

that the small companies with which I have worked have been willing to make exceptions to these rules when necessary; large companies, however, are frequently less willing to do so. Generally, this reluctance is blamed on the lawyers of those companies that are intent on protecting intellectual property, but often there is no real attempt by corporate management to convince the lawyers otherwise. A good working relationship based on mutual trust is essential to keep this issue from becoming a problem.

The second major disadvantage is the speed with which industry support can be withdrawn. Just as the flexibility offered by quick decisions on project funding can be of great advantage at the outset of these relationships, an abrupt loss of funding, can occur just as quickly, leading to loss of stability for both projects and personnel. Because the scientist generally has very little to say about whether the small company with which he or she is working will enter into an agreement with a larger company, this loss of security of funding is largely out of the scientist's control. It is also clear that, once a large company decides to stop funding a small company, it is very difficult for the small company to recover. Other investors and other larger companies are wary of putting money into a company after learning that a competitor has lost interest (and/or lost money).

There is another general problem related to industrial-academic collaborations that involves the area of conflict of interest. Most institutions, like MGH, have created effective guidelines with regard to compensation of scientists for their industrial interactions that provide safeguards against undue influence of such compensation on research. Such regulations are mandated by the NIH for all institutions receiving federal research funding. However, I consider the conflict of interest posed by requirements for secrecy to be at least as important as those related to compensation, but to be much less well-regulated to date. Many companies refuse to enter into collaboration with an academic scientist without a written agreement that results will be kept secret for a specified period of time. Generally, companies will not provide their product or their assistance without such an agreement, despite the likelihood that both parties will lose the benefit that might arise from collaboration. This situation is particularly unfortunate when it involves research that might lead to the cure for a disease.

I believe that most such requirements for secrecy are ill-founded, because scientists generally respect and appreciate the benefit of industrial support and are not interested in undermining the legitimate rights of a sponsor to profit from patents on the work they have sponsored. Scientists are willing to provide the results to the sponsor for a decision on patenting before publication, giving the company a specified time (eg, 30 days) to decide. Because it usually takes more than 30 days for a paper to be accepted by a journal, and because the information is considered confidential until it is published, this requirement should rarely cause concern. As mentioned above, I have frequently found companies, especially small companies, willing to accept

the alternative of receiving the manuscript as a privileged communication at the same time it is submitted to a journal. Therefore, a good working relationship can again help to keep this problem under control.

What, then, are my recommendations for academic scientists seeking to enter into agreements with industry? (1) Be sure that the work on which you intend to collaborate is of a high level of interest to both you and the industrial sponsor, and that you agree on the research goals and priorities; (2) try to get to know the people in the company with whom you will be interacting and assess their longevity in the company and the company's longevity of interest in your area of work; (3) work closely with your institution's corporate licensing office and make sure that you understand all the obligations in any written contract and that they do not unreasonably compromise your own academic freedom; and (4) be sure that your research is not so heavily dependent on funding from the corporate sponsor that you cannot continue without it. There is no substitute for public grant funding. It ensures stability of funding for a defined period and the quality control inherent in periodic peer review. With attention to these recommendations, I believe that the relationship between industry and research can be mutually beneficial, leading to advances that would not be possible by public funding alone.

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A BIOPSY OF FINANCIAL CONFLICTS OF INTEREST IN MEDICINE

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I GREW UP WITH THE IMAGE of the masked, gowned, and gloved surgeon as the superhero of medicine and entered medical school with aspirations to be one. However, my first surgery instructor, Dr Judah Folkman, judged my knot-tying skills sufficiently clumsy to disabuse me of this ambition, and I adopted the more prosaic uniform of an internist by default. I therefore

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accepted the editors' request to contribute an article in this top-tier surgical journal with trepidation. To prepare, I attended a recent Surgical Grand Rounds delivered by the distinguished surgeon Dr Courtney Townsend, president of the American Surgical Association, on the topic "Research in Surgery." Townsend's talk reminded me of how advances in all aspects of medicine, but especially surgery, require passion and often audacity. It also brought home that discovering the best surgical methods is a daunting trial and error exercise often laden with bitter controversies. Such disputes resolve in time—sometimes a long time—and not usually as an either-or solution but as a synthesis resulting from combining aspects of opposing ideas. Surgery seems to have thrived on sharp conflicts of interest, and I would therefore think that surgeons must find it highly peculiar that financial conflicts of interest have acquired the status of a major problem in today's medical care, medical education, and medical research.

By the middle of the last century, sanitation and other public health measures had sufficiently improved the length and quality of life in developed countries to allow medical practice to more effectively address the prevention and treatment of diseases of individual patients. Nothing better epitomizes the success of this technologic progress than the halving of mortality rates from heart disease and stroke over the past 3 decades. Furthermore, that this remarkable progress has almost entirely depended upon the entrepreneurial activities of private companies developing diagnostics, drugs, and medical devices, is an undisputable fact.¹ Academic science, supported by government and philanthropic funds, certainly has abetted this product development. However, according to a 2006 study from the Congressional Research Service, the noncommercial financial contribution to such development is 15% or less. Hence, public investment enjoys a huge return,² and the solid conclusion is that society benefits disproportionately from having academic physicians and scientists participate in product development.

A striking example of this participation was the establishment of the biotechnology industry. Academic biomedical scientists, who were influenced by their training to view "basic" research as superior to "applied" research, overcame this prejudice in the 1970s to work with venture capitalists to found companies and translate their research into useful products. These relationships resulted in, for example, novel vaccines against hepatitis B, which is the major cause of cancer in the world; diagnostic reagents to detect potentially fatal hepatitis B and C viruses in blood, which enables the removal of contaminated blood products from the transfusion supply; hormones such as erythropoietin, which allows patients with kidney disease avoid blood transfusions; blood clotting factors, which are used to treat patients with hemophilia; and powerful anti-inflammatory agents, which bring pain relief and mobility to arthritis sufferers.

As products produced by companies made it possible for medical care to extend longevity and improve quality of life, the market for more products grew, thus unlocking

investment capital for further product development. The increase in commercial activity in medicine has therefore been a natural adaptation to opportunities for good. In the late 1980s, commercial investment in biomedical research and development exceeded federal and non-profit research financing, and the gap is widening.

Entrepreneurial surgeons have also worked with industry to effect advances, especially novel devices. One example came from the partnership between surgeon Dr Albert Starr and engineer-entrepreneur Lowell Stark, which produced the first successful artificial heart valve in 1960, an accomplishment honored last year by the prestigious Lasker Foundation Prize.³ Another was the invention by Dr Carl Walter of the plastic blood bag, which led to the founding of the Fenwal Company in 1948, subsequently bought by the Baxter Corp.⁴ Although Walter profited personally from his work, he also became one of the most generous philanthropic donors to the Harvard Medical School, and the positive benefits to society at large of his invention are incalculable.

These surgical pioneers—the scientists who pioneered biotechnology, the physicians who ran trials that tested products developed by companies or provided continuing medical education (CME) to practicing physicians about the existence and properties of new medical products—all responded to intellectually exciting, personally rewarding, and socially useful opportunities. They did so freely, unhampered by authoritarian restraints until the late 1980s. Then, a handful of adverse incidents involving research physicians who had financial relationships with companies unleashed a torrent of criticism subsumed under the code words "financial conflict of interest" that has continued unabated to the present day.^{5,6} The onslaught against conflict of interest first targeted research and then spread to education and patient care. The attack has had damaging consequences and does not solve substantive problems.

One consequence of the obsession with conflict of interest has been to shift assessment of value from objective outcomes to subjective motives, which is ironic considering the critics' charge that conflicts of interest endanger objectivity and evidenced-based medicine. To ensure transparency, researchers must now disclose all of their corporate sponsorships. Then authorities, such as journal editors, decide which of these sponsorships are "relevant" to a particular case, and this search for relevance is spreading. Providers of CME now must satisfy minute requirements of the Accreditation Council for Continuing Medical Education (ACCME) supposedly assuring that educational content is non-promotional. This bureaucracy, which is not cheap, duplicates Food and Drug Administration (FDA) regulations that prohibit misleading product promotion.

"Transparency" and "disclosure" seem innocuous enough at face value, but their apparent benignity is deceptive. As amplified below, conflict of interest criticism impugns the very integrity of corporations. Hence, a disclosure of corporate sponsorship is like a "black box" warning, implying that one's word or work is suspect. The obsession with disclosure and its ad

hominem assault on investigator and educator integrity sends a message, heard and internalized by medical students, that corporations are untrustworthy. Hunting down disclosure failures and embarrassing investigators has become a sport for conflict of interest vigilantes with personal grievances.

Disclosure requirements are strangely selective; they apply only to corporate relationships. Remunerative activities of physicians, hospitals, and other nonprofit health care activities are exempt. This selectivity is probably just as well, because otherwise we would spend all of our time confessing every possible reason to discount our credibility.

Of great concern is that companies, frustrated by onerous compliance requirements, have become increasingly reluctant to provide financial support for CME. The impact of impaired CME delivery will be greatest in nonacademic settings where such education is most important. A yet more serious consequence of conflict of interest concerns is the imposition of prophylactic regulations limiting or prohibiting interactions between physicians, researchers, and private companies. Usually these rules exempt relationships involving preset "*de minimus*" amounts of money, and no logic explains the arbitrary values of these exemptions: Institutions permit prostitution and control its price. One example of such prophylactic regulation is that some journals exclude scholars with corporate relationships from writing editorials or review articles concerning topics related to the relationship. The FDA recently ruled that experts with conflicts cannot serve as voting members of product review panels, even though empiric evidence has shown that such conflicts do not affect voting behavior.⁷

Some academic institutions do not permit entrepreneurial faculty to receive sponsored research from companies in which they own equity. This prohibition penalizes small companies that lack cash to reward inventors of technologies or key advisors, and venture capitalists report having been unable to finance startup companies because of this restriction. The extreme version of this type of regulation was the total ban on paid corporate consulting imposed on intramural researchers at the National Institutes of Health (NIH) in 2005. This ban has caused dissatisfaction and personnel recruitment and retention problems.^{8,9}

The disclosure orgy and the damaging research rules might be justifiable if the consequences of conflict of interest were truly dire, but this is not the case. Considering the enormous increase in the extent to which companies interface with medicine, the number of adverse incidents has been incredibly small, and almost none are provably explicable as being financially motivated. Without a control compilation of (abundant) bad outcomes in an academic setting uncontaminated by business involvements, no conclusions as to the effect of private financial influences on scientific rigor or evidenced-based decision making are possible. In their criticisms, the critics violate the very principles they propose to be protecting.

The proponents of conflict of interest regulation invoke research misconduct as a consequence of financial conflicts,^{10,11} and this accusation gets attention because misconduct is newsworthy and resonates with common knowledge that people commit crimes for money. Misconduct allegations, however, properly demand a definition of "misconduct." In medical research, the statutory definition of misconduct is narrow, namely the fabrication or falsification of research data or plagiarism, not just behavior that some consider tacky. The vast majority of such research misconduct, and all such cases reported to the NIH Office of Research Integrity since its inception in the 1980s, have originated in academic institutions. None has involved commercial sponsorships with the exception of physicians who have fraudulently enrolled patients in clinical trials or misrepresented results of such trials. No evidence supports the conclusion that the sponsors encouraged or, indeed, benefited from such behavior. Critics, however, go beyond the narrow definition of misconduct to include, for example, failure of authors of research papers to adhere to the unreasonable disclosure requirements of some medical journals.

The conflict of interest critics have generated a conjectural laundry list of negative consequences likely to result from corporate involvements in medical research.¹² Academic laboratories and clinics, for example, would become job shops for companies, performing degraded contract developmental projects of little independent scientific interest. Commercially corrupted faculty would force students to serve as slaves of corporate research, grinding out results supporting their mentors' possible financial upside at the expense of more worthwhile projects likely to advance students' careers. Undoubtedly, such sad cases exist, but no evidence supports that they are frequent. The little data that exist indicate that researchers who are well funded by the NIH and other noncommercial agencies have the most interactions with industry.¹³ I can state from personal experience¹⁴ that it is possible for scientific and product developmental progress to blend seamlessly and benefit the careers of trainees.

A centerpiece of the case against conflicts of interest is that money leads to research "bias." Even conceding that commercial sponsorship does not necessarily influence behavior as a quid pro quo,¹² this argument darkly insinuates that the impulse to curry favor with commercial sponsors inculcates "subtle bias." Leaving aside that receiving research financing always requires currying favor with patrons, be they the NIH, voluntary health agencies, or private donors, this fear of bias acutely reflects a manifest lack of experience and obvious lack of understanding concerning research. Only researchers who have labored long to gain acceptance of their hard-won discoveries (or outsiders willing to penetrate the arcana of research sociology) can understand that researchers paradoxically feign "disinterestedness" as they passionately advocate for their discoveries and ideas.¹⁵ Despite vigorously competing biases, replicable research results emerge continuously.

A separate set of arguments concerning conflicts of interest in all aspects of medicine originates from a deeply hostile view of private industry. According to this view, drug and device companies abuse their patent monopolies to reap excessive profits, tweak patents to extend these monopolies, emphasize marketing of derivative (“me-too”) products over research and development of breakthrough ones, and flaunt FDA safety requirements. In this view, the marketing of products through detailing and sponsorship of CME is particularly heinous, involving the attraction of physicians’ attention with gifts and then plying them with misleading information.¹⁶ The sources of this information include flawed clinical trials designed to show company products in a favorable light, publications “ghost”-authored by company writers, and hired-gun physician “opinion leaders” employed by “speakers’ bureaus.”^{17,18} Responding to these accusations, the Institute of Medicine recommended and Congress approved legislation overhauling the FDA to redirect its efforts from approving products to monitoring their safety after approval.¹⁹ Medical administrators urged curtailment of detailing, abolition of gifts and samples, and the collectivization of all corporate sponsorship of research and CME, and several leading academic health centers adopted some of these recommendations.²⁰

Large pharmaceutical, biotechnology, and device companies are profitable, but no more so than large energy, entertainment, and commodities companies. No new products have come from charities, and health care companies cannot escape the dreary laws of economics. Most emerging health care companies are far from profitable and need prospects of their grownup cousins’ profits to justify their existence. And, although all of the infractions listed above have occurred, they do not make for the basis of policy.

The net positive contributions of industry to medical care are inconsistent with the idea that industry practices on balance are not more beneficial than harmful. The tension between getting effective new products to patients and ensuring their safety has not changed in the 100 years of the FDA’s existence.²¹ However, despite the agony of balancing risk and reward, which will never disappear, we have incredibly effective and safe products compared to a century ago.

However much conflict of interest activists want to believe it, no hard evidence supports the hypothesis that company marketing negatively impacts patient care outcomes.²² This inconvenient truth did not restrain prominent conflict of interest activists from deceptively misrepresenting published literature, and they have, to date, not retracted or corrected this misrepresentation.²⁰ Considering their sanctimony, their failure to adhere to evidence standards and acknowledge legitimate opposing views undermines their credibility.

Only the private sector can sustain the investment required to advance medical research and education, and efforts to collectivize it will only result in less research and education.²³ Companies cannot predict whether a development program will result in a “me-too” or a

breakthrough product, and 60% of the drugs on the World Health Organization (WHO) “essential drug list” are not first-in-class.²⁴ Nor can companies foresee what toxicities of a widely used product might emerge. Diversion of finite resources to product safety monitoring will mean less investment in product development.

Criticism of company-sponsored research highlights how the conclusions of such research favor company products, but it rarely addresses whether the conclusions are true. Most research favors investigators’ hypotheses, and because considerable de-risking precedes large clinical trials, their conclusions probably are true. Without promotion, appropriate products documentably fail to get to patients who need them and, conversely, physicians are not alerted concerning product benefits and risks.²⁵ Finally, nobody has figured out a mechanism for conveying absolutely unbiased information to physicians in the context of uncertainty and competing interests. Such perfection in education certainly is not a feature of academic medical centers, which promote themselves aggressively—with no “black box” warnings.

The conflict of interest critics incessantly warn that conflicts of interest in medical research, education, and care erode public trust in researchers, educators, and caregivers, and that this erosion will result in less public subsidies for these activities. According to opinion polls, however, no such erosion exists^{26,27} and decreases in public funding simply reflect the fact that the funds are not there. Nevertheless, the critics use loss of trust alarmism to advocate the avoidance of even the *appearance* of conflict of interest, ignoring the fact that appearances are inconsistent with rigor and evidence. Moreover, physicians and researchers are not public officials who are bound by appearances.²⁸

If empiric evidence does not support the accusations of damage caused by conflict of interest, why, despite its internal contradictions and logical inconsistencies, does the animus against conflict of interest continue to dominate discourse in academic medicine and lead to ever more disclosure and regulation? Of several answers, one is that the rules do not impact most busy clinicians and researchers, yet they accommodate the academic officials who make them. The regulations allow university presidents and medical school administrators, who do not invent technologies for which they need sponsored research, to sit on corporate boards and collect appreciated equity. Another reason is that the pace of medical progress is too slow for the average person’s attention span, and most of it is too technical or boring for the news media. In contrast, the scandal du jour, especially when embellished with prurient interest by concerning money, is riveting news. Many academic and professional administrators, distant from the drudgery of discovery and patient care, live in deadly fear of potentially disempowering negative media coverage and so attempt to ward it off with sanctimonious pronouncements and prophylactic rules. These hopes are vain because neither will prevent inevitable scandals. An additional reason is that the critics, by claiming to hold

the moral high ground, have succeeded in intimidating most potential adversaries and so have squashed dissent.

The most pervasive reason for the sustainability of conflict of interest mongering is an innate squeamishness about money in medicine. Surgeons, based on their incomes relative to other medical specialties, seem to have been less reticent than other physicians to demand value for their time. Yet, my surgeon colleague, Dr Atul Gawande brilliantly characterized the medical monetary discomfiture in a *New Yorker* piece.²⁹ Like the paradox of objectivity and bias in research, clinical medicine operates within two distressing paradoxes. One is that doctors are not supposed to be “in it for the money,” yet medicine must be awash in money to exist. No utopian scheme exists that can end the war between doctors, hospitals, and the insurance industry for that money, and doctors must fight that war to sustain their practices, however frustrating and infuriating they find it in the context of what they see as an entitlement based on years of training. The second paradox is that our health care system provides incentives for American doctors to be the world’s most skilled, technically equipped, and hard-working, yet impedes the access of too many patients to those doctors.

How then do we reconcile the incontrovertibly spectacular improvements in American health care, based on investment and profit, with the deficiencies of our health care system, allegedly also ascribable to the profit motive? There is no easy resolution. We can, like Gawande and probably most other doctors, take the money and feel guilty about it. However, it is this guilt that nourishes the scolding conflict of interest movement. Unschooled in the fundamentals of economics, medical students are easy targets for indoctrination by equally unschooled teachers that good medicine requires asceticism. Academics, demanding unattainable perfection, find it easy to pick out problems caused by the profit motive, but, lacking first-hand experience with private industry, do not have the wherewithal to arrive at practical solutions.

Given the sheer size of the biomedical enterprise and the human penchant for honest or deliberate mishaps, we cannot return to the era when heroic surgeons like Starr and Walter freely exercised innovation, unencumbered by institutional or government regulations. Indeed, I concede that the critics and the media, by calling attention to flagrant examples of corporate overreaching, have successfully and appropriately raised the general consciousness that such behavior exists and invites its discouragement. A large and growing federal legal apparatus and the tort bar exist to enforce regulatory compliance. However, I believe that oversight can and should take place with a spirit emphasizing that our goal is to advance medical technology and medical education, not to live in fear of usually misleading media opprobrium.

We should compare the track records of institutions with relatively more stringent versus more lenient rules. If, as I predict, leniency promotes academic-industry interactions without increased ill effects, institutions should accommodate more latitude. Whatever the rules, a compliance apparatus geared to enforcing the letter of the law

simply wastes money and time and stifles innovation and education. Flexible oversight, capable of adjusting to unpredictable developments, encourages these activities. As in most of our life, a system of law that emphasizes punishment over prevention is far more reasonable than the prophylactic regime to which we are evolving. Finally, let’s be transparent about transparency. Disclosure is fine up to a point. But when we approach a state where confession exceeds content, we bury the content.

Above all, we need to stop demonizing money. Medical students currently learn next to nothing about the obstacles in the way of bringing new products to market, nor do they learn how to evaluate the marketability of products. Providing them with this kind of information is a better method for teaching them how to deal with corporate marketing than indoctrinating them with metaphysical concepts of “ethics and professionalism” that contradict practice in real clinics and laboratories and ban company sales representatives from academic health centers. Even more fundamentally, students and physicians should understand basic principles of the capital markets articulated by economic scholars.³⁰⁻³² These principles have much more relevance to the practice of medicine than, say, organic chemistry.

Like Carl Walter, many doctors who profited from their discoveries have generously supported their alma maters. Far more interest in public service and giving back to the less privileged exists among medical students, physicians in postdoctoral training, and doctors in practice in today’s “commercialized” medicine than when I began my residency 40 years ago. When we engage in such service, especially in the developing world, we realize that it is not business but the lack of democratic capitalism that is bad for health. Ultimately, new products produced by private companies will not only continue to improve longevity and quality of life but will be the answer to the seemingly insoluble problem of medical care costs.

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TECHNOLOGY AND FINANCING STRATEGIES IN THE DEVELOPMENT OF LIFE SCIENCE COMPANIES

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LIFE SCIENCE–BASED technical innovations irrevocably alter the method by which care is delivered and by which standards of quality are measured. Minimally invasive catheter and surgical techniques, the explosion in molecular medicine, personalized approaches to chemotherapeutic monitoring and dosing, and a deep understanding of the cell signaling pathways that influence inflammation, healing, oncogenesis, metabolic syndrome, and so on are but a few of the examples of areas in which care has been significantly advanced by progressive science and the commercial and technologic reduction to practice necessary for innovation to reach the bedside. Many individual physicians and scientists may contribute prominently to this progress through the generation of the primary idea or through a more direct contribution on an entrepreneurial level assuming a role of advisor or central part of the management team. This necessitates interacting with sources of funding, for example, the venture capital community, the strategic investment community (pharmaceutical and device companies), and the public markets. Planning the growth of an idea from seed stage to commercialization is greatly facilitated by knowledge of these market dynamics and, although the physician-scientist is not often in a lead business role, the marriage of technology and commercial insights offers the best chance for ultimate success in helping patients and creating value.

This article reviews the following:

1. Current dynamics in the investment community: Angel, venture, private equity, and public funding;
2. The characterization of technology with regard to financing level and liquidity planning for investors;
3. The correlation between stage of company and funding sources;

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