In 1799, Benjamin Waterhouse, one of the three full-time professors at Harvard Medical School, received a copy of Edward Jenner's Inquiry into the Causes and Effects of the Variolae Vaccinæ. Armed with new knowledge of the efficacy of cowpox vaccination for the prevention of smallpox, Waterhouse proposed to test the vaccine in Boston and, if successful, to develop a monopoly under which he would inoculate New England children for a fee. (1)

After receiving the cowpox preparation from England, Waterhouse inoculated first his son Daniel, then six other members of his household. He next carried out a clinical study in which 19 children were inoculated twice, then exposed to smallpox for 20 days in a Boston hospital. Not one child came down with smallpox -- surely one of the most successful clinical trials of all time, "whatever modern day ethicists might say about the impropriety." (2) But the medical school's two other professors, John Warren and Aaron Dexter, were outraged at Waterhouse's behavior, which they saw as self-serving. Dissent engendered by this and other events led in 1812 to the expulsion of Waterhouse from the faculty, despite former U.S. president Thomas Jefferson's active support of Waterhouse as the founding father of vaccination in the United States. (3)

In this historical account, we recognize the seeds of a current debate. Over the past year, medical research involving human subjects has come under intense scrutiny. The issues of concern include the adequacy of informed consent, the surveillance of research protocols by institutional review boards, the reporting of adverse events, and investigators' conflicts of interest. (4) In this article, we address the last of these issues.

Conflicts of interest arise from investigators' financial relationships with companies whose products they are studying, whether the research is supported publicly or by the company itself. Critics charge that academic researchers are for sale, that their engagement in clinical research can be bartered, and that the outcome of research is biased by academic-industrial liaisons, whether individual or institutional. (5) Allegations have been made that these relationships have affected the quality of research. (6) Government officials have reacted with alarm to the possibility that conflicts of interest may prejudice the outcome of research. Allegations of inadequate monitoring of clinical trials by institutional review boards have led to calls for greater federal regulation of research involving human subjects. The Department of Health and Human Services has proposed fines and penalties to protect patients and to safeguard scientific integrity. (4) Coincidentally, during the past year, a committee of senior members of the Harvard Medical School faculty was convened to review guidelines for investigators performing industry-sponsored and publicly sponsored...
research and to make recommendations regarding the school's policies on these matters.

The current Harvard Medical School policy prohibits investigators from having a financial interest, above de minimis levels, in a company whose technology and products they are studying, regardless of the funding source. In addition, the policy prohibits laboratory investigators from having an equity interest, above de minimis levels, in a company that supports their research. (7)

**Conflict of Interest versus the Public Interest**

We have entered a time of unprecedented opportunity for the prevention and treatment of human disease, as was recently highlighted by the sequencing of the human genome. To exploit this opportunity fully, we will need to ensure greater interdependence of those "uneasy bedfellows," (8) academia and industry. The pressures and potential conflicts that will inevitably accompany this more porous interface demand that its operations be clearly evident to the public.

What constitutes the public interest in these matters? First, the public deserves to know that the biomedical research it supports will be a search for truth, uncontaminated by even a perception of bias. Second, the public deserves to see that discoveries with the potential to improve health are translated rapidly into practice by means of clinical trials. Third, the public needs to be confident that participation in the development of new therapies will be safe, with fully informed consent obtained from participants at the outset and access to data about outcome provided to them during follow-up. Fourth, the public has the right to know about any potential adverse effects that might influence patients' decisions about participating in the research. Finally, the public must be assured that neither the decision to ask patients to participate in a clinical trial nor the assessment of the risks patients may incur will be prejudiced by the personal profit motives of an investigator.

A historical perspective on the changing interface between academia and industry reveals a steady erosion of the cultural wall that once separated academic activities from the world of commerce. Academic principles of education without bias, of discovery driven by curiosity, and of the ownership of intellectual property by its inventor -- whether writer, artist, or scientist -- are deeply embedded in our institutions and culture. These principles stand in contrast to the industrial sector's missions of product development, marketing, and profitability.

The breach in the wall between the academic and industrial worlds has widened noticeably as, over the past 25 years, academic research has received increasing amounts of direct support from commercial entities. Examples include the contract between Monsanto and Washington University, the agreement between Hoechst and Massachusetts General Hospital (MGH), and the agreements between Novartis (previously Sandoz) and both the Scripps Research Institute and, more recently, the University of California, Berkeley. These arrangements have been widely accepted as beneficial to both the academic and the industrial partners. The academic institutions that accept support from industry have adopted a variety of regulatory policies. For example, at MGH -- which has negotiated contracts with commercial partners including Hoechst, Shiseido, and Bristol-Myers Squibb -- corporate sponsors pay full research overhead costs equivalent to the rates paid by the National Institutes of Health (NIH). At MGH, conflicts of interest (usually involving money) and conflicts of commitment (usually involving time) are managed according to the
Harvard Medical School guidelines, which require full disclosure and nonparticipation of
the investigators or the institution in any consulting or equity arrangement with the
sponsoring company.

The growth of clinical research since World War II has been facilitated by a dramatic
expansion of NIH support. The Bayh-Dole Act of 1980 not only encouraged but also
mandated the translation of NIH-supported discoveries into practice. (9) In the future,
emerging technology such as combinatorial chemistry, high-throughput screening, and
functional genomics will greatly expand our capacity to identify substances that may be
effective drugs. The number of clinical trials being conducted has already exploded.
CenterWatch, a listing service for clinical trials, estimates that about 60,000 trials were
under way in the United States in 1998, as compared with 33,000 in 1990 and 14,000 in
1980 (de Bruin A, CenterWatch: personal communication).

Among the critical issues raised by the proliferation of clinical trials is the need for research
institutions and their faculties to balance two interrelated but competing demands: the
recruitment of large numbers of patients to fill the trials and expedite the determination of
results and the careful selection of appropriate participants to maximize the probability of
obtaining meaningful results. Faculty members are commonly paid for each patient
enrolled. These payments are used to balance departmental budgets that have been hard hit
by declining revenues from patient care and hospital reimbursements. An awareness of the
institutional and personal incentives to generate income from clinical trials, as well as of the
time pressure placed on physicians by an increased work load, should inspire increased
surveillance of the enrollment of patients in clinical trials.

The Evolving Ties between the University and Industry

University-based research in science, technology, engineering, and computer science has
yielded myriad medical diagnostic and therapeutic procedures and devices. Examples
include magnetic resonance imaging, positron-emission tomography, and microscopical
surgical approaches. In general, the university owns the intellectual property -- in this case,
the inventions -- of its faculty members and establishes licensing and royalty arrangements
that provide returns on investment to the institution, the department, and the investigator.

Most research universities and academic medical centers now have offices of technology
transfer to facilitate the translation of academic discoveries into products and practices that
benefit the public. Conflicts of interest become a matter of concern when patients are
involved in the research and are thereby exposed to potential harm as well as benefit.
Research in which new drugs, biologic agents, or medical devices are tested in patients must
be performed in such a way that there is no possibility -- or even perception -- that the
investigators' judgment is clouded by the prospect of financial gain. Medical schools and
their faculties are in a difficult position. On one hand, they are the guardians of the public
investment in biomedical research; on the other, they are at the forefront of scientific
advances that must be translated through industry into benefits to the public.

We believe that, in most cases, the public is the beneficiary of academic-industrial
relationships. Translational research has benefited from collaboration between academia
and industry and has led to therapies such as recombinant growth hormone, medical
technology such as angioplasty and stenting for coronary artery disease, and many new
pharmacologic agents. Academic institutions benefit in other tangible ways, including the

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receipt of funding for drug-development programs, scientific meetings, graduate education programs, and fellowships for postdoctoral students. Support from industry has given medical schools and teaching hospitals greater flexibility. Another benefit of academic-industrial collaboration is an increased level of understanding between these two "cultures" that, despite (or because of) their differences, can often learn from each other profitably.

The primary motivation of most academic physicians is to advance scientific knowledge in ways that lead to improved health. But it would be unrealistic to ignore the part played by motives of financial reward. Therefore, medical institutions must be able to assure the public that the research results reported by its faculty are untainted by prejudice or bias.

As McCrary et al. (10) and Lo et al. (11) report elsewhere in this issue of the Journal, there are substantial differences among universities and medical schools in the creation, interpretation, and enforcement of conflict-of-interest rules. Some institutions rely heavily on the monitoring of faculty members' conflicts of interest by committees of colleagues. (12,13) Others impose virtually no limits on faculty members' income from consulting contracts, speaking engagements, equity in companies, and stock options. (12) The biotechnology boom, with the emergence of start-up companies funded by venture capital, has led both public and private universities to accept equity in the new companies in lieu of royalties on their inventions. Harvard Medical School maintains a policy that forbids the ownership of equity or stock options by individual faculty members. However, institutions, such as teaching hospitals, affiliated with the medical school now commonly accept equity in start-up companies.

Disadvantages of Breaching the Wall between Academia and Industry

Notwithstanding their benefits, emerging relationships between academia and industry are fraught with possible conflicts of interest and conflicts of commitment. The associated dangers are illustrated by several highly publicized cases of well-intentioned scientists who embarked on clinical trials, including trials of gene therapy, while holding substantial equity in companies that stood to profit greatly from these trials. (4) These cases, and their unfortunate consequences, have called into question the ability of universities to monitor their faculty members when serious conflicts of interest arise and threaten to lead to a loss of public confidence in clinical research. Biomedical researchers enjoy the confidence and goodwill of the American public, as well as strong bipartisan governmental support through the NIH. Any erosion of this support as a consequence of these conflicts would seriously threaten the research enterprise and compromise the public interest in the long term.

Other issues raised by liaisons between academia and the industrial sector include the possibility of intrusion into the academic freedom of the laboratory and the possibility that constraints might be placed by the sponsors on the sharing of data and conclusions. The consequences might include delays in the publication of research results because of disputes fueled by considerations related to the stock market rather than to scientific merit. Investments by institutions in companies founded to develop products based on discoveries made by members of their faculties increase the possibility that research might be tainted by conflicts of interest. (6)

Toward a Just and Prudent Balance
What, then, might be a reasonable stance for our institutions and faculty members to take with regard to conflicts of interest? We suggest that the criteria applied to the public sector are equally appropriate in the academic sector. Just as we expect elected officials and governmental appointees to be free from any appearance of bias, so should we expect academic scientists to adhere to the highest standards of intellectual integrity.

First, research that does not require human subjects must be considered separately from patient-oriented research. For basic research, we believe it is permissible, with full disclosure to the institution, for investigators to receive financial support from companies from which they receive consulting fees. It is considered acceptable by many institutions for researchers to hold equity in sponsoring companies in such situations. (10,11) Other institutions, such as the Howard Hughes Medical Institute, prohibit investigators from receiving monetary support for their laboratories from any company for which they consult or in which they hold equity. Harvard Medical School's policy, while not limiting consulting fees for research that does not involve human subjects, does limit equity interests to $20,000 and only permits such holdings if the company is publicly traded and the equity is acquired in a manner unrelated to the sponsored research agreement. At the national level, such prohibitions are increasingly unusual, and in general, the breach in the wall is so pervasive that expectations of a return to a stricter code of behavior may be unrealistic. In addition, in the realm of basic research in which patients' safety is not at stake, we believe that such a reversal, even if possible, could sap the entrepreneurial energies and the potential for creative collaboration engendered by closer ties between academia and industry.

Nevertheless, a few rules are needed regarding industrial support of basic research. Investigators should have no potential to influence, or be influenced by, the sponsoring corporate entity. They should not hold excessive equity or serve in management roles. For example, some institutions have attempted to minimize the potential for influence by limiting investigators' holdings to less than 5 percent of the equity of a company. (11) Some institutions stipulate that any equity held by the investigator or the institution cannot be sold until two years after the termination of the research contract with the company. Essential to any such arrangement is that the investigator disclose fully to the department, the medical school, or the university any financial relationship with the sponsoring company. Also essential are a guarantee, on the part of the industrial sponsor, of academic freedom within the laboratory; mechanisms to ensure that researchers inform students and fellows working on the research of the industrial link; and disclosure of the relationship in scientific communications, written or oral. Trainees must be permitted to pursue their own research free of the constraints that demands related to industrial support might place on their curiosity or creativity. One possibility might be to establish departmental arm's-length mechanisms to disburse research funds and consulting revenues from industry.

Clinical research, in which patients are directly involved and human life and health are at stake, presents an entirely different set of circumstances. We believe there should be minimal financial incentive for an investigator to carry out research linked to potential commercialization of a product. This restriction should apply to all patient-oriented research, broadly defined to encompass not only clinical trials of drugs, biologic agents, and devices, but also any research involving biologic samples or genetic information. We propose that an effective conflict-of-interest policy for academic institutions must have a minimum of three elements: a requirement for regular disclosure to the institution of potential conflicts by faculty members, with appropriate administrative scrutiny of financial interests; monitoring by a standing or specially appointed oversight committee; and a
mechanism for granting exceptions to the policy when they are warranted by extraordinary circumstances. Individual institutions may find it desirable to establish additional requirements.

The committee that deliberated on changes in Harvard Medical School’s conflict-of-interest policy considered the possibility of creating different standards for the involvement of faculty members with commercial entities depending on the size of the company. The assumption was that it is far less likely that an academic clinical trial will influence the market value of a large corporation than of a smaller company. The committee also considered criteria related to the nature of the clinical research protocol. For example, a randomized, double-blind, multicenter trial seems less susceptible to bias than one without those features, so that investigators involved in such trials might be permitted to have a greater financial interest in the sponsoring companies than those involved in single-center trials or trials with fewer safeguards. The committee also considered whether higher limits for consulting fees and equity holdings (currently set at $10,000 and $20,000, respectively) might be warranted. But, in the end, Harvard Medical School decided that a firm line had to be drawn in any instance in which patients are involved in order to ensure patients’ safety and to maintain public trust and confidence. Hence, we chose to retain our current strict standards.

The high degree of variability in the conflict-of-interest rules of institutions throughout the United States calls for the delineation of realistic, generally applicable guidelines. As a step toward the resolution of these important issues and the restoration of public trust, we are convening a forum of medical schools, with the aim of defining a national policy on conflicts of interest for the members of academic medical faculties. In addition to protecting the public health, a major priority of any conflict-of-interest policy is to preserve the indispensable support of the American people and their government leaders. In answering the question "In whose best interest?" our ultimate aim is to find a solution that creates the most just and prudent balance among the interests of academic science, industry, and most important, the public.

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