Divergent Views on Managing Clinical Conflicts of Interest

To the Editor: The discussion by Camilleri and Cortese[1] on conflicts of interest in medicine, including policy recommendations for addressing them at Mayo Clinic, is more measured than many other such commentaries. Nevertheless, it contains characteristic factual errors and conceptual confusion associated with this contentious topic. The intent of the article and many like it is presumably to encourage scientific rigor in medical research and evidence-based decision making in medical care. The implicit assumption of the conflict of interest literature is that financial motives interfere with these desirable attributes and that nothing short of extensive disclosure and regulation of such conflicts will ensure them.

However, almost no evidence supports that such interference exists in research.[2] Rather, as physicians and scientists increasingly have interacted with industry since the establishment and early expansion of the biotechnology industry, financial incentives afforded these physicians and scientists have resulted in incontrovertibly useful products. Only a decade after the founding of biotechnology, a handful of inevitable incidents put conflict of interest on the radar screen, unleashing a horde of critics applying "the trappings of virtue as instruments of ambition."[3] They, in turn, incited the press and Congressional demagogues to intimidate administrators of academic medical centers (AMCs). Because of these administrators' distance from research, clinical care, and education on the ground and their fear of scandal, the result has been a piling on of disclosure requirements, the empowerment of bureaucracies to enforce them, the imposition of prophylactic rules setting prices for consulting (*de minimis* sums), and the forbidding of equity incentives that encouraged entrepreneurship in the years preceding today's obsession with conflicts of interest.[4] Conflict management services are expensive, and, based on testimony of investigators and university technology transfer officers, the regulations have significantly delayed or completely inhibited technology licensing, corporate-sponsored research programs, and, of greatest concern, establishment of start-up companies.

The intrusion of commercialism into clinical practice and continuing medical education is a more complex matter. Whereas critics cited by Camilleri and Cortese aver that marketing "inappropriately" informs medical care, rigorous data suggest only that it "informs," in ways that are predominantly but not always favorable to the promoted products. The unsolved challenge is to determine whether "on balance" product promotion directs useful and safe medications and devices to patients who need them or whether it forces these modalities on patients who do not or who could use older and cheaper ones. Another way to think about this problem is to ask whether in the real world any mechanism exists for obtaining absolutely unbiased information, much less the best information, concerning the huge and growing array of technologies available to physicians. The answer is that such perfection, hardly manifest in academic, noncommercial communication, is impossible, and attempts to engineer it may do more damage than good.

Lacking data—the essence of rigor and evidence-based medicine—commentators turn to conjecture and taste. Commercial involvement "might" detract from patient care (which is always possible), for which reason such involvement is inherently distasteful, and therefore its mere "appearance" deserves censure and prohibition. Rules based on the possibility of harm are fine as long as the rules themselves are not harmful. But these rules are harmful, and proposing to preserve rigor and evidence-based medicine by regulating subjective appearances violates that which is to be preserved. The oft-repeated mantra that the appearance of conflict endangers public trust also has no basis in fact and erroneously confuses physicians and scientists with guardians—government officials—which they are not.[5]

If concern about conflicts of interest has little empiric justification and rests on shaky logic, why is it taken so seriously? The answer is complex, but one reason is a fuzzy and antiquated set of platitudes concerning medical "ethics and professionalism," which includes a bizarre, selective, and mean-spirited antipathy of academicians and physicians toward "profit." The antipathy is bizarre, because profit is an accepted, even revered goal of most other Americans who originate from the same gene pool as academicians and physicians and is demonstrably not inconsistent with good patient care. Perhaps some physicians harbor guilt that they live off the sufferings of the sick. Their guilt is selective, because conflict of interest rules apply almost exclusively to the private companies that account for less than 15% of the $2 trillion medical marketplace. This marketplace, whether "for-profit" or "not-for-profit," is extremely profitable (and handsomely rewards its administrators). The antipathy is mean-spirited, because, based in part on envy, it attacks motives rather than track records, promotes inquisitional informant behavior (pervasive in Camilleri and Cortese's recommendations), and, claiming the moral high ground, suppresses dissent. In the United States we tolerate many ideologies, but we should not base arbitrary policies on them.

Where does this leave us? First, I am pleased that Camilleri and Cortese reject the utopian proposal that companies should provide open-ended collectivized education and research subsidies to AMCs. This is wise, because companies will never be automatic teller machines for AMCs, and enacting such policies will end most corporate support of research and education. Second, the call for full disclosure seems reasonable at face value, but at present disclosure has become absurdly excessive, and the utility of the disclosed information is unclear. Oversight of disclosed conflicts also needs to be approached with humility: who guards the guardians?[6] Third, companies are willing to accommodate the wishes of AMCs regarding gifts and samples. If AMCs do want them, they will withhold them. Otherwise, they will hand them out according to industry-wide compliance standards. They report that when they try to launch new products without samples, physicians ask for them and that fewer than 4% of sample vouchers are ever redeemed. Therefore, why not let AMC faculty decide for themselves whether they will accept gifts, samples, or meals? Why not see if the

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vaunted information systems of Mayo Clinic can correlate physicians' behavior with prescribing patterns? Why is it industry's rather than Mayo Clinic's responsibility to ensure balanced education for its students and faculty amid the cacophony of promotion? Companies attest that Federal Drug Administration–approved claims form the basis of their educational programs for sales representatives and physician speakers. Rather than banning salespersons and speakers, why not educate students and faculty about the economics and logistics of product development and empower them to detect and report unwarranted marketing claims and ask the offending companies to explain or discontinue them? Such reporting could also bring data to bear on the accusations made by critics that "evidence-baseless" promotion is rampant. No policy can abolish bad behavior. But if physicians or researchers misbehave, punish them severely.

Since its inception Mayo Clinic has been a site of innovation and quality in medical care. However, without the products developed by private companies in the past half century, for example those primarily responsible for a 50% reduction in cardiovascular disease mortality in the United States,[7] Mayo Clinic would have little to offer its patients. The vain search for an " ideal scenario for dealing with clinical conflicts of interest long-term" is a diversion of energy from what really benefits patient care.

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Dr Stossel is a member of the Scientific Leadership Advisory Board of Merck and is on the boards of ZymeQuest and Critical Biologics Corporations. His employer, Brigham and Women's Hospital, has licensed intellectual property to those companies, which may or may not result in milestone payments and royalties. Dr Stossel has received fees for speaking at corporations or corporation-sponsored events (IMS Health, Pfizer, Bristol-Myers Squibb). In the past he has served on scientific advisory boards of Biogen and Dyax Corporations. None of these entities provided input or financial support to the author for this publication.

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2. Stossel TP. Regulating academic–industry research relationships—solving problems or stifling progress? *N Engl J Med*. 2005;353:1060-1065.
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To the Editor: I feel compelled to comment on the Camilleri and Cortese commentary regarding conflicts of interest. As a busy clinician in private practice, I frequently interact with pharmaceutical industry representatives and, while there is always a "potential" for conflict of interest with physicians in my situation, true conflict of interest is rare.

The practice of presenting information about a new medication over a lunch does not oblige any clinician to prescribe that medication but does provide important information regarding innovations in the field. Obtaining this information is not as easy for private practice physicians as for physicians who practice in an academic setting. I found particularly odious the comment that the distribution of gifts by pharmaceutical companies should be "appropriately managed" so that academic physicians can avail themselves of free meals and other gifts whereas those in clinical practice cannot. This is the ultimate hypocrisy. What makes academicians believe that they are more ethical than private practice clinicians? If academicians believe that the pharmaceutical industry is inappropriately influencing them, then they should not accept free meals and other gifts from those companies.

As a clinician with 25 years of experience running a solo private practice, I realize that potential conflicts of interest can arise in dealing with anyone at any level. This includes third party payers who pressure physicians to prescribe drugs on their formularies, government that strives to limit health care spending by imposing ridiculous guidelines and limitations on what clinicians can and cannot do, and health maintenance organizations that reward physicians who are "cost effective" (ie, withhold care) and punish or fine physicians who "overutilize" (ie, provide consistent care for their patients), whether by hospitalizing or obtaining multiple consultations for them if necessary. By not mentioning these other conflicts of interest that can directly harm patients, and instead concentrating on what I believe are relatively minor conflicts of interest mainly involving the financial aspect of practice, the authors are doing all professionals a disservice. By placing academic centers above private practice offices, the authors are being self-serving and arrogant. Busy clinicians "in the trenches" and their patients deserve better.

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Dr Romano is on the Speaker's Bureau of Endo Pharmaceuticals.

In reply: We appreciate the interest of Drs Stossel and Romano in our commentary in *Mayo Clinic Proceedings* on conflict of interest (COI) in clinical practice and its management in an AMC.

Dr Stossel raises several interesting questions, some of which were considered during deliberations before approval of COI policies at Mayo Clinic in 2003. Dr Stossel correctly identified a principle inherent in those policies, ie, to encourage scientific rigor in medical research and evidence-based decision making in medical care.

We offer the following responses to points raised by Dr Stossel.

Dr Stossel challenges our perception that there has been long-standing concern regarding COIs. Conflicts of interest have been on the radar screen at Mayo Clinic for several

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decades. In 1921, Dr William J. Mayo wrote "Commercialism in medicine never leads to true satisfaction, and to maintain our self-respect is more precious than gold." Mayo Clinic developed policies designed to govern medical-industry relationships and to address the issue of COI long before the institution of federal regulations in the mid-1990s.

Dr Stossel indirectly questions whether our conclusion that potential COIs compromise trust is supported by evidence. At Mayo Clinic, we have conducted patient focus groups that have provided us with unequivocal evidence that our patients do not object to Mayo Clinic physicians being involved in industry relationships. In fact, patients appreciate that the best treatments may originate from industry collaborations, and they want Mayo Clinic and its staff to have relationships with industry. However, the patients in our focus groups sent 2 other clear messages. First, patients at Mayo Clinic want to know about potential COIs for individual physicians and for the institution. Second, they expect Mayo Clinic to manage those conflicts, especially as they pertain to their clinical care.

Dr Stossel questions whether the policies proposed may be based in part on envy or on a desire to promote "inquisitional informant behavior." On the contrary, Mayo Clinic encourages staff participation in the commercialization of inventions. Mayo Clinic has an Office of Intellectual Property that receives an average of 1 disclosure per workday from members of staff who have ready and open access to the office. The resulting commercialization of these inventions provides a source of revenue for the inventor and for the institution consistent with the Bayh-Dole Act. Furthermore, an inquisitorial approach is not adopted in reviewing and managing potential COIs. Consistent with federal regulations, all applications to federal agencies for research funding must be reviewed by a COI Review Board. Mayo Clinic has chosen to apply this process uniformly, with a similar review used for industry and foundation grant applications as well as all for Institutional Review Board and Institutional Animal Care and Use Committee applications supported by intramural funding. In 2003 Mayo Clinic developed standardized and detailed approaches to manage potential COIs (individual and institutional). The management algorithm used is available on request and has been made available to other AMCs whose representatives participate in the Forum on Conflict of Interest in Academe, an organization that formally became part of the Association of American Medical Colleges in August 2006.

At Mayo Clinic, the COI Review Board's recommendations for management of actual or potential COIs are widely accepted by staff, with fewer than 10 appeals of an average of 500 reviews conducted per year in the past 3 years. Mayo Clinic's Board of Governors serves as the body to address appeals from staff who disagree with management strategies proposed by the COI Review Board.

Our commentary acknowledges the opportunity costs associated with the implementation of such policies. We agree that Mayo Clinic is responsible for educating students and staff about COIs as well as helping them recognize unwarranted marketing claims. Dr Stossel's recent statement in an article in *The Wall Street Journal* resonates with us too: "If a physician can be influenced into prescribing certain drugs just because he had pizza with a pharmaceutical guy, then it's the fault of his training and not the drug company."[1] However, there is a fundamental and strategic difference between Dr Stossel's approach and the one reached by broad consensus at Mayo Clinic. Dr Stossel favors empowering staff and students to report unwarranted claims in marketing, to interrogate offending companies, and to inflict severe punishments for severe misbehavior. Mayo Clinic has adopted a more proactive approach, developing policies that encourage recognition and management of COIs in leadership, research, purchasing, and clinical practice activities, thereby avoiding the need for punitive consequences which by definition occur after the damage is done.

Nevertheless, we agree with Dr Stossel that industry inventions and dollars are essential to sustain the academic missions of all medical centers including Mayo Clinic. We also readily acknowledge that our policy is indeed a "work in progress." We welcome continued discussion and commentary about COIs in general and about our policies in particular.

We also appreciate the comments of Dr Romano and wish to clarify that we never implied that physicians in solo or private practice were unable to manage potential COIs. We agree with Dr Romano that the same standards should apply to all physicians. We would respectfully draw attention to the goal of our article (see introduction) to address the management of COIs in clinical practice "in the modern academic medical workplace." We have no doubt that solo practitioners or groups are able to develop strategies to manage COIs. Dr Romano also refers appropriately to other factors that are beyond the control of the AMC but may have a significant impact on clinical practice. These include constraints on best practice by formularies, health care systems, or health maintenance organizations.[2,3] Because our commentary focused on issues that are under the control of the AMC, we omitted those issues that related instead to external entities and that have been the subject of other commentaries in the published literature in the past decade.[2-4]

In summary, the strategies proposed within our COI policies achieve our goal that is to provide the best (and unbiased) care to every patient seen at Mayo Clinic and the obligation we have to respond to patients' expectations that Mayo Clinic will manage any COIs that arise in the clinical care of patients.

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Mayo Clinic Conflict of Interest Review Board

Denis A. Cortese, MD
President and Chief Executive Officer
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Intrapleural Fibrinolytics for Pleural Infection: Optimizing Dosing for Future Trials

To the Editor: The recent article by Levinson and Pennington[1] shows that the use of fibrinolytic enzymes to treat organizing pleural infections continues to be attractive despite rigorous trials that show no efficacy.[2] I agree with the authors that a large, multicenter, randomized, double-blind, placebo-controlled study with appropriate methodology is needed. What I question is whether the Levinson-Pennington protocol is fully optimized, particularly given the paucity of data regarding the pharmacokinetics of intrapleurally instilled fibrinolytics.

This is evident in the wide range of dosing intervals (6-24 hours) seen in previously published trials of various fibrinolytics. It is widely known that the systemic half-lives of streptokinase, urokinase, and recombinant tissue-type plasminogen activator (tPA) are on the order of 10 to 15 minutes, with tPA being particularly short at 6 minutes.[3] No study has determined the half-life of intrapleurally instilled tPA. Some observations, summarized in the following paragraph, suggest that the half-life is likely to be very short.

The half-life of tPA may vary with the Hamm and Light[4] stages of pleural infection, with shorter half-lives seen in the earlier stages. The complexes that systemic tPA forms with fibrin are avidly phagocytized by hepatic Kupffer cells.[3] The pulmonary equivalent of a phagocytic Kupffer cell is the macrophage, which is abundant in pleural space infections. Additionally, animal studies have shown that intrapleurally administered talc disseminates systemically, suggesting that inflamed pleura is porous.[5]

If the half-life of pleurally instilled tPA is indeed similar to systemically administered tPA, it would seem logical to administer the fibrinolytic more frequently. One standard guideline is to administer the drug in intervals of 5 half-lives. Intravenous (IV) penicillin G, with a 45-minute half-life, is administered every 4 hours for serious infections. Using a 6-minute half-life for tPA, one would expect the drug to lose over 90% of its initial activity after 30 minutes. If one were to extend the IV penicillin G analogy further, pleurally instilling tPA at 12-hour intervals, as is occurring in the second Multicentre Intra-pleural Sepsis Trial (MIST2),[6] is equivalent to dosing IV penicillin G for a group A cellulitis at 4-day intervals.

Another question involves the time that should be allotted for drainage after drug instillation. Too long a drainage period could waste hospital days and allow for further organization of the remaining infection. Too short a period would waste a relatively expensive drug.

More complete knowledge of the potential toxicity of the drugs used would also be helpful in designing future clinical trials. Because the toxicity of the drugs is not well defined, doses of tPA ranging from 2 mg to 50 mg are reported in the literature.[1,2] Are we using enough tPA to show effect? At which point do larger doses deliver diminishing returns? When do complications begin to outweigh the benefits of the drug? Is the protocol described by Levinson and Pennington (2 mg of tPA every 8 h) the optimal dose?[1]

I believe it would be more expeditious and cost effective to answer these questions before undertaking additional large trials. Then, at the completion of a large trial, we could perhaps definitely say whether an optimal dose of tPA has a role in the treatment of pleural infections.

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Dr Heppler submitted a product idea to Cook Medical that involved modifying a Thal-Quick chest tube by putting a second, smaller lumen in the side wall of the main chest tube. The idea was accepted, developed, and released to market on October 31, 2006. Although the Dual-Lumen Thal-Quick is used to treat pleural disease, it is not Federal Drug Administration–approved to administer intrapleural fibrinolytics at this time (August 1, 2007).

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In reply: Dr Heppler's letter raises some excellent points regarding protocol optimization in the use of intrapleural tissue-type plasminogen activator (tPA) for pleural infection. He asks about the optimal dosing interval, dosage, and dwell time, ie, the time the tube remains clamped after instillation of each dose of tPA. Another question that remains to be answered is the optimal number of doses. Unfortunately, currently available data are insufficient to definitively answer these questions; however, we will respond on the basis of existing data and of our observations.

Dr Heppler points out that the half-life of systemically administered tPA is 6 minutes and that, if one used a dosing interval of 5 half-lives, the optimal dosing interval would be 30 minutes. Of course, that calculation assumes that the pharmacokinetics of tPA in pleural infection and in the systemic circulation are similar. Dr Heppler makes several arguments in favor of that assumption and, for purposes of this discussion, we think it is reasonable to accept them. However, Eisenberg et al[1] reported that, despite the short half-life of systemically administered tPA, there was evidence of sustained fibrinolysis for 7 to 12 hours. Such an observation is likely attributed to a pharmacodynamic effect that exceeds pharmacokinetic predictions. On the basis of the Eisenberg et al observation, an interval of 7 hours seems ideal, whereas further lengthening of

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the interval would result in more patients without lytic effect for progressively longer periods. Therefore, we believe that the 8-hour interval used in our study should be the maximum and that the 12- and 24-hour intervals used by others are too long. A clinical trial is needed to address this issue. To quickly clear the pleural space and shorten the patient's hospitalization, a shorter dosing interval such as 4 hours may reasonably be attempted, but, for the aforementioned reasons, we believe that a 30-minute interval is too short.

As Dr Heppler points out, doses of tPA range from 2 mg as in our study to 50 mg. From the standpoint of cost and safety, the lowest effective dose should be used. Before switching to tPA, we used urokinase successfully at doses of 5000 IU to 30,000 IU. Estimates of dose equivalence range from 2500 IU to 580,000 IU of urokinase per milligram of tPA.[2] When urokinase became unavailable, we chose a tPA dose of 2 mg because we estimated that it might produce an equivalent lytic effect and because tPA was packaged in that amount. We have found that this dose is safe, effective, and inexpensive, and so trials of lower doses may not be worthwhile. It is possible that higher doses would be more effective.

Dwell time is linked to dosing interval. Once the dosing interval is defined, how long should the tube be clamped? Like other investigators, we use a 2-hour dwell time. The longest dwell time that we are aware of is 4 hours.[3] If the dosing interval is 8 hours, one might wonder whether the tube should remain clamped for 7 hours to maximize lysis rather than the 2 hours that we use. We have no good reply to this interesting question other than to say that our results in loculated parapneumonic empyema are excellent with 2-hour dwell times.

What is the optimal number of doses? If one follows the chest x-ray findings daily, one can monitor the patient's progress and stop treatment when the empyema has resolved. However, in select cases, chest x-ray films alone cannot provide conclusive data. In such patients, computed tomography may be needed. On the basis of such radiologic information, we have sometimes used more or fewer than 9 doses of tPA, depending on the clinical response.

We have treated 4 additional patients with loculated parapneumonic empyema since publication of our article in the April 2007 issue of *Mayo Clinic Proceedings*, and we continue to see adequate drainage and clinical recovery without surgical intervention. We believe this treatment is safe and effective and should be used by others in appropriate clinical settings, even while details of optimal dose, dosing interval, and dwell time are being refined.

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CORRECTIONS

Incorrect value: In the article by Wermers et al entitled "Fluoride-Related Bone Disease Associated With Habitual Tea Consumption," published in the June 2007 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2007;82:719-724), an incorrect value was published on page 720, first full paragraph, right-hand column, third sentence, and in the last entry in Table 2 under the column heading "Reference range." The sentence should read as follows: "A test of her specific brand of tea confirmed that she was consuming approximately 56 mg/d of fluoride, with the typical adult consumption being **less than or equal to 2.5 mg/d.** The entry in Table 2 should read as follows: Estimated fluoride intake (mg/d) **≤2.5** recommended.

Incorrect sentence and incorrect tumor stage: In the article by Kademani entitled "Oral Cancer," published in the July 2007 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2007;82:878-887), an incorrect sentence was published in the abstract and an incorrect tumor stage was published in the legend to Figure 6. The second sentence of the abstract should read as follows: **Of the 615,000 new cases of head and neck tumors reported worldwide in 2000, 300,000 were primary oral cavity squamous cell carcinomas.** The second sentence of the legend to Figure 6 should read as follows: Lateral border of tongue tumor (**T4**) was approached via a midline lip split and mandibulectomy with modified radical neck dissection.

Incorrect pronoun: In the reply by Garza et al to a letter to the editor entitled "Role of Lipoprotein-Associated Phospholipase A in Predicting Risk of Cardiovascular Disease," written by Myerson and published in the July 2007 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2007;82:888-889), an incorrect pronoun was used. During the editing process, the word "their" was changed to "his" in 2 places because only 1 author wrote the letter, but in fact the word "their" should have been changed to **her**.

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