

SOUNDING BOARD

Regulating Academic–Industrial Research Relationships — Solving Problems or Stifling Progress?

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Biomedical research takes place in university health centers, in government laboratories, and in the laboratories of pharmaceutical and medical-device companies, but only industry translates the research into products. Until the 1970s, academic researchers rarely worked on applied technologies, although they conducted clinical trials for companies and industry exploited academic basic research. Then, the revolution in molecular genetics that enabled investigators to produce large quantities of rare molecules with medicinal properties brought these groups closer together. Academic researchers joined venture capitalists in founding the biotechnology industry, leading to immense benefits — for example, the hepatitis B vaccine.¹ The participation of prominent scientists in the first biotechnology companies instantly reversed the perception that academicians' involvement in business activities was unsavory or evidence of intellectual bankruptcy. Nor were financially bankrupt university researchers receiving research support and profiting personally from their discoveries, although the value to society of the products far exceeded any individual's accrual of wealth. Universities also profited and created offices for filing patents and licensing intellectual property to companies. Congressional edicts encouraged these activities, the number of patents awarded to academic institutions increased enormously,² and promising products discovered by academicians continually enter development by industry. 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.

Instead, the director of the National Institutes of Health (NIH) recently abolished all corporate consulting activities by NIH researchers, and all 18,000 NIH employees must sell any investments in health-related industries.³ This ban represents an extreme

version of increasingly stringent regulations imposed by many universities on researchers working with private industry. Had these rules been in force in the 1970s and 1980s, they would have prevented the scientists who were founding the biotechnology industry from making their breakthrough contributions. The stark contrast between the benefits of academic–industrial research relationships and the severity of the efforts on the part of the NIH and some universities to ban or control these relationships warrants examination.

THE EVOLUTION OF REGULATIONS

Despite misgivings expressed by some academic leaders,⁴ few problems marred the interactions between academe and industry during the first, unregulated decade of the development of biotechnology. In 1988, newspaper reports alleging misconduct during corporate-sponsored research undertaken at a Harvard-affiliated hospital provoked Harvard Medical School to regulate academic–industrial research relationships. The measures adopted forbade faculty researchers from participating in company-sponsored basic or clinical research if they had more than token investments in or had received consulting fees from those companies. These rules were toughened in 2000 and 2004.⁵ Now faculty researchers must disclose their relationships with industry to students, cannot be authors on publications that report trial results concerning technologies they have invented, and may receive only a small fraction of licensing and milestone payments from a company until the products come to market. Since few such projects do come to market, this compensation practically ceases. Not all research organizations established such strict rules, but many, such as professional organizations and the Association of American Medical Colleges, have done so.^{6,7}

Scandals drove these escalating restrictions. One

concerned a company's hindering an academic researcher from publishing results unfavorable to the company's product (the researcher had signed a contract giving the company the right to control such publication).⁸ Another involved the alleged harassment of an academic investigator by a company for publicly proclaiming that its product was ineffective and unsafe. In the most disturbing and influential event, a teenager, Jesse Gelsinger, died after participating in an experiment at the University of Pennsylvania that was conducted by an investigator with financial interest in the company supporting the research.⁹ Similarly, articles in the *Los Angeles Times* criticizing the NIH for allowing its scientists to consult with companies (which was perfectly legal at that time) and accusing some of these researchers of failing to disclose such arrangements led to the NIH director's ban on corporate consulting.³

JUSTIFICATIONS OF REGULATION AND COUNTERARGUMENTS

Institutional policies and commentaries concerning academic-industrial research relationships articulate three general problems that need proscriptive regulation. The first problem is that academic-industrial interactions promote research misconduct.⁹ The second is that commercial intrusion leads to subtle or overt bias in the interpretation of research data, violation of fundamental values accepted by researchers, limitations on academic freedom, and deterioration of the quality of research.¹⁰⁻¹² The third is that if commercial connections even appear to compromise academic integrity, public trust in and support for research erode.¹³ Thus, nearly all policy statements caution against the appearance of financial conflicts of interest in academic-industrial interactions.

RESEARCH MISBEHAVIOR

As exemplified by the incidents cited above and others⁹ that led to the stiffened regulations, academic biomedical researchers are not immune to the bad judgment, bad luck, and disagreeable behavior that afflict all human endeavors. But the adverse events associated with academic-industrial interactions fall short of the accepted definition of research misconduct — fabrication or falsification of research data and plagiarism of research reports. Accusations of scientific misconduct reported annually by academic institutions to the NIH Office of Research

Integrity have not increased in proportion to academic-industrial relationships, and none of the allegations have involved corporate-sponsored research.¹⁴ Do less serious occurrences justify more restrictive policies?

In my opinion they do not. First, problems always arise in real life, but most of them can be resolved by relatively simple, practical measures short of sweeping legislation. For example, the contracts now in place in most academic-industrial agreements ensure the freedom of academicians to publish.¹⁵ Second, universities have long had policies that codify faculty members' time commitments, and rampant neglect of teaching obligations has not risen in academic health centers. Faculty members who neglect their teaching obligations are readily identifiable. Third, the meaning of controversial incidents usually changes with new information. A researcher's questioning of the safety of an experimental drug generated immense support from other academics,¹⁶ but additional research did not support the concerns about the drug's efficacy or toxic effects.^{17,18} Last, no data exist showing that commercial involvement in academic research increases the rate of real or apparent adverse events as compared with research without that involvement. Negative anecdotes are disproportionately influential, because unpleasant experiences tend to be indelible, whereas positive outcomes, such as from the academic-industrial relationships that have resulted in useful products, receive little attention and leave a less lasting impression.¹⁹

The death of Jesse Gelsinger was a tragedy and rightfully elicited close examination of the circumstances that caused it, including financial entanglements. However, most fatal complications of clinical research that are reported occur in the absence of commercial involvement. The death rate in industry-sponsored phase 1 oncology trials has not changed during the past 10 years, despite growing collaboration between academe and industry.²⁰ To conclude that the hope of financial gain contributed at all to any errors leading to Gelsinger's death, in the absence of a confession or other evidence, is purely speculative.

BIAS

Real life contradicts the idealized view of research in which disinterested investigators robotically seek the so-called truth. Accomplishments more frequently than intentions, bias, or sponsorship determine an investigator's credibility. Researchers have

powerful biases, and these “physiologic” biases represent the passion to pursue new ideas against the prevailing wisdom.²¹⁻²³ Financial involvements have not been proved to cause “pathologic biases” — that is, resorting to fabrication or falsification. But have they nudged physiologic bias in the pathologic direction?

A widely cited report²⁴ published in the *Journal* purportedly proved a biasing effect of corporate consulting. The authors of the study correlated the presence or absence of cardiologists’ connections with the pharmaceutical industry with their published opinions on the dangers of calcium-channel antagonists, the safety of which was controversial at the time. The study found that cardiologists who were industry consultants were significantly more likely to discount the alleged danger of these drugs than those without connections to industry. The authors concluded that “the medical profession needs to develop a more effective policy on conflict of interest.”²⁴

The data in the article, however, belie the conclusions. The products of the companies with which the cardiologists consulted bore no consistent relationship to the consultants’ opinions. Consultants to companies manufacturing cardiovascular medications unrelated to calcium-channel blockers were as likely to favor calcium-channel antagonists as those consulting to the companies that produced these drugs. The only possible explanation for the occurrence of a “conflict of interest” on the basis of the information reported would have to be that cardiologists involved with drug companies slavishly favor all commercial products, no matter what these are. A more reasonable interpretation, though one not mentioned in the article, is that the experts selected by all the companies to be consultants were simply well-informed scholars. The consultants’ conclusion, that this class of drugs is not more dangerous than others, has been supported by the test of time.²⁵

SECRECY

Academic researchers with industry relationships report a greater reluctance to share information, materials, or both with other academic investigators than do researchers without commercial connections, supporting the charge that business associations diminish openness. But the investigators involved with companies are the most productive scientists (and therefore are more likely to have valuable materials and to be subject to more requests,

including frivolous ones, than they can accommodate).²⁶ Science thrives on competition, and competition is incompatible with absolute openness.²⁰

ACADEMIC FREEDOM

Academic freedom, which is not the right of researchers to do whatever they want, is important, but research is not done for free. To fund their work, university investigators obey the whims of nonprofit as well as commercial sponsors. 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.

QUALITY OF RESEARCH

Research topics pursued in academic institutions vary enormously, irrespective of sponsorship. The most productive academic institutions have the most industry sponsorship. The scope of industry-sponsored research is now so large that academic investigators can identify commercial partners with interests that can advance even relatively basic research projects. No evidence supports the claim that commercialism has lowered research standards in universities.

APPEARANCES AND PUBLIC TRUST

Policy based on appearances, or on what some people arbitrarily define as unacceptable conflicts of interest, has no basis in law.²⁷ It violates the very objectivity it purports to protect in the conduct of research. Lowering standards of evidence to appearance invites abuse of researchers. Newspapers have assaulted the reputations of academic investigators who violated no conflict-of-interest rules, simply because they profited from discoveries that were commercialized.²⁸ This kind of attack should be opposed, not encouraged.

Government agencies have strict financial conflict-of-interest regulations, although the value of these has been debated since the beginning of recorded history.²⁹ Although judges, bureaucrats, and elected officials use the force of law to impose their will on others, decreeing imprisonment, levying fines, and awarding public funds in the form of contracts and grants, academic researchers have no such power.

No evidence points to a diminution of the public’s trust in the biomedical research enterprise because of the increase in academic-industrial in-

teractions. Americans responding to a Harris poll conducted periodically since 1977 consistently rank scientist and physician as the most prestigious occupations.³⁰ Subjects volunteer enthusiastically to participate in clinical trials.³¹ Public-opinion surveys commissioned by Research!America, a not-for-profit research-advocacy organization, indicate that Americans want more, not less, cooperation at the state and national level among funders and performers of health research. A 2005 national survey by Research!America shows that 73 percent of the respondents think that government, universities, and the pharmaceutical industry do not work together to develop new treatments, and 95 percent believe that they should. When asked whether scientists should benefit financially from their discoveries, 69 percent of the respondents thought they should be allowed to do so.³² The public trusts physicians and scientists because they deliver results — not because they disdain profit.

REGULATION AS OVERREACTION

The zeal to regulate industry's collaborations with academic or government research institutions results from political responses to adverse events made under ideologic pressure. The temptation to make rules in the hope of limiting damage to public relations is understandable. Acting on this temptation, however, is inappropriate. Although scandals, real or perceived, have a short lifetime, unmet health needs persist. Scandals are inevitable, and no rules will prevent them from occurring. Legislating integrity is impossible.

Relentless pressure from prominent authorities claiming that medicine and medical science are deteriorating in a morass of commercialism³³⁻³⁶ has influenced policy. The rhetoric of such authorities is harsh as they accuse scholars entangled with industry of being engaged in "unholy alliances,"¹² "losing their 'balance' of values"³⁷ as if in "the grip of the python,"³⁸ and of being in a crisis in which the "compromises engendered by the lure of profit are potentially devastating."³⁹ Articulating these concerns are university presidents, heads of academic health centers and professional organizations, and editors of prestigious medical journals. The press, looking to such leaders as news sources, ignores opposing views⁴⁰ and amplifies these messages. One cause of this prevalent antibusiness attitude is the conviction that for the sake of money, academics use the prestige of their universities as

leverage to promote commercial products beyond the products' intrinsic value. University officials want to discourage such behavior. However, product promotion (or the overpromotion of noncommercial causes) by physicians and scientists is not equivalent to consulting for companies by medical inventors or inventing technologies for the companies to develop. To inflict prophylactic rules that restrict both of these activities is excessive, and legislation against behavior deemed objectionable according to the current wisdom always runs the risk of an oppressiveness that is greater than the outlawed behavior.⁴¹

EFFECTS OF THE REGULATIONS

Surveys of academic research institutions have documented wide variation in the severity and enforcement of policies regulating academic-industrial interactions.⁴²⁻⁴⁵ They also show that faculty members find some of the policies confusing and onerous.⁴⁶ As enthusiasts of regulations, the surveyors recommended uniformly stringent enforcement and faculty indoctrination to ensure compliance, but there is no evidence that the incidence of adverse events associated with academic-industrial interactions is lower at institutions with stricter rules. The fact that many distinguished research institutions thrive with flexible regulations indicates that the rules do not in fact solve important problems. Indeed, they may create them by inhibiting technology transfer.

The conduct of clinical trials, the testing of drugs in models of disease, and the giving of advice are relatively arms-length activities. They are allowable under most regulations but can be impermissible under the most stringent rules. The investigator who championed the development of a new drug to treat cancer participated in a company-sponsored clinical study of the drug, received research support from the company, and was an author of the article that reported the trial results,⁴⁷ thereby violating current Harvard regulations. Fortunately, his employer's rules were more lenient.

Stringent rules present problems when academic investigators make discoveries and try to commercialize them, as did the scientists who founded the biotechnology industry. Such discoveries are rarely ready for development by large pharmaceutical or medical-device companies. Academic inventors must therefore work with small companies or start new ones. Venture capitalists who back such

early-stage efforts have many investment choices that could bring large returns. In choosing among them, they focus on reducing high risks of failure. They see the intensive involvement of entrepreneurial inventors as a major ingredient of such risk reduction. Startup companies that are funded by venture capital lack the cash reserves of large corporations and instead use equity to compensate inventors. They direct their limited funds toward sponsored research in the inventors' laboratories. The strict conflict-of-interest rules in force inhibit this type of incentive, which is an established route to great success in industry and in financial management — “no conflict, no interest.”^{48,49} According to venture capitalists, university licensing officials, and the National Venture Capital Association, stringent conflict-of-interest regulations have prevented investors from entering licensing arrangements with inventors in universities that have such regulations.

THE FUTURE

The recent NIH regulations have evoked vigorous complaints and threaten to impede the recruitment and retention of the best investigators at the NIH.⁵⁰ Already, the authorities are considering retracting the most onerous provisions. In the current political climate, however, even relaxed NIH rules are liable to be as strict or stricter than those at many universities, and they epitomize the trend toward increasing regulation and the triumph of emotion over fact.

Disclosure and oversight of academic collaborations with industry are reasonable policy. Such policy affords opportunities, not just something to police. Why, for example, suppress the identity of faculty researchers in publications that describe the clinical progress of their inventions, as the strict rules require, thereby rendering these researchers invisible to students and colleagues? Instead, students and faculty members could learn, by case study, about the trials, tribulations, and occasional successes of their colleagues working with industry within a wide spectrum of relationships. This educational effort could transform a prevalent suspicion of industry into a constructive dialogue and help to recruit more investigators to the opportunities afforded by working with companies. In a transparent atmosphere, misconduct can be detected, challenged, and if necessary, purged and punished. The intense energy currently dedicated to demon-

izing 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.

Dr. Stossel reports having received consulting fees from ZymeQuest, owning stock options in ZymeQuest and Biogen, and having pending and issued patents, owned by Brigham and Women's Hospital, some of which are licensed to ZymeQuest.

I am indebted to Kerry Maguire, D.D.S., M.S.P.H., director of professional advocacy, Tom's of Maine; Stacie Probst, director of science policy research, Research!America; Harvey Silverglate, Esq.; John Stossel, ABC News; and Mary Woolley, president, Research!America, for assistance with this article.

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