detected, challenged, and if necessary, purged and punished. The intense energy currently dedicated to demonizing academic-industrial research relationships should be redirected toward developing better ways to identify and facilitate the type of partnerships that have brought more good, by far, than harm."[171] He adds, "The public wants trustworthy science, and it can get that without new ethical rules. Even more it wants results—real lives saved—and it can't get those if commercial

sponsorship of research is made difficult, or impossible."[172] It would be tragic if commercial ties, so often a wellspring of good science, were to be singled out as the sole imaginable source of bias—leaving science diminished but groups with other regulatory, Luddite, or anti-corporate axes to grind free to influence debate and shape scientific review panels. Other such sources of bias should be treated equally with conventional financial ties, if the entire issue as currently framed is not to be dropped altogether.

"Activists, bureaucrats, and lawyers are hampering promising research and making it more costly," writes economic historian Joel Mokyr. "But the achievements made possible by new useful knowledge in terms of economic well-being and human capabilities have been unlike anything experienced before by the human race. The question remains, can this advance be sustained?"[173]

Sustaining progress will mean, in part, remembering that science is not, as the COI activists, merely a series of one-time pronouncements to be shaped by public relations experts. It is an ongoing, self-correcting process of hypothesis, experiment, report, peer review, criticism, and attempts at replicating results—with a crucial distinction to be made (routinely overlooked by journalists and activists alike) between studies that rigorously and deliberately test a hypothesis and ones that merely generate a new hypothesis, no matter how dramatic and intriguing that new hypothesis may be. Errors and false claims will tend to be corrected over time, not by political processes, but by the traditional mechanisms of science itself. While bias of various sorts can undeniably influence scientists, science, more than any other system of human knowledge, places marvelous constraints on bias and, sooner or later, efficiently punishes cranks, propagandists, and even the most well-meaning and brilliant of scientists who happen down intellectual blind alleys.

Appendix: The Canonical Conflict of Interest Cases.

At the end of the 1990s, a few widely reported financial conflict of interest "scandals" became the touchstones for what blossomed into today's full disclosure movement in biomedical and other research. COI activists constantly cite the same handful of cases to argue for the imposition of increasingly stringent government conflict of interest regulations on reporting scientific results and for participation on government scientific advisory boards.

1985 The Tseng Case

In 1985, young Harvard Medical School researcher Scheffer Tseng published scientific articles reporting he had discovered that treating 22 people with a chronic dry eye condition called keratoconjunctivitis sicca with a topical vitamin A ointment could relieve the condition.[174] Based on this work, Harvard authorized Tseng to do another study of up to 50 patients. Tseng ignored the restrictions put on his research by the university's Human Subjects committee and forged ahead treating perhaps as many as 300 people. In the meantime, Tseng and his colleagues founded a company, Spectra Pharmaceutical Services Inc., to produce and distribute the vitamin A treatment and sold stock to the public. Tseng and his relatives made more than $1 million dollars from the sale. Later research showed that the ointment was no better than placebo.

By the time officials at Harvard had caught on to Tseng's shenanigans, his two year fellowship was nearly over and he took a position as a professor at the University of Miami. In 1988, the *Boston Globe* broke the story of how Tseng had profited from his research.[175] The *Globe* correctly observed that "the increase in medical scientist-entrepreneurs has sparked a kind of controversy that similar activities by engineers, for example, never did." Indeed, COI activists still focus almost solely on biomedical research. Nevertheless, even as it was reporting Tseng's activities, the *Globe* noted that supporters of industry/university research partnerships counter that without the ties many medical discoveries would not be turned into life-saving products. Janet Trubatch, an associate vice president for research at the University of Chicago, told the *Globe*, that for years, "all sorts of things were being discovered by scientists, but nothing much was happening." Now, she added, that was changing because more researchers realize "they can get rich off what they're doing."

Harvard reacted to the Tseng controversy by instituting some of the strictest rules governing university researchers' financial ties to private business. Even today, Harvard researchers may not own stock in companies that attempt to translate their discoveries into medicines. The good news is that while Tseng's ointment was ineffective it also caused no harm. Patient health was not compromised. In 1992, a Massachusetts administrative magistrate found that Tseng had violated study protocol and hospital policy by enlarging the size of the study and changing the dosage of the ointment without telling

an oversight committee first. The magistrate also found "there was no evidence that Dr. Tseng engaged in fraudulent or unethical behavior" and that he "is a tireless, dedicated physician." As a consequence, the Massachusetts Board of Registration in Medicine dropped the charges against Tseng. Board chairman Dinesh Patel told the *Boston Globe*, "There was no patient harm and so...we felt that this was really the best thing to do."[176] Up until 2002, Tseng was a chaired professor at the Bascom Palmer Eye Institute University of Miami School of Medicine. Twenty years later, Tseng sits on the boards of directors of three biomedical companies[177] and still receives National Institutes of Health research grants.[178]

1997 The Dong Case

In 1987, University of California at San Francisco School of Pharmacy researcher Betty Dong contracted for $250,000 with the U.K.-based Boots Pharmaceutical company to test whether its thyroid drug Synthroid was bioequivalent to the cheaper compounds produced by competitors. Synthroid replaces the hormone thyroxine in patients whose thyroids are underactive. To the dismay of the company, Dong found that the cheaper compound was bioequivalent to Synthroid. After five years of sparring with the company, Dong had arranged in 1995 to publish her results in *Journal of the American Medical Association* (JAMA). The company reacted by threatening to sue her and the university to prevent it. The university initially backed Dong, but later withdrew its legal aid after its lawyers found out that, in direct contravention to university policy, Dong had signed a research contract stating that "the study results were not to be published or otherwise released without the written consent" of Boots.

The whole sorry controversy was revealed to the public in a front page story in the *Wall Street Journal* on April 25, 1996 which reported that Dong's article had been yanked from JAMA at the insistence of the company. The *Journal* added that Dong's article had "concluded that the U.S. health-care costs could be cut by $356 million a year if Synthroid were replaced by cheaper but equally effective drugs."[179] Boots responded that it was blocking publication because Dong's article was scientifically flawed and out of concern for the health of 8 million users of the drug.[180] Company spokespeople failed to mention that the publication of the article might also have had a deleterious effect on the sale of Boots for $1.4 billion dollars to Knoll Pharmaceuticals.

After the *Wall Street Journal* article, Boots Pharmaceuticals was widely (and properly) condemned for interfering with academic freedom. "This entire episode is damaging to everyone involved, and it highlights the potential pitfalls of corporate-funded university research when the results are antithetical to the interests of the funder," warned an editorial in *Science*.[181] In the face of the bad publicity, the pharmaceutical company relented and Dong's study was published a year later in JAMA.[182] Boots (and Knoll) soon stumbled into one of the pitfalls that *Science* predicted when it was hit with a number of class action lawsuits alleging that the company had overcharged patients and insurance com-

panies. The drugmaker eventually settled a patient class action suit for up to $135 million[183] and another by 37 state attorneys general for $41.8 million.[184] As other drug companies would eventually learn, trying to suppress research findings might temporarily protect a company's bottom line, but doing so will cost the firm much more in terms of profits and reputation in the long run. Of course, this situation could have been avoided had Dong followed proper university procedures. In addition, the university's lawyers could have defended her academic freedom despite her flagrant violation of university policies with regard to research contracts.

Interestingly, Synthroid, now produced by Abbott Laboratories, still dominates the market for synthetic thyroid hormone with an 85 percent share. And the battle over bioequivalence continues. Representatives from three leading professional endocrinology organizations have testified at the FDA expressing concerns about the bioequivalence of Synthroid with other synthetic thyroid hormones. The activist group Public Citizen pointed out that all three groups "take significant funds from Abbott."[185] The good news is that while patient's pocketbooks may be a bit emptier, their safety and health have not been harmed by this dispute.

1998 The Olivieri Case

Another notorious conflict of interest case was the Nancy Olivieri "scandal." Treating the inherited blood disorder thalassemia requires repeated transfusions which lead to the damaging build up of iron in the heart and liver tissues. In the early 1990s, Canadian thalassemia researcher Olivieri had contracted with the pharmaceutical company Apotex to investigate the effectiveness of chelating compound deferiprone in removing iron from the body. Olivieri came to believe that her research indicated that deferiprone caused substantial liver damage to some of her research subjects and she asked the company for support for further research along those lines. The company showed her results to other researchers who disagreed with her interpretation and the company decided not to continue to support her research. Olivieri then told the company that she was going to publish her negative results. The company responded by threatening to sue her.

The threat to sue turned Olivieri into an academic hero. By 1998, her cause was taken up by the editors at the *Journal of the American Medical Association* and the *New England Journal of Medicine*, who publicized her dispute with Apotex as an egregious example of greedy commercial interests trying to "gag" a courageous researcher. So was this a case of a feisty honest academic David fighting against a greedy dishonest commercial Goliath? Not really. More than 50 peer-reviewed studies have now shown that most patients respond well to deferiprone and that it protects them from heart disease resulting from excess iron built up through blood transfusions.[186] None of the studies support Olivieri's conclusions and the drug is now approved for use in more than 40 countries. The company was scientifically right and the scrappy researcher wrong, but that hardly matters in the ongoing battles over conflicts of interest. As one of Olivieri's collaborators

reportedly said, “There’s a lot of motives out there besides money. There’s academic advancement, self-promotion, self-aggrandizement.”[187]

1999 Gelsinger Case

One of the often expressed concerns about conflicts of interest is that researchers will harm subjects and patients as they inappropriately rush treatments to market. But is there evidence that commercial concerns have in fact ended up hurting patients? One case stands out—Jesse Gelsinger. The 18-year old Gelsinger suffered from the genetic disorder, partial ornithine transcarbamylase (OTC) deficiency, which put him in constant danger of building up toxic amounts of ammonia in his blood. He volunteered for a gene therapy study at the University of Pennsylvania in which he was injected with cold viruses modified to carry the normal version of the OTC gene.

Shortly after the injections, Gelsinger suffered from a severe immune reaction and he died of multiple organ failure. There were a number of irregularities in the trial including the fact that the researchers had failed to inform the FDA that some earlier subjects had experienced severe reactions to the treatment. In addition, the consent forms had failed to disclose the death of monkeys that had received more powerful versions of the treatments administered to Gelsinger.[188] Why not? Perhaps because the researchers were overconfident that their treatment would work and couldn’t be bothered with bureaucratic details and animal studies they believed irrelevant. Most damningly from the point of view of conflicts of interest, the principal investigator of the Penn gene therapy study, James Wilson, did not disclose that a company, Genovo, provided a quarter of the University of Pennsylvania’s gene therapy institute’s budget. In addition, Wilson did not disclose that he had a strong personal financial interest in the research. If the treatment had been successful, Wilson would have received stock worth $13.5 million. In 2005, the University of Pennsylvania eventually made a $517,000 settlement with Gelsinger's family.[189]

Jesse Gelsinger’s death is a tragedy, but is fortunately atypical. Tens of thousands of clinical trials have been conducted over the past 30 years without causing controversy. Yet the atypical cases cited above have provoked heaps of regulations and raised public suspicion about the motives of researchers, which may impede biomedical innovation.

2005 The Hwang Case

A spectacular example of scientific self-aggrandizement came to light in 2005, when it was revealed that Seoul National University stem cell researcher Woo Suk Hwang had completely fabricated a study, whether in hopes of financial gain or professional glory, purporting to have cloned and derived 11 human embryonic stem cell lines. Hwang’s fraudulent studies were peer-reviewed and published in *Science* in 2004 and 2005. In accordance with an editorial committee’s peer review recommendations, editors of

Science have modified the journal's peer review process and will identify "high-risk papers," based on criteria such as counter-intuitive findings, potential media interest, political concerns, and subject them to greater scrutiny. Among other things, the editors will demand access to primary research data for the journal's reviewers. Despite these changes, the committee report correctly noted, "No realistic set of procedures can be completely immune to deliberate fraud."

About the Author/Disclosure

I am the science correspondent for *Reason* magazine. I would like to make the following disclosures:

Financial: I work on a contractual basis for the non-profit, non-partisan libertarian magazine *Reason*. As I understand it, *Reason* is funded largely by private individuals, foundations and some corporations, but I have no idea who most of those individuals, foundations, and corporations are nor how much they contribute. *Reason* makes most of that information available online so I could find out if I were interested, as could anyone else. I have never been asked to alter my reporting in order to conform with the wishes of any *Reason* supporter.

I produced this report on a contractual basis with American Council on Science and Health for a fee of $4,000. It took much longer than either or the Council had anticipated. The agreement specified that the report would be peer-reviewed, and I am grateful for many insightful comments from them that I have incorporated into this report.

I am also an adjunct scholar at two Washington, DC-based libertarian public policy think tanks, the Cato Institute and the Competitive Enterprise Institute. It was explained to me that being an adjunct scholar means that I don't get paid anything, but that the institutes can use my name for media and fundraising purposes. I have worked on a contractual basis as an editor of three books on environmental policy for the Competitive Enterprise Institute, all of which were published by commercial publishers.

I regularly drum up grants from non-profits to pay for my reporting habits. This is not an exhaustive list, but I have received travel grants to cover United Nations Climate Change conferences and World Trade Organization conferences from the Altas Economic Research Foundation and the International Policy Network. None have ever exercised any editorial control over my reporting.

In addition, I have spoken at scores of universities, conferences and non-profit organizations around the world—mostly for just travel expenses (although on a few happy occasions I have received a small speaker's fee).

I am very happy to acknowledge (as I did in the book) that I received grants from the Richard Lounsbery Foundation, the Bruce and Giovanna Ames Foundation, and the Alliance for Aging Research to support my work on my latest book, *Liberation Biology: The Scientific and Moral Case for the Biotech Revolution* (Prometheus, 2005).

I also own shares in various biotech and pharmaceutical companies (no more than 1,000 in any one company, alas). I purchased all of the shares with my own money and all are held in my retirement accounts. May your deity of choice have mercy on you if you even think about taking any investment advice from me.

Past and current charitable contributions and memberships (that I can recall):

American Civil Liberties Union
Society of Environmental Journalists
Drug Policy Alliance
Center for Reproductive Rights
Committee to Protect Journalists
Equality Virginia
National Rifle Association
Marijuana Policy Project
Second Street Gallery
Whitman-Walker Clinic
Nature Conservancy
USO
CARE

—Ronald Bailey, February 2008

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