

Academic Relationships With Industry

A New Model for Biomedical Research

Hamilton Moses III, MD

Joseph B. Martin, MD, PhD

A SPATE OF RECENT ARTICLES IN MEDICAL JOURNALS,^{1,2} pharmaceutical industry publications,³ and the popular press⁴ highlight conflicts of interest among investigators, their institutions, and their patients. These articles have drawn attention to the increasingly complex web of financial relationships between corporate sponsors of research and the investigators who perform laboratory research and clinical trials on their behalf. As Korn has written:

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.⁵

But how is this to occur? If the benefits of research and incentives for innovation are to be enhanced while protecting against the potential pitfalls, a new model of collaboration is needed between patients, faculty, their institutions, and the commercial world.

Opportunities giving rise to conflicts of interest are not new. But only recently have the potential financial value of discoveries and the ease with which they can be realized by individual researchers become sufficiently great to pose a significant problem. Physicians in private practice are also exposed to the same financial opportunities, as increasing numbers of clinical trials of drugs and devices are occurring outside academic institutions. We believe existing safeguards are inadequate.

The size of the potential problem can be seen in the ownership and control of patented genes and related discoveries. The number of new gene patents granted increased from about 400 in 1990 to 2800 in 1999, with universities' share increasing from 55% to 73%.⁶ Although the proportion controlled by universities may decrease as commercial investment in gene discovery reaches fruition, the absolute number (and probably the financial value) will remain substantial. While most obvious in genetics, this pattern of patent awards also holds true for many other key discoveries in basic biomedical science, as well as for advances in engineering such as biological microarrays and new algorithms and devices for functional imaging. In dollar terms, the large amount of public- and industry-supported academic research sug-

gests this trend will continue.⁷ Published estimates are incomplete, but our analysis using available information suggests that a substantial proportion of the total \$55 billion to \$60 billion of industry research and development (R and D) investment in basic biomedical discovery and clinical trials occurs within universities. Typical figures may range from about a fifth of a large company's R and D budget to more than half for a small company. By comparison, the total US federal spending in 2000 was about \$25 billion, with an additional \$8 billion to \$10 billion of private foundation support going to biomedical research.^{8,9}

The implications of this pattern of funding are illustrated by 2 recent cases in which universities forcefully asserted rights to potentially hundreds of millions of dollars of royalties: one is a claim by the University of Minnesota for a key anti-HIV therapy,¹⁰ and the other is a claim by the University of Rochester for a cyclooxygenase-2 inhibitor.¹¹ Undoubtedly, these are the first of many claims. The network connecting academic laboratories, academic institutions, and companies is growing denser, more complex, and much more lucrative for all involved.

Academic institutions currently rely on both formal and informal means to limit conflict. Requirements for disclosure of commercial ties, limitations on equity holdings by faculty, insistence on the freedom to publish both negative and positive results, and restrictions on sources of commercial support of clinical trials are the chief formal means. Informally, the peer review process for grant applications and publications and day-to-day pressures from colleagues also influence the process. However, there is growing reason to think that these safeguards are inadequate for the foreseeable opportunities ahead.

Most safeguards focus on the individual investigator or faculty member. However, an even greater conflict may be posed when the university itself owns equity or receives royalties. Can universities police themselves? Can the university effectively oversee an investigator when the interests of both are in parallel, when income and equity are shared by the institution and senior investigator? Further, because junior participants in the laboratory group are commonly ex-

Author Affiliations: The Boston Consulting Group, Bethesda, Md (Dr Moses), and Office of the Dean, Harvard Medical School, Boston, Mass (Dr Martin).

Corresponding Author and Reprints: Hamilton Moses III, MD, The Boston Consulting Group, 4800 Hampden Ln, Bethesda, MD 20814 (e-mail: moses.hamilton@BCG.com).

cluded from such financial rewards, this inequity between scientists may prove destructive to the fragile dynamics that have made academic laboratories so immensely productive.¹² Any remedy needs to account for the interests and potential for conflict among the institution and its senior and junior investigators.

In searching for a solution, several general principles should guide its development:

1. *Veracity of results of basic research and of clinical trials should not be compromised.* The validity and any perception of validity should never be left open to question. Remedies should isolate research from economic pressure whenever possible.

2. *Oversight should occur by a disinterested party.* Those without a financial stake should examine the relationship at its inception and at key points along the way.

3. *Proprietary rights and control of intellectual property ought to be acknowledged at the outset and assurances made regarding the right to publish.* Limits on nondisclosure and confidentiality provisions need to be kept at a minimum. To preserve free academic inquiry while still allowing commercial and academic agendas to be met, agreements must permit changes in research direction in light of new discoveries.

4. *Financial and nonfinancial incentives should be designed to address institutional, senior investigator, and junior faculty needs.* While this may be the most difficult goal, it is also one of the most important.

These principles might be accomplished using several possible remedies, as follows:

1. *The research institute.* Universities might create, with their industrial partners, separate research institutes. These could be administered either inside or outside the university and could be geographically separate or within the university's walls. However structured, such an institution should isolate commercially supported research from other research while still allowing the migration of individual researchers back and forth within certain limitations. Potential models with a variety of flexible organizational structures can be found. The Howard Hughes Medical Institutes' laboratories at many sites and the Whitehead Institute at the Massachusetts Institute of Technology are examples within a parent university. In both cases, universities that serve as "home" have evolved mechanisms to effectively manage research having different funding streams (some commercial and others traditional public or private grants) and to sustain a workable relationship over many years with an external entity. Potential conflicts of interest have been minimized by creating barriers between commercial and academically focused research. This solution does not, however, overcome the university's own potential for conflict of interest.

2. *Enhance external oversight.* This was the philosophy that guided the creation of institutional review boards (IRBs) in the 1960s. These boards, which were created to mitigate conflicts in the early days of organ transplantation, from the out-

set had explicit requirements for representatives from the community who were without medical or scientific backgrounds or ties to the institutions involved. If the IRB structures are generally ineffective in policing academic commercial ties, it must be remembered that this was not their initial mission. The IRB system has generally been more successful in meeting its primary goal to ensure and enhance protection of research subjects, although recent concerns call for heightened compliance with safeguards. Extrapolating this model to monitoring research conflicts of interest is worth exploring, although such oversight will not, by itself, obviate the inherent conflict posed by institutional and individual equity ownership.

3. *Create a new entity separate from the university to hold equity and receive royalties.* The most problematic aspect of the current situation, and the one that creates the most potential for conflict of interest, is the ownership of equity by individual investigators. Ownership of even a small amount of stock in a small publicly traded or private company, whose value can depend on the outcome of a clinical trial or access to a key laboratory discovery, has proven difficult to manage. It is arguable that no amount of oversight can fully prevent the inevitable appearance or reality of conflict, which may operate at both conscious and unconscious levels to sway an individual's judgment, even among those with the best of intentions. These pressures can best be reduced by diluting them, ie, minimizing the potential for individual actions to influence the value of their personal or institutions' holdings by combining all equity in a new vehicle. This could then be managed, at arm's length, like a mutual fund.

Such a solution might work as follows: a university could create a separate entity that would hold and control equity in companies that are providing funds for basic or clinical research. On behalf of individual investigators and the university itself, the new organization would make all decisions about owning or disposing of company holdings. Individual components of equity would be managed as a portfolio of investments, and individuals would be assigned units of equity. A variety of structures can be envisioned. It could be a nonprofit corporation, a for-profit corporation, or a foundation. While there are pros and cons to each structure, oversight would occur by appointment of a controlling board that has wide representation, including representatives from outside the university, who may even be in the majority.

This solution is similar to the structure used for many faculty practice plans, especially by state universities. Clinical practice foundations, often having community representatives in the majority, have proven to be a durable vehicle to create appropriate incentives for faculty practices while ensuring that the practices are serving the public good. They have proven flexible enough to balance interests of physicians and universities with broader community interests. In some cases, oversight and governance have been extended to constituencies outside the local community to further ensure the faculty's com-

mitment to education and scholarship. This is increasingly the trend also at private universities.

The rationale for the Bayh-Dole Act of 1980 was to foster and reward translational research, to hasten new products to market, as well as to lessen universities' dependence on federal sources of support.¹³ Universities generally followed suit by apportioning proceeds of commercialized research among the institution as a whole, the investigators' department, and the principal investigator (typically one third to each). These purposes can also be served by the new entity, which can acquire increased sophistication in managing equity holdings, including valuable experience in technology transfer, in interaction with venture capital investors, and in negotiating relationships with industry sponsors. The new entity could also apportion proceeds to all participants in a discovery, including junior faculty and other staff members who have contributed. Since science is nearly always a collective undertaking, these group incentives are appropriate. The commercial world has learned the importance of incentives and actively uses them to reward all participants in a discovery.

An additional step can be envisioned in which groups of universities and investigators jointly create a new entity to manage equity and royalties. Again there is precedent for this. When the malpractice insurance liability markets turned unfavorable in the early 1970s, coalitions of universities and hospitals created "captive" insurers to solve the problem. The members of these groups soon learned to work together. For example, at Harvard University, the Controlled Risk Insurance Co (CRICO) has served admirably as a self-insurance vehicle, as has the Medical Center Insurance Corporation for another consortium of East Coast teaching hospitals (originally founded by Johns Hopkins Hospital, The New York & Presbyterian Hospitals, the University of Rochester, and Yale University). These groups developed innovative quality improvement programs long before doing so was in vogue and gained valuable experience in sharing sensitive information to improve care.¹⁴ A positive outcome was realized as the cost of insurance soon dropped, as did the cost of administration. That these survived after insurance markets improved is testimony to the durability of the concept. If applied to the problem of academic industry collaboration, a multiuniversity consortium would provide an additional layer of protection, further isolate the locus of financial management from academic and clinical activities, enhance oversight, and reduce the chances that research will be swayed by economic interests.

It might be argued that these measures to hold and manage funds would be insufficient or ineffective solutions to resolve conflicts of interest. To be successful, any solution must acknowledge and balance the twin arms of the dilemma: promoting innovation while improving protection. Achieving one without the other would be no gain. Any solution must also preserve the personal incentives that motivate innovation while minimizing the risk of perturbing judgment. In the long run, fostering innovation can be best assured by broadening participation to both junior and senior investigators while making the rules for financial arrangements open and explicit. Additional protection can be achieved not only by enhanced external oversight, but also by openness, transparency, and recognition of the explicit nature of conflict, with a renewed commitment to manage it.

The pressures that converge on academic investigators, both in the laboratory and in the clinic, are intense. As Korn notes, the existing motives driving biomedical researchers—faculty advancement, recognition by peers, the need to publish, to win research funding, and most importantly, to improve medicine's ability to assuage pain and suffering—are complex enough.⁵ Fortunately, these forces have served medical discovery well for a century. Inescapably, money also fuels innovation, and funds are now flowing from new sources and in larger amounts. If financial forces are not to perturb the century-old equilibrium, a new solution is required.

REFERENCES

1. Angell M. Is academic medicine for sale? *N Engl J Med*. 2000;342:1516-1518.
2. DeAngelis CD. Conflict of interest and the public trust. *JAMA*. 2000;284:2237-2238.
3. Commander H. Biotechnology industry responds to gene therapy death. *Nat Med*. 2000;6:118.
4. Stolberg SG. Financial ties in biomedicine get a closer look. *The New York Times*. February 20, 2000:A1.
5. Korn D. Conflicts of interest in biomedical research. *JAMA*. 2000;284:2234-2237.
6. The Boston Consulting Group. *From Serendipity to Strategy: The Pharmaceutical Industry in 2000*. Boston, Mass: The Boston Consulting Group; 1999.
7. Hesseberth J. Companies squeeze the patent pipeline. *MIT Tech Rev*. 2000; 103:82-93.
8. US Census Bureau. *Statistical Abstract of the United States, Science & Technology*. Washington, DC: US Census Bureau; 1999:614-624.
9. Ernst & Young Consulting and Quantitative Analysis. *The Economic Contributions of the Biotechnology Industry to the US Economy*. New York, NY: Ernst & Young; 2000:1-6.
10. Pollak M. Royalty deal for AIDS drug. *The New York Times*. October 13, 1999: B11, B13.
11. Malakoff D. Patent prompts Rochester to sue for slice of profits. *Science*. 2000; 288:410-411.
12. Ducor P. Coauthorship and coinventorship. *Science*. 2000;289:873-875.
13. Bayh-Dole Act, Pub L No 96-517, 35 USC (1980).
14. Burstin HR, Conn A, Setnik G, et al. Benchmarking and quality improvement: the Harvard Emergency Department Quality Study. *Am J Med*. 1999;107:437-449.