

Virtual Mentor

American Medical Association Journal of Ethics

July 2003, Volume 5, Number 7: 235-285

Medicine and Industry

From the Editor

- Match Made of Necessity** 237
Audiey Kao, MD, PhD

Case and Commentary

- Drug Company Sponsorship of Clinical Conferences, Commentary 1** 239
Commentary by Robert Goodman, MD

- Drug Company Sponsorship of Clinical Conferences, Commentary 2** 242
Commentary by Ashley Wazana, MD

- Clinician and Researcher, Commentary 1** 247
Commentary by Timothy F. Murphy, PhD

- Clinician and Researcher, Commentary 2** 251
Commentary by Matthew Wynia, MD

Medical Education

- Commercial Support for Continuing Medical Education** 255
Murray Kopelow, MD

Health Law

- Is it Legal for a Physician to Receive Payment for Prescribing a Drug?** 260
Kristin A. Sorenson

AMA Code Says

- The Code on Physicians' Relationship with Industry** 263
Audiey Kao, MD, PhD

State of the Art and Science

- Treating Hypertension** 265
Audiey C. Kao, MD, PhD

Policy Forum

Undergraduate and Graduate Medical Education and the Pharmaceutical Industry 268

Greg E. Manship, MDiv, MA

The PhRMA Code: A New Roadmap for Industry-Physician Interactions 273

Michael Scott Labson, Esq

Medicine & Society

Setting Biomedical Research Priorities in the 21st Century 276

David B. Resnik, JD, PhD

Personal Narrative

The Twelve Days of Christmas 281

Audiey C. Kao, MD, PhD

Viewpoint

Safeguarding the Quality of Clinical Research 283

Joel Lexchin, MD

Upcoming Issues of *Virtual Mentor*

August: Pediatrics

September: Physician Well-Being and Burnout

October: Psychiatry

November: Public Health Ethics

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 237-238.

FROM THE EDITOR

Match Made of Necessity

Audiey C. Kao, MD, PhD

Recently, the Office of Inspector General (OIG) at the US Department of Health and Human Services issued new guidance on voluntary compliance programs for pharmaceutical manufacturers in reducing fraud and abuse and promoting cost-effective, quality health care.¹ In part, the OIG guidance was a response to recent high profile violators of federal anti-kickback statutes² such as TAP Pharmaceuticals. In many respects, this increased government scrutiny and oversight is reflective of how highly the public values a well-functioning relationship between medicine and the drug industry.

In this heated debate about medicine's relationship with industry, there are some who argue that there should be limited, if any, interactions between physicians and the drug industry because of potential undue influence and conflicts of interest. There are others who believe that there should be little, if any, regulation on industry dealings with the medical profession because pharmaceutical companies are responding to consumer demand, and physicians can be trusted to use professional judgment in prescribing for patients. Both of these positions, in my judgment, are oversimplified views of reality and ultimately do not benefit patients.

Drug companies and medical device manufacturers invest tens of billions of dollars annually to develop new therapies for many debilitating diseases that affect millions of people. Many of these treatments are expensive, however, and those who need them most often cannot afford them. Moreover, industry decisions on clinical research priorities can be significantly influenced by the potential market for a given treatment. Treatments for so-called "orphan" diseases and common diseases that affect millions in developing countries are often neglected.

The pharmaceutical industry also spends billions of dollars each year to fund continuing medical education (CME) programs for physicians. Supporters of industry-sponsored CME contend that without the financial commitment from industry some physicians would not be educated about the latest clinical treatments and procedures. Critics of industry-supported CME programs argue they are simply a means for marketing products to physicians and can lead to over prescribing of costly, and not necessarily more effective, treatments.

As you can imagine, these are only a few examples of the many challenges to a well-functioning relationship between medicine and industry necessary for the

ultimate good of patients and society. In this issue of *Virtual Mentor*, we explore the many issues that individual physicians and the medical profession must consider in their interactions with the drug industry.

The learning objectives of this issue are:

1. Understand medicine's role in defining research priorities for the public good and the profession's responsibility to inform industry of those priorities.
2. Understand how gifts and financial support from the drug industry pose ethical challenges to physicians in their roles as clinicians, researchers, and educators.
3. Understand the joint efforts made by the medical profession and industry to educate their members about guidelines for interactions.
4. Understand the goal of guidelines for gifts to physicians from industry: to minimize physician conflicts of interest while allowing industry representatives to educate physicians about new products.
5. Learn guidelines for managing conflicts of interest between physicians and industry that could compromise or appear to compromise medical judgment.

References

1. HHS Office of Inspector General. Compliance program guidance for pharmaceutical manufacturers. April 2003. Accessed June 25, 2003.
2. 42 USC. 1320a-7B(b).

Audiey C. Kao, MD, PhD is editor in chief of *Virtual Mentor*.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 239-241.

CASE AND COMMENTARY

Drug Company Sponsorship of Clinical Conferences, Commentary 1

Commentary by Robert Goodman, MD

Case

Dr. Mathews is director of the internal medicine residency program at a large teaching hospital. The department chairman asked him to seek sources of funding for the weekly noontime conferences, adding, "With all those drug companies out there wanting time with physicians, you shouldn't have a problem finding someone to buy us a sandwich and chips once a week."

Dr. Mathews asked, "That's okay with you and the department, allowing a drug company to buy lunch once a week?"

"I think so," the chairman said. "Everyone knows by now that each drug rep is going to tout his own wares. It's a wash, in the end. Most 6-year-olds know how to discriminate among fast-food ads on television; I think residents can make sound independent decisions, don't you?"

Dr. Mathews had, in fact, been talking with a rep from Melissima Inc who was trying to push Melissima's ACE inhibitor. If any product message could be neutralized by the sheer number of competing ads, an ACE inhibitor ad would be it. The rep okayed the plan. She would be there at the weekly conferences, but only in case someone had a question, she explained.

Dr. Mathews thought that, with a few words from him to the residents before the Melissima sponsorship kicked off, everything would be okay. After a while, he'd switch companies and let a Melissima competitor buy lunch. Or if it turned out that the Melissima rep was being too chatty, having too much to say to the residents, he'd switch. These things needed to be judged on a case-by-case basis, Mathews thought. All company sponsorship cannot be condemned as bad. By rough calculation, though, Melissima would be spending about \$650 to \$700 on the food per week. He wasn't sure that information would pass the "how would it look in the headlines" test.

Commentary 1

There are several reasons why Dr. Matthews and his chairman ought to rethink their decision to allow a pharmaceutical representative to buy lunch for their housestaff once a week.

First, while perhaps it is true that a 6-year-old can distinguish among fast food ads (though I doubt this), there is ample evidence in the medical literature that physicians *are* influenced by promotion and that physicians who practice on the basis of promotion are more likely to prescribe inappropriate or expensive medication.¹ If all ACE inhibitors are the same, then we can hope that the housestaff will prescribe the least expensive and most convenient one, not the one made by the company that provides the best lunch.

A second reason for rejecting the offer is that *someone* is paying for this supposed free lunch, and arguably it is patients, in the form of higher drug prices. Pharmaceutical companies spend billions of dollars every year in the US on research and development; they also spend billions of dollars each year on promotion. The industry maintains that one reason for the high cost of pharmaceuticals is the high cost of R & D that goes into each product. If this is so, then must not the high cost of promotion also go into each product? It is true that residents work hard and don't make all that much money, and perhaps their hospitals or departments should be buying them lunch; but certainly their patients—many of whom earn far less than they do—should not be buying it for them.

But the third and most important reason why the department should turn down this lunch is that the department is serving as a very bad role model for its residents if it accepts. The doctor-patient relationship is a fiduciary relationship. Fiduciaries, because of their specialized knowledge and the trust that is placed in them by the public (in this case, patients), have an obligation to avoid conflicts of interest. Gifts—whether large or small, educational or not—influence behavior, create relationships, and thus create conflicts of interest. Physicians, like judges, journalists, and basketball referees, must avoid even the appearance of conflict of interest and therefore should accept no gifts from drug companies. Residency programs, as well as faculty entrusted with the training and development of future physicians, must take the lead in role-modeling this behavior for trainees.

Last year, the Accreditation Council for Graduate Education (ACGME), which establishes the standards for the more than 7000 residency programs in the United States, produced a White Paper entitled *Principles to Guide the Relationship between Graduate Medical Education and Industry*.² The paper acknowledges the "proven" potential for conflict of interest resulting from pharmaceutical promotion, the "proven" influence on medical decision making, and the well-documented inability of physicians to recognize this influence. While the council found itself unable to follow its own arguments and prohibit interactions between trainees and industry representatives altogether (as it could and should have), it did state that "programs and sponsoring institutions must determine through policy, which contacts, *if any*, between residents and industry representatives may be suitable, and exclude occasions in which involvement by industry representatives or promotion of industry products is inappropriate" (italics added).

Programs must do more than this; to transmit to trainees without interference the core value (and competency) of professionalism, training programs—like individual physicians—must wean themselves entirely of pharmaceutical industry largesse and the conflicts of interest that come with it. Dr. Matthews and his chairman should, therefore, *just say no* to this free lunch.

References

1. Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA*. 2000;283(3):373-80.
2. Accreditation Council for Continuing Medical Education (ACCME). Principles to guide the relationship between graduate medical education and industry. 2002. Accessed June 30, 2003.

Robert Goodman, MD is an assistant professor of medicine in the Division of General Medicine at Columbia University's College of Physicians and Surgeons in New York, New York.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 242-246.

CASE AND COMMENTARY

Drug Company Sponsorship of Clinical Conferences, Commentary 2

Commentary by Ashley Wazana, MD

Case

Dr. Mathews is director of the internal medicine residency program at a large teaching hospital. The department chairman asked him to seek sources of funding for the weekly noontime conferences, adding, "With all those drug companies out there wanting time with physicians, you shouldn't have a problem finding someone to buy us a sandwich and chips once a week."

Dr. Mathews asked, "That's okay with you and the department, allowing a drug company to buy lunch once a week?"

"I think so," the chairman said. "Everyone knows by now that each drug rep is going to tout his own wares. It's a wash, in the end. Most 6-year-olds know how to discriminate among fast-food ads on television; I think residents can make sound independent decisions, don't you?"

Dr. Mathews had, in fact, been talking with a rep from Melissima Inc who was trying to push Melissima's ACE inhibitor. If any product message could be neutralized by the sheer number of competing ads, an ACE inhibitor ad would be it. The rep okayed the plan. She would be there at the weekly conferences, but only in case someone had a question, she explained.

Dr. Mathews thought that, with a few words from him to the residents before the Melissima sponsorship kicked off, everything would be okay. After a while, he'd switch companies and let a Melissima competitor buy lunch. Or if it turned out that the Melissima rep was being too chatty, having too much to say to the residents, he'd switch. These things needed to be judged on a case-by-case basis, Mathews thought. All company sponsorship cannot be condemned as bad. By rough calculation, though, Melissima would be spending about \$650 to \$700 on the food per week. He wasn't sure that information would pass the "how would it look in the headlines" test.

Commentary 2

Interactions between physicians and the pharmaceutical industry start as early as medical school, continue well into practice, and take on many forms. Residents meetings with pharmaceutical representatives (PR) occur up to 4 times per month (more in the later years) and more frequently if one also considers briefer contacts.

Residents receive more industry-paid meals and samples than faculty, while faculty receive more honoraria, conference travel, and research funding. Unfortunately, there is little available to guide most residents through many of these interactions, which impact on the behavior and practice of physicians.¹

As Dr. Matthews states in the case discussed above, the pharmaceutical industry sets aside great sums of funding for promotion. In 2000, an estimated \$15.7 billion was spent by industry in promotion and marketing, more than the amount they spend on research and development.² Of that, \$5 billion goes to pharmaceutical representatives (PRs), whose workforce numbers more than 60,000. These numbers amount to 1 PR and at least \$100,000 for every 11 practicing physicians in the US. Industry-sponsored events in 2000 numbered 314,000.²

Such numbers and scale have a tendency to drown the critical issue of physician conflict of interest. Medicine's relationship with industry is often considered as a free market exchange where physicians interact with pharmaceutical representatives who bear gifts. In this free enterprise light, physicians' relationship with the industry is normal, if not expected, and simply reflects various stakeholders' attempts to capture a greater portion of the market share. Pens, books, educational materials, samples, meals, and conference travel funding become legitimate means to establish confidence and comfort between the promoter and the promotee.³

This comparison with marketplace interactions is not appropriate, however, because the practitioner of medicine has a very different relationship with his or her patient. Doctors have fiduciary duties to their patients. As caregivers, they make decisions about treatments for their patients, and their relationship with the patient is their primary interest. The one who will be the ultimate recipient of the promoter's influence, in this case, is the patient, not the physician, hence the interaction is not a standard market exchange.⁴

The conflict of interest in the industry-physician relationship differs from other forms of ethical dilemmas. The common form of ethical dilemma (eg confidentiality, consent to treatment issues), assumes that 2 or more "competing interests have a presumptive claim to priority, and the problem is in deciding which to choose."⁵ A conflict of interest, however, is "a set of conditions in which professional judgment concerning a primary interest (such as patients' welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."⁶ In the relationship between physicians and the pharmaceutical industry, the physician's responsibility to the patient has priority over his or her responsibility to any industry "partners," so industry influence creates a conflict of interest. A number of other circumstances expose physicians to similar conflicts: research on patients, physician risk sharing in health maintenance organizations and hospitals, and self-referrals.

A conflict of interest, however, is a condition and not necessarily a behavior. One can *be in* conflict of interest and not *act* a way that conflicts with one's primary

interest.⁷ In the case of industry-physician conflicts, the physician must give priority to patient welfare and care and prevent the secondary interest from influencing that priority.

The outcomes of industry-physician interactions, the secondary interest, have been studied. One study found a positive outcome (improved ability to identify the treatment for complicated illnesses); 21 studies found negative influence associated with the secondary interest.³ The outcomes of industry-physician interactions include an impact on knowledge (inability to identify wrong claims about medication), attitude (positive attitude toward pharmaceutical representatives; awareness, preference, and rapid prescription of a new drug), and behavior (making formulary requests for medications that rarely held important advantages over existing ones; non-rational prescribing behavior; increasing prescription rate; prescribing fewer generic but more expensive, newer medications at no demonstrated advantage.)

In the case of Dr. Matthews and the noon conferences for residents, there is good evidence to support the belief that drug company sponsorship of continuing medical education (CME) affects presentation content in that the sponsor's drug is preferentially highlighted and changes in prescribing practice have been shown to favor the sponsor's drug.^{8,9} Resident exposure to pharmaceutical representative speakers at lunch rounds is likewise associated with dissemination and learning of inaccurate information about the sponsor's and competitor's drug.¹⁰

It is a mistake on Dr. Matthew's part to believe that the sheer number of ads will neutralize the effect of any single ad. The case of ACE inhibitors is a case in point; we now know that, although Beta blockers and a diuretic are first line treatment for hypertension, clinical practice does not reflect that knowledge.^{11, 12, 13, 14, 15} Exposing oneself to promotion of a medication from "saturated" markets exposes one to class-specific, not drug-specific marketing techniques. This does not necessarily provide prescribing information or an antidote to marketing influence.

Finally, the "headline test" Dr. Matthew mentions alludes to the American College of Physicians' suggestion that physicians should be guided in making decisions about their activities by whether they would be willing to have their interactions widely known.¹⁶ Of concern, though, is that, according to one study, patients believed gifts to be less appropriate and more influential than did their physicians.¹⁷ Equally relevant is the evidence that physicians are often not aware of how interactions affect them.¹⁸ The guidelines by the AMA have been one such attempt to acknowledge this limitation for all physicians.¹⁹

References

1. Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA* 2000;283(3):373-380.
2. Statistics available at <http://www.nofreelunch.org>. Accessed June 30, 2003.

3. Wazana A, Primeau F. Ethical considerations in interactions between residents and the pharmaceutical industry. *Psychiatric Clin N Amer*. Fall 2002.
4. Chren M-M, Landefeld CS, Murray TH. Doctors, drug companies, and gifts. *JAMA* 1989;262(24):3448-3451.
5. Thomson AN, Craig BJ, Barham PM. Attitudes of general practitioners in New Zealand to pharmaceutical representatives. *B J Gen Pract* 1994;44(382):220-223.
6. Thompson DF. Understanding financial conflict of interest. *N Engl J Med* 1993;329(8):573-576.
7. Smith R. Beyond conflict of interest. *BMJ* 1998;317(7154):291-292.
8. Bowman MA, Pearle DL. Changes in drug prescribing patterns related to commercial company funding of continuing medical education. *J Contin Educ Health Prof* 1988;8(1):13-20.
9. Bowman MA. The impact of drug company funding on the content of continuing medical education. *Mobius* 1986;6(1):66-69.
10. Ziegler MG, Lew P, Singer BC. The accuracy of drug information from pharmaceutical representatives. *JAMA* 1995;273(16):1296-1298.
11. Pahor M, et al. Health outcomes associated with calcium channel antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. *Lancet* 2000;356(9246):1949-1954.
12. Blood Pressure Lowering Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet*. 2000;356(9246):1955-1964.
13. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med*. 1997;157(21):2413-46.
14. Hyman DJ, Pavlik VN. Self-reported hypertension treatment practices among primary care physicians: blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. *Arch Intern Med* 2000;160(15):2281-2286.
15. ALLHAT - So What? *J Inform Pharmacother* 2003;12:1.
16. American College of Physicians. Physicians and the pharmaceutical industry. *Ann Intern Med*. 1990; 112(8):624-626.
17. Gibbons RV, Landry FJ, Blouch DL, et al. A comparison of physicians' and patients' attitudes toward pharmaceutical industry gifts. *J Gen Intern Med* 1998;13(3):151-154.
18. Orłowski JP, Wateska L. The effects of pharmaceutical firm enticements on physician prescribing behavior: there's no such thing as free lunch. *Chest* 1992;102(1):270-273.
19. American Medical Association Council on Ethical and Judicial Affairs. Gifts to physicians from industry. *JAMA*. 1991;265(4):501.

Ashley Wazana, MD is a master's student in epidemiology in the Mailman School of Public Health, Columbia University, New York. He is also an affiliate psychiatrist at the Bronx-Lebanon Hospital Center in New York and at the Centre Hospitalier Vallée de l'Or et de soins psychiatriques régionaux, Val d'Or, Quebec.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 247-250.

CASE AND COMMENTARY

Clinician and Researcher, Commentary 1

Commentary by Timothy F. Murphy, PhD

Case

Internist Michael Hoover has been in practice in a mid-sized city for 12 years. He is a member of an internal medicine group practice, so he frequently sees patients of his partners when their own physician is unavailable. The group's patients range in age from early 30s to late 80s, the majority are in the 40- to 75-year-old range. Those whom Dr. Hoover sees on a regular basis have hypertension, heart disease, headaches, arthritis, or respiratory and other organ system complaints, often related to aging. Some have cancers; a few have chronic conditions such as diabetes and lupus. Most of the group's patients have some health insurance or Medicare; 8 to 10 percent of care is uncompensated.

Dr. Hoover is prompted to think about the illnesses and demographics of his patients in this way when he receives a letter from a contract research organization that matches pharmaceutical companies that are conducting clinical research to physicians. One of the contract organization's current client companies has an antidepressant drug in Phase III randomized clinical trials and is looking for physicians who can recruit patients to participate. The company is particularly interested in testing the drug's effectiveness on men. They invite Dr. Hoover to enroll up to 25 participants.

Initially, Dr. Hoover is eager to participate. He has a significant number of male patients who, he thinks, suffer from depression of various kinds—some because they are aging and losing abilities they once had or have chronic illness that brings increasing disability with it. Others because they have lost a wife, or a job, or their rights to see their children. Still others seem depressed regardless of their current life circumstances. Most have been reluctant to try medication or to see counselors of any sort. "If only I could get a good night's sleep," they say, or "had a little more energy," or "had a job," or "could see my kids." They rarely entertain the notion that treating depression might enable them to get more sleep, or a job, or have more energy, because they don't think they're depressed.

Dr. Hoover reckons that, given the good relationship he has with his patients, and by offering them the opportunity to do their part for medical science, he could persuade many of his depressed male patients to participate in the study. As the decision time draws close, however, Dr. Hoover begins to have second thoughts. The pharmaceutical company will pay him \$3,000 for each patient he enrolls in the

study. He will follow the participating patients for 2 years. These visits will be free to the participants. Is it taking advantage of his patients' trust that he can probably "persuade" them to participate, he wonders? Does the offer of a free visit every 3 months constitute financial pressure for his jobless patients with depression? Is the \$3,000 per subject an incentive for him to participate? Will the clinician and researcher roles conflict?

The study is double-blind, so Dr. Hoover will not know which patients are receiving the trial drug and which are not. Dr. Hoover has no financial interest in the company that is conducting the trials, and believes that a good anti-depressant with limited side effects would be a therapeutic advantage over what is currently available. If he doesn't participate, will the doctor who the contract organization ends up recruiting handle the patient trust and conflicts of interest issues better than he can?

Under what conditions, if at all, should Dr. Hoover agree to be a clinician-researcher for the pharmaceutical company testing its anti-depressant drug?

Commentary 1

Capitation fees are financial incentives that sponsors of clinical trials offer to physicians who help identify and enroll subjects in studies of medical drugs and devices. In the case here, Dr. Hoover might enroll as many as 25 subjects over the course of 2 years. At \$3,000 per subject, he could take in \$75,000. The purposes for which this money can be used depend on the rules of his group practice. One use would be to cover the costs of running the study. For example, Dr. Hoover could use the money to hire an assistant to coordinate the study and make sure that appointments are kept and data are sent to the pharmaceutical corporation as appropriate. Some medical practices might allow Dr. Hoover to use any money left over for professional purposes. For example, he could use the money to attend medical conferences and seminars or to buy medical equipment. Depending on the rules of his group practice, he might even be able to use the money as part of his salary or for personal purposes.

Dr. Hoover wonders whether it is ethical to involve his patients in this study or whether he has conflicts of interest, both medical and financial. A conflict of interest involves a situation in which someone has a private or personal interest that could influence the way in which professional decisions are made. In conflicts of interest, people could make decisions that serve their own interests rather than the interests of the people they have an obligation to serve.

The notion of *equipoise* should be helpful to Dr. Hoover in coming to a decision about whether it is appropriate to enroll his patients in this trial. Equipoise refers to indeterminacy about whether one medical drug or device is better than another. A clinical trial is designed to resolve this uncertainty. Before such studies begin, there should be good reasons for thinking that a new drug should be tested: it has shown strong promise in animals; there are scientific reasons for expecting it to offer

superior therapy; or it might be an improvement in that it could be taken only once a day rather than 4 times a day. It is this expectation that the new intervention is superior in some way together with uncertainty about that superiority that justify asking people to enroll in clinical trials. If Dr. Hoover is convinced *that* there are good reasons to expect this drug to be better in some way than other drugs *and that* it is unclear whether this new drug is in fact superior, he is justified in asking patients to enroll in the study. In other words, he has no reason to think that he is depriving a patient of a clear benefit by offering that patient the opportunity to take a new—and possibly better—drug.

Enrolling patients will bring money to Dr. Hoover, and he therefore wonders whether capitation fees generate a financial conflict of interest. One danger arising from capitation fees is that Dr. Hoover might be tempted to enroll patients who are not appropriate for this study. The way to control this temptation is to ensure that the study in question has very clearly identified inclusion and exclusion criteria. These criteria spell out the subjects of interest to the research, and when defined in a precise way they can work against dubious enrollment practices. Dr. Hoover should also remember that it is not his decision to enroll patients in the study; that decision belongs to them. To minimize any conflict of interest he should make sure that the patients receive thorough information about the study in a way that lets them decide free from any possible bias from him about the importance of enrolling.

Federal regulations governing clinical research require that researchers disclose certain financial aspects of subjects' involvement: whether they will receive any free care, compensation, or treatment in the case of an emergency. For some people, free medical care—even experimental medical care—can influence decisions about enrolling in clinical trials. To be sure, some people might not get medical care except for their participation in clinical trials. It is not unethical to offer free medical services as part of a clinical trial. If those services cross the line to the point where they have an undue influence in decisions to enter the trials, Dr. Hoover would be right to wonder how free his patients were to make their own decisions about enrolling. Free services should not force people to accept risks they would not otherwise accept.

Federal regulations do *not* require researchers to disclose capitation fees to subjects, and the vast majority of researchers make no such disclosures. Dr. Hoover is not alone in wondering whether there are ethical concerns here. Good practices in study design and informed consent should work to prevent any lapses of judgment on Dr. Hoover's part. However, potential subjects could be in a better position to evaluate *for themselves* whether the offer of enrollment is disinterested if they knew what benefits the researcher would receive. If Dr. Hoover is worried that capitation fees might influence his judgment in some way, or if Dr. Hoover wanted to avoid even the appearance of a conflict of interest, he could exceed federal requirements and disclose to those patients he considers to be prospective trial participants the terms of his own financial arrangements with the sponsors of the research.

Timothy F. Murphy, PhD is a professor of philosophy in the biomedical sciences at the University of Illinois College of Medicine at Chicago.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 251-254.

CASE AND COMMENTARY

Clinician and Researcher, Commentary 2

Commentary by Matthew Wynia, MD

Case

Internist Michael Hoover has been in practice in a mid-sized city for 12 years. He is a member of an internal medicine group practice, so he frequently sees patients of his partners when their own physician is unavailable. The group's patients range in age from early 30s to late 80s, the majority are in the 40- to 75-year-old range. Those whom Dr. Hoover sees on a regular basis have hypertension, heart disease, headaches, arthritis, or respiratory and other organ system complaints, often related to aging. Some have cancers; a few have chronic conditions such as diabetes and lupus. Most of the group's patients have some health insurance or Medicare; 8 to 10 percent of care is uncompensated.

Dr. Hoover is prompted to think about the illnesses and demographics of his patients in this way when he receives a letter from a contract research organization that matches pharmaceutical companies that are conducting clinical research to physicians. One of the contract organization's current client companies has an antidepressant drug in Phase III randomized clinical trials and is looking for physicians who can recruit patients to participate. The company is particularly interested in testing the drug's effectiveness on men. They invite Dr. Hoover to enroll up to 25 participants.

Initially, Dr. Hoover is eager to participate. He has a significant number of male patients who, he thinks, suffer from depression of various kinds—some because they are aging and losing abilities they once had or have chronic illness that brings increasing disability with it. Others because they have lost a wife, or a job, or their rights to see their children. Still others seem depressed regardless of their current life circumstances. Most have been reluctant to try medication or to see counselors of any sort. "If only I could get a good night's sleep," they say, or "had a little more energy," or "had a job," or "could see my kids." They rarely entertain the notion that treating depression might enable them to get more sleep, or a job, or have more energy, because they don't think they're depressed.

Dr. Hoover reckons that, given the good relationship he has with his patients, and by offering them the opportunity to do their part for medical science, he could persuade many of his depressed male patients to participate in the study. As the decision time draws close, however, Dr. Hoover begins to have second thoughts. The pharmaceutical company will pay him \$3,000 for each patient he enrolls in the

study. He will follow the participating patients for 2 years. These visits will be free to the participants. Is it taking advantage of his patients' trust that he can probably "persuade" them to participate, he wonders? Does the offer of a free visit every 3 months constitute financial pressure for his jobless patients with depression? Is the \$3,000 per subject an incentive for him to participate? Will the clinician and researcher roles conflict?

The study is double-blind, so Dr. Hoover will not know which patients are receiving the trial drug and which are not. Dr. Hoover has no financial interest in the company that is conducting the trials, and believes that a good anti-depressant with limited side effects would be a therapeutic advantage over what is currently available. If he doesn't participate, will the doctor who the contract organization ends up recruiting handle the patient trust and conflicts of interest issues better than he can?

Under what conditions, if at all, should Dr. Hoover agree to be a clinician-researcher for the pharmaceutical company testing its anti-depressant drug?

Commentary 2

Doctor Hoover faces a situation that is becoming increasingly common. In the more than 20 years since the Belmont Commission issued its landmark report that laid out ethical considerations for research on humans and resulted in greater government regulation of federally funded research, clinical research has become increasingly commercialized. More clinical research is now performed by private industry than is funded by the government. And more clinical research is moving into individual doctors' offices, away from large academic medical centers. There are many reasons for this, and the trends carry some benefits and some risks.

Clinical trials, wherein real patients affected by an illness agree to try an experimental therapy, provide the clearest and quickest route to demonstrating that a new treatment is safe and effective. Phase III trials, like the one Dr. Hoover is considering, are designed to demonstrate that a new treatment works better than a placebo, or better than standard therapy, and they are required for approval of new drugs by the FDA. Because clinical trials are necessary for regulatory approval, and because the number of potential new treatments under development continues to balloon, demand for clinical trial participants will continue to rise. Clinicians like Dr. Hoover, who does not practice in an academic medical center and has not previously been a clinical researcher, hold the key to enrolling new patients into these trials. Therefore, it is to be expected that future physicians practicing outside of academic medicine will face even more requests to participate, along with their patients, in clinical trials.

In many ways, bringing traditionally "non-academic" clinicians and their patients into the research enterprise represents a potentially healthy democratization of the process. In the past, clinical trials often involved only large academic institutions. But being involved in clinical trials is a useful way for physician participants to

keep abreast of new developments. Patients may see the opportunity to enroll in clinical trials as a way to "do their part" for medical science, and they may benefit if the new treatment ends up being better than existing options. Enrolling in clinical trials has been an important avenue to obtain new therapies among patients with HIV infection, for example. For researchers and drug developers, clinical trials that include a broader cross-section of patients may better assess the real-life effectiveness of the treatment under study.

But there are also risks associated with bringing clinicians inexperienced in conducting clinical trials into the clinical trials enterprise. And some of these risks are increased when for-profit corporations are ultimately running the trials.

One risk is that inexperienced clinicians, like their patients, will fall into a "therapeutic misconception" about the trial. That is, they may, perhaps subconsciously, believe that the trial drug being given is already known to be better than existing options. Dr. Hoover might believe this; why else would he believe he could convince his depressed patients to try a new experimental treatment, where he has been unable to convince them to try existing therapies that are already known to be somewhat effective?

As for patients, they are especially likely to mistake an experiment for a therapy when the person asking them to enter the experiment is the same one that usually offers them proven therapies. Patients facing a physician-researcher may not be able to distinguish these different roles. Large academic medical centers are in a better position to address this by having another doctor or nurse who has not been involved in the patient's care help to ensure informed consent when patients are deciding whether to enroll in a trial. But in a small clinic, this may not be an option. Therapeutic misconceptions, especially when they are eventually proven wrong, can have serious negative consequences, both on health and on the patient-doctor relationship.

Industry-sponsored trials are prone to additional problems. Bringing a new drug to market is expensive, often costing upwards of \$500 million. It is also time consuming, and many drugs spend years of their limited patent protections awaiting the results of clinical trials before they can finally go on the market. By the time a drug reaches the Phase III clinical trial stage, the company will already have made an extremely large investment, all of which is at risk based on the performance of the drug in the trial. At the same time, good performance in a trial by a new drug to treat a common illness, such as depression, could be worth hundreds of millions or even billions of dollars in profit for the company. Thus, while pharmaceutical companies have clear incentives to produce newer and better treatments, since new and improved products sell, they also have clear incentives to rapidly convince regulators, doctors, and patients that their new and improved drug really *is* new and improved, perhaps even when it is not.

The pressure to recruit patients quickly and demonstrate good results can lead to inappropriate incentives to recruit trial participants and to designing trials that optimize the chance of a positive results. For instance, a large payment to the physician for recruiting patients may tempt the physician to recruit inappropriate candidates. A rough calculation shows that Dr. Hoover will receive \$3,000 up front for seeing each patient 8 times—a payment of more than \$300 per visit. Presuming that very ill patients will be excluded from the trial, many of these visits should be fairly routine and in some cases the visits might also be billed to, and covered by, insurance. If this is the case, then this payment seems much more than generous—it seems more like a kickback. On the other hand, if Dr. Hoover must establish a new system for following these patients, hire new staff, and so on, then perhaps this level of payment is appropriate. In fact, since this would be his first involvement in a clinical trial, Dr. Hoover probably has little information with which to determine whether the amount is appropriate. He would do well to have his attorney or business manager evaluate the proposed research contract.

Dr. Hoover's inexperience might also lead him to participate in a trial that is methodologically or ethically unsound. Industry-sponsored trials, since they are not federally funded, may not have undergone review by an Institutional Review Board, for example. While we do not know enough about the trial at issue to make a judgment as to its ethical and practical merits, an inexperienced physician might not know what questions to ask. Medical researchers should demand that clinical trials meet ethical standards and that they be designed to provide meaningful new information—not simply to provide information that will allow a new drug to make it to market.

Finally, Dr. Hoover should not be concerned whether another physician might take the contract and be even less prepared to handle these issues. He should be concerned about his own ethical and legal standing, and his relations with his patients. Clinicians outside of academic medical centers can and ought to be involved in clinical trials—but Dr. Hoover should receive training in both the ethics and the practicalities of conducting clinical trials before he signs up to be an investigator.

Matthew Wynia, MD an internist, is a clinical associate professor of medicine at the University of Chicago and the director of The Institute for Ethics at the American Medical Association.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 255-259.

MEDICAL EDUCATION

Commercial Support for Continuing Medical Education

Murray Kopelow, MD

Virtual Mentor interviewed Murray Kopelow about some of the ethical issues involved with the growing levels of commercial support for CME. Dr. Kopelow oversees the Accreditation Council for Continuing Medical Education (ACCME). The council's new draft standards for commercial support (SCS) are under discussion as part of the ongoing debate over the relationships between physicians and manufacturers of pharmaceuticals and medical devices.

Q. How do the new draft standards set the stage for better continuing medical education?

A. It is important that the standards for commercial support that we eventually adopt reflect the needs of the physicians and the CME enterprise for the 21st Century.

One important factor present in 2003 that was not as prominent in 1992 is the prevalence of professionals and CME providers with financial relationships with FDA regulated industry. (Editor's note:http://www.accme.org/dir_docs/doc_upload/dcd182a-bf21-49da-933f-d6c13409b011_uploaddocument.pdf—Link to "new ACCME standards for commercial support." The current standards date from March 1992.).

Q. What is the evidence of that growing relationship?

A. The amount of disclosure that's required by people at Continuing Medical Education activities. It seems that virtually everyone who is speaking has a relationship with industry. The data show that 60 to 80 percent of research is now funded directly by FDA-regulated firms. In association with this, researchers have been recognized by industry as "influentials" and change agents. Many researchers have been recruited to a new role involved in the education and promotion activities done by regulated industry. In this capacity they can effectively become the "agents" of FDA-regulated industry with the concomitant duties of loyalty and care.

These investigators could then be put in the position of controlling the content of the CME developed by an ACCME accredited provider.

Now, at that point a conflict of interest could exist. A conflict between the interest of the public and the interests of the FDA-regulated industry.

Simply telling the learner that the relationship exists does nothing in itself to resolve or reconcile the conflict. It simply reveals it. It might even go unrecognized by the learner.

Q. The learner has to sleuth out whether there's a subtle promotional bias in each particular CME event?

A. Yes. The existing 1992 ACCME standards for commercial support only demand disclosure. The responsibility for detecting bias is formally on the shoulders of the learners. Realistically, however, a great many providers already are "managing" conflict of interest intuitively. For example, salespeople from FDA-regulated industry are not invited speakers at CME events.

Q. Who *should* have that responsibility for detecting bias, according to the new standards?

A. The teachers and the CME providers have a role in reconciling those conflicts—*before* the education activity is developed and presented to the learner. (Editor's note: The list of ACCME-accredited CME providers includes institutions and organizations such as professional societies, medical schools, and hospitals as well as physician- and non-physician-owned medical education companies or MECCs—see Table 7 at <http://www.accme.org/find-cme-provide>) That's new.

When people come to learn, asking them to be expert enough to decide whether this is biased or not—we shouldn't depend on that.

Q. How can industry participate in CME without overstepping the bounds of propriety?

A. From the point of view of the kind of CME I am talking about, continuing medical education is by physicians for physicians. The *content* is created by them for them. It is separate from promotion in time and place. The pharmaceutical industry has no role in CME content at all, unless they are invited.

Industry knows best about the pharmacotherapeutics of their drugs—for example, what the complications are. The physicians need access to that. The drug company speakers have a role. But it needs to be controlled, monitored, and regulated by the physicians.

Q. Could physicians afford the same CME without the current subsidies from the pharmaceutical industry?

A. It seems to us that there could be a substantial reduction in the amount of money spent on CME without a loss of quality in CME activity, if less money were spent on meals and amenities--and objects—pens, books, brief cases—and documents, expensive handout materials, for example. There's a billion dollars spent, half of that comes from commercial sources. Do we need to spend a billion dollars? That question needs to be very, very carefully examined. Even if people say that the new ACCME standards for commercial support are going to decrease the amount of industry support, that does not mean there is going to be a decrease in the amount of education.

There are many funding sources, potentially. Clearly the two choices are the profession or someone beyond the profession. And that issue has not been debated very strongly yet. There's a movement among the medical students who believe that doctors have a professional responsibility to pay for their continuing medical education. (See www.nofreelunch.org.) So there's an important debate that needs to occur. There's quite a range of beliefs in the profession as to what should be paid for; it's a complicated issue.

Q. Can any one group resolve that?

A. Well, the physicians can. The doctors can say this is how we want to be. We don't want to take funds, or we do want to take funds.

Q. In some of the published articles on the subject, you made an estimate that 30 percent of CME providers did not disclose all conflicts of interest. Would these new requirements help with that?

A. While we are working on reducing that number through education and clarifying instructions, its existence does beg the question, "Is there anything else that can be done to mitigate against commercial bias?"

Q. Have you seen a drop-off in funding?

A. It's too early to say. Our data is 6 months late when we get it. It would be 2004 before we could tell. We don't see any reason for anything we've published to have any effect on the commercial support or the total amount of CME.

Q. Do you think physicians could pay for medical education themselves if companies reduce their support for CME? Could physicians pay for it themselves?

A. I'm not sure. That's not for me to postulate. If you take the billion-plus dollars a year, and divide by the 750,000 doctors who may be practicing, that's about \$1333 a year right? If it's 400,000 practicing doctors, it is closer to \$2400. Is that too much? Doctors have to answer that.

Q. Would the new standards or any anticipated policy of the Office of Inspector General at the U.S. Department of Health and Human Services make it impossible to have the kind of meetings we've had in the past?

A. The Office of the Inspector General made some important observations when they said it was possible to perceive the commercial support of continuing medical education as a kickback. And that funds coming into a health care institution that makes decisions on Medicare could be designed to influence those decisions. If CME is viewed as a kickback, that's dramatic and that's serious.

What our standards say is that no one who has a relationship with a pharmaceutical firm can be in a position to control *content* in CME. So CME becomes a safe harbor, not in the legal sense, but a safe harbor conceptually.

That's why drug companies have taken a role. Merck was the first to say "We are giving our money to ACCME-accredited providers because they manage money properly. We're not giving our money to a person, where the intent of our money could be misconstrued."

Q. How many CME providers are there?

A. Over 700 accredited by us. About 1700 including those accredited by state licensing authorities.

Q. Will there be enough CME providers?

A. The system can accommodate the delivery of CME, absolutely.

Q. What was the ethical thinking that went into the new SCS draft guidelines?

A. The fact that the people who are part of the profession today have relationships with industry that need to be accommodated and accounted for in our standards of commercial support. That was reflected in the draft and will be in further iterations.

Q. The five themes in the draft were the linchpins of connecting ethics to the real world? (Editor's note: The five themes are independence, absence of commercial bias, disclosure of required information and relationships, appropriate management of funds from commercial interests, and appropriate management of advertising and exhibits.)

A. Yes, right. Those were in the old standards too. Those aren't really new. Those are different ways to articulate what we now felt.

Q. What is the timeline for debating the new standards?

A. There are two major elements dictating the time line. One is that ACCME is a thoughtful and reflective organization and will take some time to develop a final document. The task force is working on it now. The council has not yet seen or heard it. So if the council can hear a report in November—a report that may or may not have attached to it a recommendation for action—the council could take action to adopt a document. The second element is that action is subject to review by our member organizations, and they could take 90 days for review to say yea or nay. So if it is adopted on that time line, it could be in the middle of 2004, and after that there would be an implementation time, when we'd give CME providers time to come into compliance.

Murray Kopelow, MD is the chief executive of the Accreditation Council for Continuing Medical Education (www.accme.org), which has its offices in Chicago. Dr. Kopelow is a graduate of the Faculty of Medicine, University of Manitoba and certified as a specialist in pediatrics by the Royal College of Physicians and Surgeons of Canada. Prior to coming to the ACCME in 1995, Dr. Kopelow was in critical care, emergency, and general pediatric practice in the Department of Pediatrics, as well as Associate Dean for Continuing Medical Education, in the Faculty of Medicine of the University of Manitoba, Winnipeg, Canada.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2004 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 260-262.

HEALTH LAW

Is it Legal for a Physician to Receive Payment for Prescribing a Drug?

Kristin A. Sorenson

Colin Mudd, MD, specializes in pediatric endocrinology. He began prescribing a growth hormone, GrowTall, to a number of patients whose parents were worried about their children's projected adult statures. The parents were pleased with the results—their children rose to mid-percentiles in growth rate—and told other parents about Dr. Mudd. His reputation spread rapidly by word of mouth throughout the community and beyond, and soon he was treating dozens of patients with the hormone. Dr. Mudd's prescribing habits came to the attention of GrowTall's manufacturer, DrugCo, Inc, who approached Dr. Mudd and asked him to enter into an exclusive marketing agreement, under which he would help them in their post-market research by prescribing only GrowTall and reporting patient outcomes to DrugCo. Dr. Mudd, who was generally satisfied with the results his patients were achieving on GrowTall, agreed to the exclusive arrangement. He did not tell the parents of his patients about his financial arrangements with DrugCo, Inc. Over the next 8 years, Dr. Mudd treated more than 200 children with GrowTall. During this time, DrugCo, Inc paid him more than \$1 million under the marketing agreement in the form of research grants and consulting fees. None of his patients' parents complained about the treatment or its cost, nor did their insurance companies issue any complaints.

Legal Analysis

The above facts are adapted from *US v Brown*¹ and *D.A.B. v Brown*.² Dr. David Brown was one of the largest prescribers of Protropin, a genetically engineered human growth hormone made by Genentech and distributed in the US solely by Caremark, a home health care company. Over an 8-year period, Dr. Brown was paid more than \$1.1 million by Genentech and Caremark, including \$509,000 in research grants, \$110,000 labeled as a marketing agreement, \$224,468 paid to the office and staff, and various "consulting" fees.

In *US v Brown*, the government prosecuted Dr. Brown, Genentech, Caremark, and Caremark executives for violating the Medicaid/Medicare anti-kickback statute.³ Under this statute, it is illegal for a physician to receive remuneration for referring a patient for a service that will be paid in whole or in part by a federal health care program or for prescribing or recommending the purchase of a drug that will be paid in whole or in part by a federal health care program. Violation of this statute is a felony. The person or entity that pays the remuneration is also guilty of a felony

under this statute. Illegal remuneration includes kickbacks, cash, rebates and discounts, even alcohol.⁴

Before the *US v Brown* trial, Caremark pleaded guilty and paid \$161 million in fines and restitution. As part of the plea agreement, Caremark stipulated that it made payments to Dr. Brown to induce him to refer patients for Protropin use. After deliberations, the jury determined that Brown was guilty of soliciting or receiving kickbacks in violation of the statute. However, the district court ended up granting a new trial for Dr. Brown because jurors had been exposed to outside information about the fines paid by Caremark, despite the judge's instruction not to consider that fact. The Court of Appeals for the Eighth Circuit affirmed the order of the court for a new trial.

In *D.A.B. v Brown*, the patients of Dr. Brown brought a private suit against him for breach of fiduciary duty, fraud, negligent misrepresentation, and violation of a Minnesota state statute that prohibits doctors from receiving compensation for prescribing a manufacturer's drugs. The trial court dismissed the case for failure to state an acceptable claim, and the patients appealed. The Court of Appeals found that Dr. Brown was in violation of the Minnesota state statute that prohibits a physician from accepting compensation for prescribing a manufacturer's drugs. Violation of this statute subjects a doctor to state disciplinary action by the Board of Medical Examiners, but does not allow patients to bring private legal action against the doctor. The court declined both the "breach of fiduciary duty" and the fraud claims because, according to Minnesota law, both claims need to be supported by allegation of injury or harm. In this case, the plaintiffs (patients) alleged no harm from the prescriptions or improper treatment, no increase in premiums or co-payments; no monetary damages for the price difference between Protropin and another drug; nor did they allege that they would have stopped treatment or purchased another drug if the physician had disclosed his financial arrangements with DrugCo, Inc. Therefore, the case was dismissed.

Conclusion

There are several causes of action against physicians for taking kickbacks. The federal government has a cause of action for violations of the Medicare/Medicaid statute. If a physician participating in a kickback scheme has Medicare or Medicaid patients, then the physician is subject to this law. Also under new HIPAA regulations, the Department of Health and Human Services may fine a physician who provides a patient's protected health information for marketing purposes without specific authorization and disclosure of the remuneration involved.⁵ State governments have their own statutes governing kickbacks, such as Minnesota statute §147.091, subd 1 (p)(1), under which a physician is prohibited from receiving compensation for the referral of patients or the prescription of drugs. A violation of this statute subjects the physician to disciplinary action by the state Board of Medical Examiners. Patients may have a private legal claim against the physician if the kickback scheme caused either monetary or physical injury to the

patient. Such claims fall under malpractice or negligence if injury was caused by the breach of a duty.

Questions for Discussion

1. Does receiving money from the pharmaceutical industry necessarily mean that a physician's medical judgment is compromised? Can you think of situations when no conflict of interest would arise?
2. Do you agree that a physician has a duty to disclose to patients payments of any kind they are receiving from a drug company? Does a physician have a duty to disclose receiving gifts from industry?
3. The Medicare/Medicaid statute says a violation of its kickback statute is a felony, punishable by fines not to exceed \$25,000 and 5 years in prison. Are these appropriate punishments for doctors who receive kickbacks for prescribing one medication rather than others?

References

1. *US v Brown*, 108 F3d 863 (8th Cir 1997).
2. *D.A.B. v Brown*, 570 NW2d 168 (Minn Ct App 1997).
3. 42 USC sec 1320a-7b(b).
4. *US v Perlstein*, 632 F2d 661 (Mich Ct App 1980).
5. 46 CFR sec 164.508(a)(3)(ii).

Kristin A. Sorenson is a contributor to *Virtual Mentor*.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 263-264.

AMA CODE SAYS

The Code on Physicians' Relationship with Industry

Audiey C. Kao, MD, PhD

This issue of *Virtual Mentor* highlights a topical area of professional conduct concerning which the *Code of Medical Ethics* offers much guidance: physicians' relationship with industry. *Code* Opinion 8.061 "Gifts to Physicians from Industry," focuses on gifts proffered, chiefly to clinicians, by pharmaceutical and medical device manufacturers and other proprietary health care-related entities. The Opinion issues 7 guidelines for recognizing and managing conflicts of interest that can arise whenever physicians accept gifts, and provides a lengthy clarification of each guideline. Opinion 8.061 considers company-sponsored continuing medical education and company-sponsored drug or product information conferences under the definition of "gifts" to physicians.

Other *Code* opinions offer guidelines for professional conduct in a variety of relationships where financial interest may create conflicts of interest. These include:

Opinion 8.051, "Conflicts of Interest under Capitation"

Opinion 8.054, "Financial Incentives and the Practice of Medicine"

Opinion 8.06, "Drugs and Devices: Prescribing"

Opinion 8.062, "Sale of Non-Health-Related Goods from Physicians' Offices"

Opinion 8.063, "Sale of Health-Related Goods from Physicians' Offices"

Opinion 9.011, "Continuing Medical Education"

Prompted by the rising price of prescription drugs, media reports of drug company influence on physicians, and the growing influence of direct-to-consumer marketing, the AMA convened the Working Group for the Communication of Ethical Guidelines on Gifts to Physicians from Industry in August 2000. The group was composed of representatives of the medical profession and industry and was charged with developing better strategies for educating both physicians and the industry about the *Code's* guidelines.

Audiey C. Kao, MD, PhD is editor in chief of *Virtual Mentor*.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 265-267.

STATE OF THE ART AND SCIENCE

Treating Hypertension

Audiey C. Kao, MD, PhD

Hypertension is the primary reason for millions of doctor's visits each year. In the past there were few drugs to treat hypertension; physicians today, however, have more than 60 different medications at their disposal.

In the past year, several important peer-reviewed papers were published that provide practical guidelines for hypertension prevention and management and evidence on different classes of antihypertensive drugs' relative efficacy in lowering the incidence of coronary heart disease and other cardiovascular events such as stroke.

New guidelines from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) highlight several important issues, including the following:¹

1. In persons older than 50, systolic blood pressure (BP) of more than 140 mm Hg is a much more important cardiovascular disease (CVD) risk factor than diastolic BP.
2. The risk of CVD, beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg.
3. Individuals with a systolic BP of 120 to 139 mm Hg or a diastolic BP of 80 to 89 mm Hg should be considered as prehypertensive and encouraged to adopt health-promoting lifestyle modifications such as weight reduction, dietary sodium reduction, and regular physical activity.
4. Thiazide-type diuretics should be prescribed for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes.
5. Most patients with hypertension require 2 or more antihypertensive medications to achieve goal BP (140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease).
6. If BP is more than 20/10 mm Hg above goal BP, consideration should be given to initiating therapy with 2 agents, 1 of which usually should be a thiazide-type diuretic.

Results from 2 large randomized clinical trials comparing the outcomes of different classes of antihypertensive drugs seemed to offer conflicting data about the initial medication of choice. Data from the ALLHAT study,² indicated that thiazide-type

diuretics (chlorthalidone) were better than angiotensin-converting enzyme inhibitors (amlodipine) or calcium channel blockers (lisinopril) in preventing 1 or more major forms of CVD, and they are less expensive. In the ANBP-2 trial, however,³ data revealed that angiotensin-converting enzyme inhibitors (enalapril) led to better CVD outcomes than diuretics (hydrochlorthiazide).

Given these apparently conflicting clinical results, what is a physician to make of the new guidelines from the JNC 7? Recent expert commentaries on the ALLHAT and ANBP-2 studies^{4, 5} provide some useful analyses and the following guidance for physicians:

1. Don't get caught up in the debate of which antihypertensive drug is better. In fact, the diuretic and ACE examined in the 2 trials were different.
2. These clinical studies describe population averages, and the treatment of individual patients with hypertension requires attention to the medical history and clinical response of each.
3. Diuretics can reduce the risk of CVD despite concerns by some physicians of their adverse metabolic effects such as elevating blood sugar or total cholesterol.
4. Since most patients require more than 1 medication to control their blood pressure, it is likely that a patient will benefit from both a diuretic and an angiotensin-converting enzyme inhibitor.

References

1. Chobanian AV, Bakris GL, Black HR, et al, and the National High Blood Pressure Education Program Coordinating Committee. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC report. *JAMA* 2003;289(19):2560-2571.
2. Wing LMH, Reid CM, Ryan P, et al for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;348(7):583-592.
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack (ALLHAT). *JAMA*. 2002;288(23):2981-2997.
4. Frohlich ED. Treating hypertension. What are we to believe? *N Engl J Med*. 2003;348(7):639-641.
5. Moser M. Results of ALLHAT. Is this the final answer regarding initial antihypertensive drug therapy? *Arch Intern Med*. 2003;163(11):1269-1273.

Audiey C. Kao, MD, PhD is the editor in chief of *Virtual Mentor*.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 268-272.

POLICY FORUM

Undergraduate and Graduate Medical Education and the Pharmaceutical Industry

Greg E. Manship, MDiv, MA

By professional patriotism [in medicine] . . . I mean that sort of regard for the honor of the profession and that sense of responsibility for its efficiency which will enable a member of that profession to rise above the consideration of personal or professional gain. . . . If the medical education of our country is in the immediate future to go upon a plane of efficiency and of credit, those who represent the higher ideals of the medical profession must make a stand for that form of medical education which is calculated to advance the true interests of the whole people and to better the ideals of medicine itself.¹

Nearly a century later, tight medical school budgets and managed care make promotional gifts and educational and research funding from the pharmaceutical industry financially attractive. Pharmaceutical industry generosity arguably entices compromise of ethical standards in medical education and professionalism.²⁻⁵ Evidence of compromise prompts calls for renewing and reclaiming professionalism by minimizing and even eliminating the influence of the pharmaceutical industry in medical education.⁵⁻⁷ This article focuses on policy issues pertaining to interactions between the pharmaceutical industry and undergraduate and graduate medical education.

In 2001, the pharmaceutical industry spent \$19 billion on promotion, which includes direct-to-consumer (DTC) advertising, medical journal advertising, product samples, and costs associated with sales representative interactions with office-based and hospital-based physicians and pharmacy directors.⁸ Promotional activities directed at office-based and hospital-based physicians involve medical students serving clerkships, interns, and residents.⁹ Additionally, the pharmaceutical industry contributed to the approximately \$540 million spent on graduate and continuing medical education (GME and CME, respectively) by companies who manufacture products regulated by the FDA.¹⁰ The economic influence of the pharmaceutical industry has generated numerous articulations of ethical and legal guidelines to regulate industry interaction with medical research, practice, and education.¹¹⁻²⁰

The federal government and professional organizations provide guidelines for interactions between GME and the pharmaceutical industry.¹⁵⁻²⁰ The Accreditation Council for Graduate Medical Education (ACGME) and the Association of

American Medical Colleges (AAMC) require each GME site and program to develop, implement, and enforce policies that regulate interactions between residents and the pharmaceutical industry.^{16, 18} Wazana's analysis of the literature demonstrated that prior to the release of these guidelines, residency programs differed in their policies regarding the permissibility of pharmaceutical industry gifts and educational funding.⁴

Publications after Wazana continue to note differences in policies and attitudes. Two articles in *Health Affairs* described the frustrations and "conversion" of a former resident and a former GME site committee member as they struggled against the lack of policies regulating interactions between residents and pharmaceutical representatives.^{21, 22} Ferguson, et al, reported that practicing internists who came from residency programs with policies restricting pharmaceutical industry contact were no less likely to interact with and accept samples from pharmaceutical representatives than internists who came from programs with no restrictive policies.²³ McCormick, et al, reported that restrictive policies appeared to alter residents' attitudes toward pharmaceutical representatives, thereby reducing the frequency of contact between representatives and practicing physicians.²⁴ A study of factors influencing interns' prescribing behaviors concluded that educational interventions and multi-disciplinary mentoring would be more effective than restrictive policies.²⁵ These representative studies demonstrate the disparity among the results of policies restricting residents' interaction with the pharmaceutical industry.

Despite the disparity in restrictive policies, the above-mentioned authors agreed that educational interventions to equip residents to interpret and interact with pharmaceutical industry promotion are necessary. This conclusion is bolstered by studies that described educational interventions to train residents to interact with pharmaceutical industry promotion.^{26, 27} The importance of educational experiences in conjunction with restrictive policy is reported by the Association of Program Directors of Internal Medicine (APDIM).²⁸ A survey of all APDIM member programs demonstrated that certain benchmarks of financial and staff support correlated with indicators of quality. One correlation was that programs that accepted higher amounts of financial support from the pharmaceutical industry also had lower pass rates for the American Board of Internal Medicine certification exam. Although the survey did not ask about policies involving interactions with the pharmaceutical industry, the conclusions of the report suggest that residents' success does depend on educational quality that is independent of financial influence from the pharmaceutical industry.

The guidelines for interactions between undergraduate medical students and the pharmaceutical industry are not as extensively developed as those for GME. Nevertheless, their presence in hospitals, practitioners' offices, clinics, and educational events make undergraduate medical students susceptible to pharmaceutical industry promotion. A recently published survey of fourth-year medical students reported that students were not "highly knowledgeable regarding

pharmaceutical marketing," yet they "reported greater confidence in the accuracy of information received from PSRs [pharmaceutical sales representatives] . . . than did pharmacy students."²⁹ The study concluded with recommendations for developing, implementing, and monitoring educational experiences regarding the pharmaceutical industry throughout the entire medical school experience. These recommendations corroborated the results of an earlier survey study, which described third-year medical students' understanding of pharmaceutical industry promotion, and proposed an intervention to improve students' understanding of ethical issues and guidelines.³⁰

Despite the apparent lack of a "core" curriculum on the ethics of interactions with the pharmaceutical industry,³¹ not all medical students are unaware of the influence of pharmaceutical industry promotion. The American Medical Student Association (AMSA) has called upon all medical students to "revitalize" professionalism in medicine by rejecting all pharmaceutical industry promotional activities.³²⁻³⁵ This pursuit is enhanced by the activism of Dr. Bob Goodman and his No Free Lunch organization.³⁶ Thus, while the interactions between the pharmaceutical industry and undergraduate medical education seem to garner less formal attention, the ethical issues are no less important, and the necessity to address them all the more imperative.

Should medical education eschew all financial support from the pharmaceutical industry? Is the rejection of restrictive policies no more than acquiescence and laissez-faire? Professional, ethical, and legal norms combine education and regulation to deter and monitor abuse. While such norms cannot hold each individual in check, they do promote an atmosphere of mutual concern and respect that can foster optimal cooperation in the provision of effective health care, which recaptures the vision Flexner and Pritchett articulated nearly a century ago.

References

1. Pritchett HS. Introduction. In: Flexner A, ed. *Medical Education in the United States and Canada: A Report to the Carnegie Foundation for the Advancement of Teaching*. reprint. New York: Arno Press Inc; 1972:xiii-xiv.
2. Coyle SL. Physician-industry relations. Part 1; Individual physicians. *Ann of Intern Med* 2002;136(5):396-402.
3. Coyle SL. Physician-industry relations. Part 2: Organizational issues. *Ann of Intern Med* 2002;136(5):403-406.
4. Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000;283(3):373-380.
5. Wazana A, Primeau F. Ethical considerations in the relationship between physicians and the pharmaceutical industry. *Psychiatric Clin of N America* 2002;25(3):647-663.
6. Rothman DJ. Medical professionalism: focusing on the real issues. *New Engl J Med* 2000;342(17):1284-1286.
7. Wolfe SM. The destruction of medicine by market forces: teaching acquiescence or resistance and change? *Acad Med*. 2002;77(1):5-7.

8. IMS Health Incorporated. Total US promotional spending by type. March 2003. Accessed May 28, 2003.
9. Barzansky B, Etzel SI. Educational programs in US medical schools, 2000-2001. *JAMA* 2001;286(9):1049-1055.
10. Accreditation Council for Continuing Medical Education. Income and expense for all ACCME accredited providers--2001. Accessed May 15, 2003.
11. Accreditation Council for Continuing Medical Education. Accreditation policy: commercial support. Accessed May 15, 2003.
12. Opinion 9.011 Continuing Medical Education. American Medical Association. *Code of Medical Ethics 2002-2003 Edition*. Chicago, IL: American Medical Association; 2003.
13. Opinion 8.061 Gifts to Physicians from Industry. American Medical Association. *Code of Medical Ethics 2002-2003 Edition*. Chicago, IL: American Medical Association; 2003.
14. Ethics Manual: Fourth Edition. *Ann of Intern Med*. 1998;128(7):576-594.
15. Accreditation Council for Continuing Medical Education. Standards for commercial support of continuing medical education. Accessed May 15, 2003.
16. Accreditation Council for Graduate Medical Education. Principles to guide the relationship between graduate medical education and industry. Accessed March 24, 2003.
17. Council on Ethical and Judicial Affairs. E-Addendum II: Council on Ethical and Judicial Affairs clarification of gifts to physicians from industry (E-8.061). June 2002. Accessed May 31, 2003.
18. Santana S. AAMC executive council sets guidelines on industry marketing to residents. Association of American Medical Colleges. Accessed May 27, 2003.
19. US Food and Drug Administration. FDA: Final guidance on industry-supported scientific and educational activities. 62 FR 64074.
20. Office of Inspector General. Compliance program guidance for pharmaceutical manufacturers. 68 FR 23731.
21. Brody H. A matter of influence. *Health Affairs* 2002;21(2):232-234.
22. Jung P. No free lunch. *Health Affairs* 2002;21(2):226-231.
23. Ferguson RP, Rhim E, Belizaire W, Egede L, Carter K, Lansdale T. Encounters with pharmaceutical sales representatives among practicing internists. *Am J Med* 1999;107(2):149-152.
24. McCormick BB, Tomlinson G, Brill-Edwards P, Detsky AS. Effect of restricting contact between pharmaceutical company representatives and internal medicine residents on posttraining attitudes and behavior. *JAMA* 2001;286(16):1994-1999.
25. Pearson S-A, Rolfe I, Smith T. Factors influencing prescribing: an intern's perspective. *Medical Education* 2002;36(8):781-787.
26. Kelcher S, Brownoff R, Meadows LM. Structured approach to pharmaceutical representatives. *Can Fam Physician*. 1998;44:1053-1060.

27. Razack S, Arbour L, Hutcheon R. Proposed model for interaction between residents and residency training programs, and pharmaceutical industry. *Annals of the Royal College of Physicians and Surgeons of Canada* 1999;32(2):93-96.
28. Wolfsthal SD, Beasley BW, Kopelman R, et al. Benchmarks of support in internal medicine residency training programs. *Acad Med* 2002;77(1):50-56.
29. Monaghan MS, Galt KA, Turner PD, et al. Student understanding of the relationship between the health professions and the pharmaceutical industry. *Teaching and Learning in Medicine* 2003;15(1):14-20.
30. Wilkes MS, Hoffman JR. An innovative approach to educating medical students about pharmaceutical promotion. *Acad Med* 2001;76(12):1271-1277.
31. DuBois JM, Burkemper J. Ethics education in US medical schools: A study of syllabi. *Acad Med* 2002;77(5):432-437.
32. American Medical Student Association. Revitalizing professionalism. Accessed May 31, 2003.
33. American Medical Student Association. AMSA PharmFree Campaign. Accessed May 31, 2003.
34. Adams C. Student doctors protest largess of drug makers. *Wall Street Journal*. June 24, 2002;B1.
35. Romano M. Student rally. *Modern Healthcare*. May 13 2002;32:24-25.
36. Goodman B. No free lunch. Available at: <http://www.nofreelunch.org>. Accessed May 31, 2003.

Greg E. Manship, MDiv, MA is currently a PhD student in the Center for Health Care Ethics at Saint Louis University. He holds current registration with the American Society for Clinical Pathology as a medical technologist. He is an ordained Minister of Word and Sacrament in the Presbyterian Church. His research interests include interactions between medical professionals and industry, end-of-life care, and theological aspects of medicine.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 273-275.

POLICY FORUM

The PhRMA Code: A New Roadmap for Industry-Physician Interactions

Michael Scott Labson, Esq

On April 18, 2002, the Pharmaceutical Research and Manufacturers of America (PhRMA) adopted a new marketing code to govern the pharmaceutical industry's relationships with physicians and other health care professionals. PhRMA is a voluntary association of leading research-based pharmaceutical and biotechnology companies, and its new *Code on Interactions with Healthcare Professionals* (the PhRMA Code) took effect on July 1, 2002. This paper provides an overview of the PhRMA Code and discusses the potential impact of the Code on the relationships between the drug industry and physicians.

Legal Background

The Medicare-Medicaid Anti-Fraud and Abuse Act (the "anti-kickback" statute) is a federal law that prohibits providing or receiving anything of value to induce a person to use a product if the product will be paid for in whole or in part by a federal insurance program.¹ Many states have similar laws. These federal and state statutes are generally intended to guard against increased costs through higher utilization of services or substitution of higher-cost products and to preserve the integrity of health care programs by prohibiting inducements that could bias treatment. Violations carry substantial criminal and civil penalties.

The scope of these laws is extremely broad and potentially encompasses marketing practices that are common in other industries. As the Office of Inspector General (OIG) of the Department of Health and Human Services once explained, "many relatively innocuous, or even beneficial, commercial arrangements are technically covered by the statute and are, therefore, subject to criminal prosecution."²

Despite the breadth of these laws and the difficulty in distinguishing between lawful and unlawful arrangements, the government has historically been reluctant to provide guidance. For example, in 1991 the OIG stated that "there is no way to predict the degree of risk" for certain arrangements, and that "it is impossible as a practical matter to give meaningful advice with respect to liability in the context of a letter ruling."²

The PhRMA Code was a step by industry to fill the vacuum left by the government's reticence on the issue. OIG has since issued a *Compliance Program Guidance for Pharmaceutical Manufacturers*,³ which reinforces the PhRMA Code

and provides additional guidance on compliance and practices that the government believes present risks.

The PhRMA Code

The first tenet of the PhRMA Code is that interactions with physicians "should be focused on informing health care professionals about products, providing scientific and educational information, and supporting medical research and education." To that end, the Code provides a series of rules for particular activities. It is not possible to cover all of the Code here, but a brief review of its key provisions will illustrate the approach.

Under the Code, it is not appropriate for a company to provide a physician entertainment or recreational activities such as golf, tickets to theatre, etc. Companies are permitted to provide occasional meals in connection with presentations by sales representatives or other speakers, but the meals must be modest and conducive to informational exchange. Similarly, companies are allowed to offer educational "gifts" (eg, stethoscopes, textbooks), provided they are primarily for the benefit of patients and not of substantial value (\$100 or less). Practice-related gifts of minimal value (pens, notepads, etc) are permitted, but not items such as golf balls that are only of personal benefit.

Physicians may be paid for bona fide consulting services and for serving on a company's speakers' bureau. However, there must be a legitimate need for the services, documentation of the terms of the engagement, payment based on fair market value for services rendered, and other safeguards. Companies are allowed to provide financial support for conferences and professional meetings, if the support is given to the organizer and meets other limitations, and for scholarships that permit medical students, residents, and others in training to attend conferences.

In no event may any benefit (grant, consulting contract, gift, etc) be offered in exchange for a physician's agreement to prescribe a product. The PhRMA Code states that nothing should be provided "in a manner or on conditions that would interfere with the independence of a health care professional's prescribing practices."

Industry-Physician Relationships

In light of PhRMA's prominent stature, the PhRMA Code establishes a de facto benchmark for industry practices, although adherence to the Code is voluntary. Moreover, the PhRMA Code was endorsed by the OIG.³ This endorsement establishes the Code as a measure for compliance with the legal requirements that govern health care marketing, and ensures that it will be followed.

The PhRMA Code articulates a set of concrete rules and broader principles that had not been collected before in a comparable industry or government document. It is fair to say that the PhRMA Code provides the most explicit guidance available to date in an area where guidance is sorely needed. For that reason, the PhRMA Code

will have a substantial influence on industry-physician interactions for some time to come, as both groups try to navigate what is potentially treacherous legal and ethical terrain.

References

1. 42 USC sec 1320a-7b(b)(2).
2. HHS Office of Inspector General. Medicare and state health care programs: fraud and abuse; OIG anti-kickback provisions. *56 Federal Registrar* 3592. July 29, 1991.
3. HHS Office of Inspector General. OIG compliance program guidance for pharmaceutical manufacturers. *68 Federal Registrar* 23731. May 5, 2003.

Michael Scott Labson, Esq is a partner at the law firm of Covington & Burling in Washington, DC and represents PhRMA and various research-based pharmaceutical companies.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 276-280.

MEDICINE AND SOCIETY

Setting Biomedical Research Priorities in the 21st Century

David B. Resnik, JD, PhD

Setting biomedical research priorities is one of the most important issues in health policy and ethics because it has broad implications for the advancement of medical knowledge, the improvement of clinical practice, the promotion of public health, and access to health care. For example, funding research on the human immunodeficiency virus (HIV) can enhance our knowledge of HIV; improve the treatment, diagnosis, and prevention of HIV; and increase access to health care for HIV patients. But since neither the government nor the private sector has an unlimited supply of money to spend on research and development (R & D), determining how to slice the research funding pie raises social and ethical questions related to justice and fairness.

Most of the publicly funded biomedical research in the United States is sponsored by the National Institutes of Health (NIH), which had a \$27 billion budget in 2002-2003. In the last 5 years, the NIH budget has nearly doubled.¹ Although the US government spends a great deal of money on biomedical research, private corporations spend more. In 2001, the companies belonging to the Pharmaceutical Research and Manufacturers of America (PhRMA) spent \$30 billion on R & D, and companies belonging to the Biotechnology Industry Organization (BIO) spent \$15.6 billion on R & D.²⁻³ Seventy percent of the clinical trials conducted in the US are industry-sponsored.⁴ Any realistic policy that addresses research priorities must come to terms with the fact that private industry outspends the public sector when it comes to biomedical R & D.

How Biomedical R & D Priorities Are Set in the United States

The economics of medical product development determines how pharmaceutical and biotechnology companies establish their funding priorities. According to industry estimates, it takes an average of \$800 million and 10-15 years to develop a new drug, medical device, or biologic and bring it to the market.⁵ Since a patent on a new product lasts 20 years, a company will have 5-10 years to recoup its R & D investment while the product is still under patent. Once the patent expires, the company will lose its exclusive control over the product and its ability to make a significant profit. Although pharmaceutical companies tend to have relatively high profit margins (ie, 10 percent or more), they also take significant economic risks when they develop new drugs. Only 33 percent of new drugs are profitable, and very few drugs become "blockbusters," like Viagra or Prozac. Companies also

frequently must withdraw profitable drugs from the market, due to adverse effects or litigation.⁶

Given these economic conditions, it is easy to see how private industry decides upon allocation of its biomedical R & D funds. Basically, pharmaceutical and biotechnology companies set R & D priorities based on market potential, liability costs, the scope of intellectual property protection, market lead time, the expected time from the laboratory to the market, and other factors that affect the profitability of a research investment. As a result, they tend to shy away from investing their funds on basic research, on rare diseases, on diseases with low consumer demand, or on drugs that will take a long time to get to the market or will have potentially high liability costs. Given these guidelines, private industry's R & D decisions can leave large gaps in our medical knowledge and may fail to promote the interests of all people in society. For example, 90 percent of the money spent on biomedical R & D focuses on conditions responsible for only 10 percent of the world's burden of disease.⁷ Moreover, many of the drugs prescribed to children have not been tested on pediatric populations.⁸

Fortunately, the NIH fills in these gaps in medical knowledge and biomedical research. The NIH, established by the US government in 1887, consists of 27 different institutes and centers, such as the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Human Genome Research Institute (NHGRI). Its mission is "to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability, from the rarest genetic disorder to the common cold."⁹ The NIH has more than 100 study sections, which review grant proposals and make recommendations to the NIH Advisory Council. In deciding how to prioritize research proposals, study section members consider several factors, including, (1) the proposal's impact on the burden of disease, (2) the proposal's potential contribution to biomedical science, (3) the qualifications of the researchers, and (4) institutional support for the proposal.¹⁰

To determine the burden of disease, one must balance and weigh a variety of factors, such as the incidence of the disease, the mortality rate of the disease, the degree of disability caused by the disease, the impact of the disease on life expectancy, the social and economic impacts of the disease, and public health considerations. Since value judgments enter into the weight and balance one gives these factors, the NIH solicits public input from elected officials, professional and scientific associations, disease advocacy groups, and special conferences, workshops, and review panels in assessing the burden of disease and establishing its research priorities. In addition, the NIH has established a Council of Public Representatives that provides the NIH director with advice on funding priorities.¹⁰

How Biomedical Research Priorities Should Be Set

Although private corporations tend to set their funding priorities based on profitability, one might argue that they should also consider their social

responsibilities when allocating their R & D funds. Private corporations have social responsibilities because they are accountable as moral agents in society and make decisions that have a tremendous impact on the economy, the environment, culture, and human health.⁸ Pharmaceutical and biotechnology companies should exercise their social responsibilities by funding research to reduce the burden of diseases that affect people in developing nations and by sponsoring research on rare diseases, such as Huntington's disease or Tourette's syndrome.¹¹ They should also be willing to conduct research on pediatric populations, provided that they adhere to appropriate safeguards and regulations.¹² Pharmaceutical companies should, like the NIH, solicit public input and advice relating to their funding priorities. They should consult with many of the same groups that provide advice to the NIH, such as professional and scientific associations and disease advocacy groups.

While the NIH's system for setting biomedical research priorities is generally fair and effective, it also has some weaknesses. First, interest group politics can undermine both the fairness and the effectiveness of the system. Well-organized and well-funded disease advocacy groups can exert a disproportionately strong influence over funding priorities and can skew the research agenda. As a result, some diseases may not receive their fair share of research funding. Advocacy groups can also undermine the progress of biomedical research by urging the NIH to support research that lacks scientific merit, by deterring the NIH from committing funds to long-term projects or basic research, or by applying a political litmus test to research proposals. Second, prejudices, the "old boys network," and other biases can also adversely affect the fairness and effectiveness of priority setting.

In order to diminish these potential weaknesses, the NIH should seek the appropriate balance of public and expert input. It should give a fair hearing to proposals that lack the support of powerful interest groups; and it should establish procedures for overcoming the biases that can affect even well-designed systems. The NIH should maintain a strong commitment to funding basic research, research on rare diseases and conditions, and research on new and emerging diseases. It should listen carefully to public opinion but it should not allow its funding priorities to wave back and forth in the political winds.

Public-Private Cooperation

Major challenges in medicine and public health require public-private cooperation. For example, no single country, pharmaceutical company, or humanitarian organization can deal with the HIV/AIDS crisis in sub-Saharan Africa. Although this crisis continues to grow worse, the international community is beginning to see some meaningful cooperation among governments, multinational corporations, and humanitarian organizations. Developed nations, such as the US, have pledged to devote additional money for research, treatment, and prevention in Africa, and pharmaceutical companies have discounted their drug prices to make HIV medications more affordable. Governments must work with humanitarian organizations towards the goal of eradicating the spread of HIV. Governments can,

for example, fund basic research, while private companies can develop useful products and applications. Developing nations and humanitarian organizations can improve the health care infrastructure, while developed nations can contribute economic and medical resources.

The Medical Profession's Role

Physicians should take an active role in setting biomedical research priorities by advocating for fair and effective allocations of public and private biomedical R & D investments. Physicians should encourage pharmaceutical companies to make socially responsible funding decisions. Although it is often difficult to affect decisions made by large, multinational corporations, physicians can have considerable influence over pharmaceutical companies, especially when they focus and organize their lobbying power. Physicians should also help government agencies determine funding priorities and lobby the government. They should provide information and advice to the NIH and serve on study sections and advisory boards when asked.

The Council on Ethical and Judicial Affairs of the American Medical Association (AMA) has not issued any opinions dealing with biomedical research priority setting. However, the AMA's *Principles of Medical Ethics* lend support to the physician's role as an advocate for fair and effective research priorities to promote the advancement of medical knowledge, the betterment of public health, and increased access to care.¹³

References

1. Makoff D. Science agencies get most of what they want, finally. *Science* 2003;299(5610):1160-1161.
2. PHRMA. Research and development. Accessed: May 27, 2003.
3. BIO. Biotechnology industry statistics. Accessed: May 27, 2003.
4. Bodenheimer T. Uneasy alliance: clinical investigators and the pharmaceutical industry. *N Eng J Med* 2000;342(20):1539-1544.
5. PHRMA. Intellectual property. Accessed: May 27, 2003.
6. Goldhammer A. Current issues in clinical research and the development of new pharmaceuticals. *Accountability in Research* 2000;8(4):283-291.
7. Resnik D. Developing drugs for the developing world: an economic, legal, moral and political dilemma. *Developing World Bioethics* 2001;1(1):11-32.
8. Kopelman L. Children as research subjects: a dilemma. *Journal of Medicine and Philosophy* 2000;25(6):745-764.
9. NIH. Questions and answers about the NIH. Available at: <http://www.nih.gov/about/FAQ.htm>. Accessed: May 27, 2003.
10. Resnik D. Setting biomedical research priorities: justice, science, and public participation. *Kennedy Institute of Ethics Journal* 2001;11(2):181-204.
11. Congress enacted the Orphan Drug Act (ODA) (Public Law 97-414) in 1983 to encourage drug companies to sponsor research on rare diseases and conditions. The ODA, which has been amended several times, gives companies that develop drugs on rare diseases and conditions exclusive

rights to manufacture and sell those drugs for 7 years and also provides tax incentives to companies.

12. Congress enacted the Best Pharmaceuticals for Children Act (21 USC 505) (BPCA) in 1997 to encourage drug companies to test drugs on pediatric populations. The BPCA gives companies an extra 6 months of patent protection for drugs that are tested pediatric populations. Although the BCPA has provided effective economic incentives for the pharmaceutical industry to conduct clinical trials on pediatric populations, the goal of including more children in research raises its own ethical and policy dilemmas. See Kopelman, *supra* note 8 and Tauer C. Ethical dilemmas on research on children. *Accountability in Research*. 2002;9:127-42
13. American Medical Association. Principles of medical ethics. Accessed: May 27, 2003.

David B. Resnik, JD, PhD is a professor in the medical humanities and director of new programs at The Bioethics Center at The Brody School of Medicine at East Carolina University.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 281-282.

PERSONAL NARRATIVE

The Twelve Days of Christmas

Audiey C. Kao, MD, PhD

On the first day of Christmas, my drug rep gave to me a partridge in a pear tree.

On the second day of Christmas, my drug rep gave to me, 2 ballpoint pens and a partridge in a pear tree.

On the third day of Christmas, my drug rep gave to me, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the fourth day of Christmas, my drug rep gave to me, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the fifth day of Christmas, my drug rep gave to me, a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the sixth day of Christmas, my drug rep gave to me, 6 baseball tickets, a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the seventh day of Christmas, my drug rep gave to me, a 7-course meal, 6 baseball tickets, a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the eighth day of Christmas, my drug rep gave to me, 8 gift certificates, a 7-course meal, 6 baseball tickets, a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the ninth day of Christmas, my drug rep gave to me, 9 holes of golf, 8 gift certificates, a 7-course meal, 6 baseball tickets, a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the tenth day of Christmas, my drug rep gave to me, 10 movie tickets, 9 holes of golf, 8 gift certificates, a 7-course meal, 6 baseball tickets, a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the eleventh day of Christmas, my drug rep gave to me, 11 oz of caviar, 10 movie tickets, 9 holes of golf, 8 gift certificates, a 7-course meal, 6 baseball tickets,

a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

On the twelfth day of Christmas, my drug rep gave to me, 12 long-stemmed roses, 11 oz of caviar, 10 movie tickets, 9 holes of golf, 8 gift certificates, a 7-course meal, 6 baseball tickets, a 5-lb ham, a 4-volume textbook, 3 handy penlights, 2 ballpoint pens, and a partridge in a pear tree.

Audiey C. Kao, MD, PhD is editor in chief of *Virtual Mentor*.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.

Virtual Mentor

American Medical Association Journal of Ethics
July 2003, Volume 5, Number 7: 283-285

VIEWPOINT

Safeguarding the Quality of Clinical Research

Joel Lexchin, MD

Three colleagues and I have just published a systematic literature review demonstrating that pharmaceutical research funded by drug companies is more than 4 times as likely to favor the drug made by the sponsor than research funded by other sources.¹ This finding extended to pharmaceuticals that treat a wide range of diseases such as osteoarthritis of the knee, multiple myeloma, various psychiatric problems, Alzheimer's disease, and venous thromboembolism. The totality of the evidence reported in our meta-analysis of a subset of homogeneous studies suggests that there is some kind of systematic bias to the outcome of published research funded by the pharmaceutical industry.

Our results are quite disturbing given that in Canada and the United States the pharmaceutical industry is the largest direct funder of medical research. In the US in 2002, the industry outspent the National Institutes of Health by \$26.4 billion to \$24 billion.² All of the world's leading medical journals publish industry-sponsored research; doctors and scientists need to be able to have confidence in the conclusions of this research. We are calling for a major push toward making the process of research and publication more transparent.

The data we examined did not allow us to reach any definitive answers about the source of outcome bias, but we think there are 2 possible sources—publication bias and the use of inappropriate comparator agents. The reluctance of journals to publish negative findings is a well-known form of publication bias, but there are other forms this bias can take. In the case of some negative findings, pharmaceutical companies may own the data, and, naturally enough, are not interested in submitting these unfavorable findings to a journal. Researchers may self-censor, reasoning that if they publish results showing the inferiority of a company's products it may be more difficult to obtain research funding from a company. In some instances, companies help researchers write up their results because the investigators do not have the time or lack the necessary skills to do it themselves. Will a company be willing to assist in writing up a research trial that does not favor its product?

Appropriate comparative trials between drugs are frequently lacking and are often replaced by trials against placebos. In instances where there is a strong placebo effect or where the course of a disease is highly variable, placebo-controlled trials are justified. In other instances, however, trials may use a placebo for comparison

as a way of producing positive results for the drug being tested. In trials where 2 active drugs are being compared, the doses may not be equivalent. For example, the dose of the comparator may be too high—leading to more side effects—or too low—leading to lesser efficacy. It should be noted that, in the literature we examined, we could not determine who was responsible for the choice of the comparator agent—the sponsoring company, the investigators, or a regulatory authority.

Some steps have already been taken to improve the reporting of randomized clinical trials. An international group of investigators, statisticians, epidemiologists, and biomedical editors met to revise the CONSORT statement in 2001.³ Journals that follow these recommendations, give their readers a transparent rationale for why the study was undertaken and how it was conducted and analyzed. That same year, the editors of 13 major medical journals, including *JAMA*, *CMAJ*, and *Lancet*, issued a declaration regarding publication requirements for their respective journals. These standards require authors submitting a manuscript to disclose all financial and personal relationships between themselves and others that might bias their work. They must describe the role of the study sponsor(s) in study design and the collection, analysis, and interpretation of data. Authors must also disclose the trial funders' involvement in the writing of the report and the decision to submit for publication; and, in certain cases, editors may ask authors to sign a statement such as "I had full access to all of the data in this study, and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

In my opinion, and that of my collaborators, more needs to be done to improve the integrity of clinical research reports. We echo the repeatedly made suggestion that all clinical trials be registered prospectively in order to prevent publication bias. Such a registry would allow interested parties to see if there were trials that did not make it to publication and analyze any links between funding status and publication. We also recommend that authors and editors consider including a statement about the beliefs of the investigators prior to conducting research about the uncertainty of the treatments they plan to study. Uncertainty about the superiority or inferiority of the different agents being compared would assure readers that comparators were not chosen to ensure the final outcome of the study.

We recommend other measures such as, to the extent possible, disengaging pharmaceutical companies from the design of clinical trials; this is the responsibility of the investigators. Drug companies should restrict themselves to funding the trials. Assessment scales for the methodologic quality of research should be expanded to include a measurement of the appropriateness of the comparator(s). All journals that publish clinical trials should embrace the statement from the 13 editors on publication requirements. Finally, readers need to be alert to the funding sources of clinical trials, whatever they may be, and take into consideration whether the sponsoring group may have influenced the trial results.

References

1. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326(7400):1167-1170.
2. Pharmaceutical Research and Manufacturers of America. PhRMA: Industry Profile 2003 (Chapter 2). Accessed June 30, 2003.
3. The CONSORT statement is an important research tool comprising a checklist and flow diagram to help improve the quality of reports of randomized controlled trials. The statement offers a standardized way for researchers to report trials and is intended to make experimental process more transparent so that readers can more appropriately evaluate the study's validity. See CONSORT. Available at: <http://www.consort-statement.org/>. Accessed June 27, 2003

Joel Lexchin, MD teaches health policy at York University and also works as an emergency physician at the University Health Network, both in Toronto, Canada. He has written extensively on the relationship between physicians and the pharmaceutical industry and has served as a consultant on pharmaceutical issues to the province of Ontario, the Canadian and New Zealand governments, the Australian National Prescribing Service and the World Health Organization.

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2003 American Medical Association. All rights reserved.