Conflicts of Interest in Biomedical Research

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FINANCIAL CONFLICTS OF INTEREST IN ACADEMIC BIOmedical research first entered the public consciousness during the 1980s, along with a series of widely publicized episodes of scientific misconduct. In some of these episodes, faculty investigators were accused of having fabricated or falsified research data on therapeutic products in which they had substantial financial interests. The linkage was unfortunate because it has imprinted indelibly in the minds of members of Congress and the media that financial conflicts of interest in biomedical research are inherently wrong and often accompanied by scientific misrepresentation or misconduct.[1] These issues are again before us, in a context of increasing administration, congressional, and public concern about the adequacy of the current system of protections of human subjects in general, and more specifically, in response to recent tragic events that occurred in gene transfer experiments in settings in which both investigators and their institutions are alleged to hold financial interests have been linked to the deaths of several research participants.[2-7] Once again, there are calls for increased federal interposition into the conduct of academic biomedical research and strengthened federal guidance, if not regulation, of faculty researchers' behaviors and privileges.

In the early 1990s, both the Association of American Medical Colleges and the Association of Academic Health Centers published monographs that provided guidance to academic centers for the management of individual[8,9] and institutional[10] financial conflicts of interest in research. The guidelines were well received at the time, and their insights and wisdom are worth recalling as academic medicine again finds itself on the defensive in the face of renewed public concern about financial conflicts of interest in research and demands for expanded governmental oversight. At times like these, it becomes easy to lose perspective about conflicts of interest and forget the reasons the public is so generous in its support of biomedical research and the public policy that shapes the process that creates new products to ease suffering and disability. Absence of context can lead to proposed remedies that could damage both the scientific process and the translation of scientific discoveries into public benefit.

On the other hand, it is of equal concern that the nation's medical schools and teaching hospitals, which remain the fount of new medical knowledge from which most novel diagnostic methods and treatments derive,[11,12] may have been insufficiently responsive to the profound changes that have transformed the culture of academic medicine since the birth of recombinant DNA technology in the early 1970s and the passage of the Bayh-Dole Act in 1980,[13] and thereby allowed themselves to become vulnerable to corrosive public skepticism. This Commentary addresses both of these issues in the hope of providing perspective and context that will help inform the renewed public debate.

See also pp 2156, 2193, 2203, 2209, and 2237.

Conflicts of Interest in Academic Medicine

Conflicts of interest are ubiquitous and inevitable in academic life, indeed, in all professional life. The challenge for academic medicine is not to eradicate them, which is fanciful and would be inimical to public policy goals, but to recognize and manage them sensibly and effectively. Successful scientists cannot be totally dispassionate about their work, nor can academic medical researchers be immune from the jumbled and often intense conflicting pressures that envelop them. These pressures, not primarily financial, include the desire for faculty advancement, to compete successfully and repetitively for sponsored research funding, to receive accolades from professional peers and win prestigious research prizes, and to alleviate pain and suffering. The last, which likely first led the researcher to choose an arduous academic career and then persist despite its demands, uncertainties, and disappointments, may be the most enduring pressure of all. All of these nonfinancial pressures may generate conflicts by creating strong bias toward positive results, and all of them may more powerfully influence faculty behavior than any prospect of financial enrichment.

These kinds of pervasive academic conflicts are of little note to the public but well recognized within academe, and institutional policies and procedures, as well as scientific processes and the scientific method itself, have long been in place to manage them. In contrast, financial conflicts tend to be unrecognized unless disclosed, but they can be alarming to the public. For this reason, financial conflicts pose a special risk to the credibility of academic institutions. Nonfinancial and financial conflicts that can affect research differ in another

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important way: the oversight of nonfinancial conflicts traditionally has been left to the academic community and the professions, but during the past decade financial conflicts have become a shared and contingent responsibility of academe and the federal government. The academic community has reluctantly acknowledged the government's legitimate interest in the issue, while arguing successfully that that interest be circumscribed to ensure that research is conducted with integrity and in compliance with federal laws and regulations, and that data supporting decisions that affect public health are sound and trustworthy. These boundaries, however, are not fixed, but contingent on the diligence of the academic community in meeting the responsibilities that accompany its fiercely defended claim to the privilege of self-governance and academic freedom.

Preserving Public Confidence and Trust in Research

A remarkable feature of US science policy during the past 50 years has been the relatively light hand of federal oversight of the scientific process and the deference shown to scientific and academic self-governance, which, in turn, rests on sustained trust in the integrity of faculty and scientists. It has helped that the vast majority of federal funding for basic science has flowed through universities, which have benefited enormously from their public image as independent and disinterested creators and arbiters of knowledge. As the American Association of University Professors stated in 1915:

> All true universities, whether public or private, are public trusts designed to advance knowledge by safeguarding the free inquiry of impartial teachers and scholars. Their independence is essential because the university provides knowledge not only to its students, but also to the public agency in need of expert guidance and the general society in need of greater knowledge; and . . . these latter clients have a stake in disinterested professional opinion, stated without fear or favor, which the institution is morally required to respect.[14]

Today, there is good reason for concern that this idealistic image of academic virtue and the public's willingness to trust in it may be tottering. The Bayh-Dole Act[13] has been enormously successful in achieving its goal of accelerating the transfer of academic scientific discoveries into practice. In so doing it has increased the flow of revenues from patenting and licensing activity into research institutions and their faculties,[15] thereby creating a positive feedback loop that drives the interest of both toward ever more vigorous commercialization of their intellectual property, while arguably creating a new and perhaps dangerous dependency on it. The result has been deepening entanglement of research universities with industry and progressive blurring of the boundaries that once reasonably, albeit not perfectly, demarcated academic interests and values from those of the world of commerce. Nowhere in academe have these changes been deeper or had a more profound effect than in medicine, which has spawned a flourishing biotechnology industry, generated an insatiable public appetite and impatience for ever more wondrous treatments, and in the eyes of some observers[16-19] created a veritable pandemic of financial conflicts of interest.

Certainly, the embrace of commerce by academe is not limited to biomedicine, or even to research. This was recently illustrated at Harvard University when an eminent law professor prepared a videotape of one of his courses to sell to a new Web-based virtual law school,[20] and thereby caused a major review of that university's faculty policy.[21] But when faculty or institutional conflicts occur outside of medicine, they typically do not generate front-page stories or become featured on the evening news.

Simply, the relationship between the public and academic medicine is special, different from any other in academe, and rooted in trust that is nowhere more evident or fragile than in medical research involving the participation of human subjects, where even the perception that faculty investigators or their institutions have financial interests that might compromise their independence and credibility cannot be tolerated. This is especially so when those interests have not been openly disclosed from the onset. Admittedly, this sets a very high standard for academic medicine, much more stringent than that faced by any other faculty. But academic medicine and medical research have flourished in this country since World War II in a unique state of grace that continues to yield remarkable benefits, including a likely fiscal year 2001 congressional appropriation to the National Institutes of Health of approximately $20.5 billion.[22] To preserve the public confidence and trust on which this special status rests demands that a very high standard be met.

Managing Financial Conflicts of Interest

Like most federal oversight of research, that of financial conflicts of interest in biomedical research has been accomplished by guidance rather than prescription, and has been managed through the mechanism of institutional assurance. However, such light-handed oversight is neither preordained nor guaranteed. When financial conflicts were last being considered by Congress, the Department of Health and Human Services (DHHS) proposed guidelines[23] that were roundly denounced by the scientific community, academic medical centers, and universities alike for being too sweeping, prescriptive, and unacceptably intrusive into matters of faculty behavior traditionally reserved to academe and the professions. The intense opposition led to quick withdrawal of the proposal and subsequently to the issuance of the more gentle guideline in place today, in which the management of financial conflicts is deferred to the institutions and is based on disclosure. The most prescriptive element of this guideline is the establishment of a federal threshold to define "significant financial interest."

In light of the deep and extensive financial entanglements that may exist between medical school researchers (and often their parent institutions) and industry, it is fair to ask, as DHHS Secretary Donna Shalala recently did,[24] whether the federal guideline is still sufficient, whether disclosure alone contin-

ues to suffice for purposes of institutional management and public reassurance, and whether medical schools and teaching hospitals have been appropriately diligent in adjusting and enforcing institutional policies. Although systematic data are lacking, the academic medical community has reason for concern that disclosure alone is no longer sufficient in every instance and that some forms of alleged financial conflicts of interest, both individual and institutional, that recently have come to public attention would seem to be unacceptable and should be prohibited. But to "prohibit" raises difficult cultural and policy issues for academic institutions. Universities and their academic medical centers typically manage their faculties' outside professional interests with circumspection by limiting time spent, but not money earned or the kind of outside professional activity pursued, with 2 common exceptions. The first has to do with teaching, to which the employer-university may commonly lay claim by not allowing a faculty member to teach his or her course in another institution; ergo, the Harvard episode noted earlier. The second exception dates to the creation of the system of full-time faculty appointment in clinical disciplines and the later establishment of faculty practice plans. It involves limitation (or outright prohibition) of individual faculty earnings from outside clinical practice.

Among academic medical institutions, Harvard Medical School may have been the first to set limits on the historic research prerogatives of its faculty and establish explicit boundaries when, in 1990,[25] it limited the amount of financial interest and the kinds of commercial relationships that could be held by a full-time faculty investigator engaged in clinical research. More recently, the American Society of Gene Therapy (ASGT)[26] went further by declaring certain kinds of financial arrangements off-limits for major participants in gene therapy trials. Whether one agrees with Harvard's thresholds or the ASGT's specific prohibitions is beside the point. What is important is that these entities have begun to define professional boundaries of acceptability in research involving human participants. Although promulgation of such policies will not eradicate public misunderstanding and concern, it would help if more medical schools, teaching hospitals, and scientific societies would step forward and follow their lead.

Conclusions

Public discourse about financial conflicts of interest in biomedical research is confounded by deep-seated conflicts in the public's understanding and expectation of how biomedical research and development are accomplished. The 2 most salient of these conflicts of public interest are the following: First, research universities are being forced to walk an unprecedentedly fine line between societal demands that they become engines of economic development and the public's unwillingness to tolerate even a tinge of suspicion that the academic community's deepening embrace of industry might distort the conduct or reporting of research. Nowhere is this contradiction, and the dilemma and exposure it creates, greater than in academic medicine, which finds itself struggling to create a precarious equipoise between the world and values of commerce and those of traditional public service, a balance between Bayh-Dole and by-God.

Second, both the public and congressional supporters of biomedical research are impatient for new medicinal products, disease preventions, and cures. However, they either fail to understand or too easily forget that in our capitalistic economy the pathway by which research invention becomes beneficial application is often totally dependent on venture capital, the availability of which commonly demands the active participation of the academic inventors in the commercial venture; put simply, no participation, no money. It is this demand, more than any other cause, that has driven the dramatic increase in medical faculty entrepreneurship. Those who propose new remedies to deal with financial conflicts of interest in academic biomedical research should take care that in their zeal to recreate an idealized state of virtue in which financial conflicts of interest no longer exist, they do not interdict a developmental pathway of immense social benefit.

Since these conflicts of public understanding and expectations will not disappear, academic medical centers and biomedical professional societies must unite to enhance public understanding and inform public perception of their profoundly changing relationships with the world of commerce. Specifically, they should promulgate and enforce uniformly high standards of individual and organizational behavior that the public will understand and find credible, and equally important, work much harder to explain to the public the processes by which discoveries made by academic biomedical researchers become beneficial products. The problem is inarguably a community responsibility, because lapses or transgressions by any single member inevitably shake public confidence and trust in the entire enterprise. Recent reports claiming inadequacies in university systems of protection of human research participants and alleging linkage of individual and institutional financial conflicts of interest to the deaths of research participants sound a clarion call to the academic medical community to come together to address these critical issues.

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EDITORIAL

Conflict of Interest and the Public Trust

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THIS ISSUE OF THE JOURNAL CONTAINS A CLUSTER OF articles that address students', residents', and faculty members' conflicts of interest with pharmaceutical and other companies that financially sponsor teaching and research. Why is this important? University-based educators and researchers, as well as private practitioners, are in frequent contact with representatives from for-profit companies that provide "gifts" and financial support for teaching and research. The enticement begins very early in a physician's career: for my classmates and me, it started with black bags. Dr Kassirer's colleague[1] is not alone in remembering which pharmaceutical company provided them. The timing of presenting the black bags early in our first year was wonderfully strategic, as was the inscription of our names on each. I must admit I was very happy to finally have a real symbol of the medical profession after so many hours of what seemed like year 5 of college. It took me a few days to come back to reality and store the bag in my closet. I'm not sure what happened to it, but I never carried it after that first day. On the other hand, at that time I did not have the courage to publicly state my unease with the unearned "gift."

Subsequently, offers came for "free" lunches, dinners, and tickets to various events followed by offers to serve as an "expert" with the usual lineup of speaking engagements and serving on advisory panels and boards, for an "honorarium" of course. There should be little question about the expected effects of accepting free food, tickets, and even black bags. It has been shown that clinicians' decisions are affected by their interactions with pharmaceutical companies.[2] This is no revelation; why else would anyone provide these "free" gifts except ultimately to assist in the selling of a product? The public is well aware of this problem, and it has become a favorite subject of recent newspaper articles.[3,4]

The issue of receiving reimbursement for providing time and expertise, as a speaker (teacher), advisor, or researcher, is more complex. Persons asked to provide expertise as teachers or researchers generally are selected from a pool of those best prepared and experienced in the field. Who is better equipped to teach or perform the studies, and why shouldn't they be rewarded for their work? The problem lies in the conflict of interest that results from these relationships. It is vitally important to understand that a conflict of interest does not necessarily result in an outcome different than the result would have been without such conflict. The potential for differing results is the problem at hand.

Balance must be maintained between the need for research projects to be reasonably funded and performed by the best possible investigators and the relative paucity of public funds for clinical research. In 1999, the National Institutes of Health (NIH) provided $17.8 billion for research, and the major proportion was expended for basic research; the top 10 pharmaceutical companies spent $22.7 billion, primarily on clinical research (Hamilton Moses III, MD, The Boston Consulting Group, personal communication, 2000). The likelihood that a clinical investigator would be funded

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