Conflict of Interest: The Achilles Heel of Evidence-Based Dentistry

In their book titled *Freakonomics*, Leavitt and Dubner utilize sophisticated statistical analysis of massive datasets to try to understand why humans do what humans do. They describe why drug dealers live with their mothers and why the homes of real estate agents sell for more than your home or mine. Indeed, another chapter is dedicated to learning what factors positively and negatively affect the performance of children in school. At the end of the book, the authors conclude that almost all human decisions are based upon one simple concept: incentive. They persuasively argue that, whether done overtly or subliminally, analyzing the positive and negative repercussions of our actions or inactions drives almost everything we do. So incentive deserves a little attention in the bigger context of repercussions.

Incentives

Each culture has broad, let's say, rules for individual conduct. "Western culture" is based to a great extent upon Christian beliefs. However, similar rules and beliefs pervade every culture and are an expression of the ideal qualities to be manifested by every person. For those of us raised with more than one religion and more than one culture impinged upon us, the daily contradictions soon give way to daily acceptance that, at their roots, one finds far more commonality than disparity. The concept of tolerance is merely a smokescreen for an unwillingness to accept that another's view has as much validity as one's own.

I set this religion versus culture backdrop simply as an introduction. Clearly, all religions and cultures promote certain desirable conduct, and 2 such forms of conduct are that one should not steal and that one should not lie. When it comes to the world of dental academe, then, where do we stand on stealing and lying?

I once heard a speaker make the statement that "One does not have to teach people how to be funny; one has to give them permission." I believe this type of sentiment holds true for many desirable human qualities, such as kindness, compassion, honesty, generosity, and altruism. But, what of altruism in scientific research? Does altruism still win the day or has altruism been relegated to the status of nothing more than a goal of the naïve? Have we created a culture where we no longer have permission to be altruistic? And to potentially make matters worse, do we now live in a culture where we have permission to ignore altruistic behavior?

A research mentor of mine, when urging me to publish some of my data, stated, "If you don't publish your results, they might as well never have existed." So let us examine the process of scientific inquiry with the goal of recognizing how altruistic behavior is manifested or submerged at each stage. I will focus, but not to the point of exclusivity, on research conducted with corporate sponsorship. From this point on, I will use the words *corporation* and *sponsor* interchangeably.

Corporate sponsorship, of course, is to many investigators a source of funding to conduct research. Government and foundation funds in many countries are hard to appropriate, and corporations are willing to fill some of this void. However, the motives of these sponsors must be acknowledged and indeed accepted. Most corporations exist to make a profit and their raison d'etre is to satisfy shareholders. After all, surely altruism is in the eye of the beholder. It would, in my opinion, border on arrogance to pretend that North on my compass is the North that should apply to everyone's compass.

Hypothesis and Experimental Design

When it comes to scientific research, let us begin with the tasks of generating a hypothesis and generating design concepts. The influence of corporate sponsorship can be subtle or overt at this pivotal stage of the process. Is the research question at hand one of importance to our patients or to the sponsor? Is the design of the study well-suited to benefit our patients or to benefit the sponsor? In an ideal world, the answer to these questions is "all of the above."

But why is it that there are almost no comparative therapeutic studies in medicine or dentistry? Pharmaceutical companies rarely design studies to compare their new therapy to an industry standard, especially if the standard is manufactured by a market competitor. The poor substitute, placebo, is used as the comparison to the study drug; while other drugs that are standard of care practice are ignored. When it comes to medical devices, such as medical implants, a similar situation occurs. The new device is investigated thoroughly, but its effectiveness and efficacy compared to other devices are left to the number-cruncher statisticians and epidemiologists to determine many months and years down the road—by which time the device is obsolete.

Under these circumstances, facts and truth threaten to become irrelevant. Dentistry has lagged behind

medicine in certain ways and one of those used to be our unwillingness to "partner with industry." Clearly we have put aside the stigma, but not without also embracing the accompanying compromises. Corporate sponsors now have a large say in what research is conducted in many dental academic institutions; in the rush to be funded, and with the need to further our discipline through scientific inquiry, we have been challenged to maintain the proverbial "arm's length."

This form of partnership challenges all parties to stay true to the path of altruism. Obviously the convenient way out is to ignore the potential conflicts of interest and pretend that since everyone else is party to the culture change, then one is just changing with the times. Nevertheless, although many of us have taken the hand of our new dance partner, the corporate sponsor, doing so with disdain would be hypocritical. Harkening back to the good-old days would be akin to sticking one's head in the sand. Industry-sponsored research is a vital fragment in dental research. It is here to stay and we are best served by establishing mutually beneficial parameters. If and when our integrity is threatened, we would do well to err on the side of an approach beyond reproach.

Conduct of the Research Study

Investigators, based upon their relationship with corporate sponsors, may or may not have the independence to control the conduct of the research. More often than not, nowadays, sponsor-initiated studies come with 2 key documents from the sponsor. The first is the investigator brochure. This document is often lengthy and complex, and provides a verbose description of the background to the therapy or intervention, including its safety profile and results to date in earlier studies.

The second document, the protocol, may carry some of the same information found in the investigator brochure, albeit in abbreviated form. However, the focus of the protocol is a nuts-and-bolts description of how the study will be conducted. Details related to inclusion and exclusion criteria, subject recruitment, screening procedures, study methods, data collection, data analysis, and reporting of serious adverse events are typical elements of the protocol. Clearly, each of these steps in a study protocol is open to bias, and a sponsor angling to have its product test well (and what sponsor isn't angling for its product to test well?) will set up the protocol for maximum potential. In medicine, it is not at all uncommon for a sponsor to intend to enroll hundreds of subjects in a study and to utilize many different centers to attain enrollment. For example, I recently reviewed a study submitted by a major biotechnology company in which over 1,000 subjects were to be enrolled at over 35 sites worldwide. Mayo Clinic was to enroll less than 25 subjects. One outcome of this distribution of resources is that investigators are hard pressed to insist on changes to the protocol if they have concerns about it. The sponsor typically presents a "take it or leave it" attitude to the investigator, as it knows that other investigators at other institutions will participate under the sponsor's protocol. It would not surprise me if dental corporations take this approach more and more when they sponsor research. Having specific investigators who bring credibility to research will be less important, in my opinion, as favorable data become more important than who generated it.

Liability During the Conduct of a Sponsor-Initiated Study

This is an extremely sensitive issue these days. Many consent forms for human subjects research include a section that addresses what happens to a participant who is injured while involved in the study. Injury or harm is a definite possibility in dental implant studies, especially those that involve additional irreversible procedures like grafting. It is typical for consent-form language to state that medical costs over and above those that would be paid by a patient's insurance, and which are related to the proper conduct of the study, will be covered by the sponsor. Although this seems like a reasonable commitment for the sponsor to make, recent legal cases in the US have rendered this commitment moot. Two different but similar decisions in the courts have placed the burden for providing care unequivocally on the investigator and his/her parent institution.

The courts reason that it is our responsibility, as the clinicians providing the care, to ultimately be responsible for our patients regardless of whether they are a subject in a research study. When a patient signs a consent form, their relationship is with us—and not with the sponsor. As a result, sponsors are no longer obligated to cover these costs—we are. And if "we" includes private practitioners involved in corporately funded research, the ramifications could be considerable. If the therapy results in undesirable results, even if we fol-

lowed the sponsor's protocol completely and without deviation, we are left to deal with the fallout.

Publication of Results

Today, there are many gatekeepers in a process that used to have few. In the good-old days, journal editors were guardians of the peer-review process and they wielded significant influence. Here, too, however, times have changed, as there are extraneous pressures from a variety of sources. And I am not talking about issues of authorship such as who should be an author and the order of authorship. I am aiming my arrow at the circumstances influencing what data are actually published and when these data are published.

Again, when looking from the viewpoint of a corporation that is supporting the research with financial backing, it is quite likely that the research would not be conducted without this support. As a corporation, I am asking myself: "What am I getting for my money?" In essence, "Where is the payoff here for my investment?"

The totally altruistic view is that the money is a gift for the researchers to do with as they please, akin to a donation. Clearly this is not the purpose of most industry-supported research. There is a quid pro quo in place, and I would propose that the relationship has drifted over the years toward the corporation being in the ascendant position of power. The researcher is, in my opinion, more indebted to the corporation than the corporation is to the researcher. There are, after all, many more researchers than there are corporations, and it is a matter of supply and demand. So what does a corporation seek to impose upon a researcher as a result of this power play?

If we turn to medicine as the guide, for many years data generated by individual investigators at individual institutions involved in multicenter trials have been submitted (without patient identifiers) to the sponsor. The sponsor holds the key to the data vault, and often the investigators only have access to the data they generated at their site. They do not have access to the entire dataset. This is beginning to occur in dentistry and will likely be more pervasive in the years ahead. Another common stipulation is that an investigator may only present his/her own site's data. This is extremely limiting if we use the example from before of a trial at Mayo Clinic; reporting data from 22 subjects is not noteworthy, especially if the complete trial involves 1,100 subjects. The net effect is that the sponsor holds the dataset and the investigator can merely access one small piece of the puzzle. If information is indeed power, you and I, as investigators in a multicenter trial, are at a significant disadvantage. The sponsor, in contrast, is all-powerful.

What Do We Know, When Did We Know It, and When Can We Publish It?

The Watergate affair involving US President Richard Nixon brought the following question to light: "What did the President know, and when did he know it?" In all types of research, an investigator has to make a decision on what data to publish and when to publish them. This decision is fraught with challenges to the altruism of the investigator. What if the data are not consistent with previous findings? What if they will offend powerful colleagues? For those who went into a life in science as a calling, as a way to quench their duty to be altruistic, the rigors and politics of science can be daunting.

As if these factors were not stressful enough, the interplay between investigator and sponsor complicates matters further. Investigators may, on their own, choose not to publish or present data that they expect will upset a sponsor and hence damage their relationship and future prospects for funding. Some sponsors have specific rules that they invoke regarding publication or presentation of data. For example, data that could be construed as undesirable from the sponsor's perspective may be delayed in publication or not published at all. Selectively leaving out data that serve the sponsor's goals correlates to a lie of omission and also challenges the altruistic approach. In addition, many investigators will present draft versions of manuscripts to the sponsor for review (and for tacit approval) prior to manuscript submission. In other instances, sponsors ask for or demand a delay, perhaps up to a year, before manuscript submission to develop a response of some kind.

The Relationship of Peer-Reviewed Dental Journals and Corporations

Let us assume that an investigator who has received funding from a corporation opts to take the altruistic approach and submit a manuscript with information detrimental to the corporation's cause. The peer-review process, in its purest sense, is the ultimate form of inspection and appraisal of a body of scientific work. Unfortunately, our peers are human and, therefore, are vulnerable to the fragilities of human nature. Today, many manuscript reviewers have formal relationships with corporations. In some instances, they have relationships with multiple corporations. The effect of these relationships on the peer-review process is unknown, but likely there is some effect. Even though in the conduct of research, present-day guidelines call for disclosures of potential conflicts of interest, disclosure by those who review the same manuscript is not commonplace in dentistry or medicine. If transparency is the

goal, this is a circumstance that could change. To accentuate the problem further, some journal editors, those to whom I referred earlier as the gatekeepers of scientific information, also may have relationships with corporations. The relationships are complex, undoubtedly. Full disclosure of the relationships is a healthy first step to provide as much information as possible to readers.

The Speaker Circuit

Dentists and dental laboratory technicians are the large markets of opportunity for dental corporations, and those who are persuasive enough can influence these markets. Continuing education programs; invited lectures at national, regional, or local dental society meetings; and even study club presentations are ideal venues where a speaker's message can influence change. The potential for this type of information dispersion to gather in momentum is high, since certain speakers have star appeal and great credibility in the eyes of the rank and file dental practitioners.

Many activities are now being called research, even being called good research, and the unknowing practitioner can become an innocent victim easily. The information dispersers—the speakers—have been targeted as a group. The corollary is that the speakers enjoy being targeted and many receive honoraria or consulting fees from sponsors to make presentations. It is difficult to know exactly how much objectivity a speaker can possess when he or she knows there is a check waiting for them at the end of the presentation.

Scientific Meetings

The high cost of putting on a scientific meeting has forced most professional organizations to seek corporate sponsorship. The basic elements of hotel space and meals are becoming so costly that sponsors are approached to support meetings. The budgets set aside by sponsors for this type of activity must be reasonably large given the preponderance of sponsorship arrangements. This is an awkward spot for a professional organization to be in, especially one that cherishes an intimacy based upon a limited membership and limited attendance policy. Small meetings do not benefit from economies of scale, and sponsorship allows them to maintain a sense of quality otherwise impossible. Running a revenue-neutral meeting these days without corporate sponsorship seems like a pipe dream unless one wants the reputation of running a cheap meeting.

As corporations do well and coffers are flush with disposable income, professional organizations and their meetings will be supported well. But, as the saying goes, there is no such thing as a free lunch. In some instances, sponsors want publicity for their products embedded within the scientific program. In the long run, to become dependent upon corporate support to the point where one relies on it for one's existence is a shortsighted and potentially devastating strategy. When, and not if, the economy takes a downturn, fewer sponsorship dollars will crimp and maybe even devitalize some organizations. Saving for the rainy day that is a certainty would be most prudent.

Speakers at study club meetings, local district meetings, and large meetings may have corporate relationships. It's a worthy aim to have speakers in these venues declare the nature of their relationships with corporations so as to permit the audience to have full awareness of their background.

Patents

The competition for revenue has led to a relatively quick culture shift within universities on many fronts. Not only are researchers partnering with industry, they are looking at ways to help their own cause by taking on the role of entrepreneur. Especially in the field of biotechnology, it is not uncommon for university professors to form companies, sometimes within and sometimes outside the university structure, to maximize the potential of their discoveries.

One of the underpinnings of this entrepreneurial atmosphere is to file for patents. Many remote discoveries are being patented, and ethical debates over issues like gene patenting are commonplace. So it is important to understand that corporate sponsors are but one entity changing the face of science. Academic institutions themselves are just as much a part of the change by promoting this form of commercial behavior within their own walls.

There is no doubt that one has permission to be entrepreneurial at the expense of altruism. One of Michael Crichton's latest books, *Gene*, spins a good tale about exactly this moral dilemma for universities and for society. Crichton's website is dedicated to fighting against gene patenting, as it will lead to slower development of therapies and will increase the costs of research and clinical therapy.

Déjà vu?

Some share a feeling of indignation at the hijacking of scientific integrity by the corporate world. They feel that scientific conduct is being tainted by the potential conflict of interest and that the resultant work is contaminated. This is not apropos, in my opinion, as there are many examples of sound sponsor-supported work. But, it was not that long ago that there was a hullabaloo over insurance coverage. Insurance companies, with

their motives no different than those of a dental implant manufacturing company, bow at the altar of cold hard cash. However, despite our disdain for the fact that our patients cannot get certain types of care, even when evidence is strong that the care results in positive outcomes and has excellent cost-utility, we have come to accept this compromise for what it is. We accept that some insurance coverage for some things is better than no coverage at all. The same is true for sponsor-supported research given the fact that the alternative is only government- or foundation-sponsored research. We need to accept the compromise.

The High Road, the Low Road, and the "Middle of the Road" Road

To take the high road in scientific research is an option open to those who are in a position where they have sufficient funding to bypass corporate support. There are also those who do not conduct research themselves, but who profess an ethical imperative to state that corporate support is an evil to be shunned at all costs. This group of high roaders feels justified in their view when prestigious journals prefer not to publish clinical research that received corporate support. Needless to say, in this scenario, the high road and the road less traveled are the same. The low road, in contrast, is taken by those who demonstrate a reckless abandon for altruism and whose priorities are to remain funded at all costs. Matters of integrity and scientific rigor are mere trifles and are laid aside for the convenience of a continued revenue stream.

I would suggest that a middle-of-the-road approach is the more practical one in today's environment. Research that is corporately supported is woven into the fabric of many research institutions and universities; there is no turning back without unraveling the entire patchwork quilt. Instead of spending valuable time and energy on fighting the wrong battle, it would be wise to expend resources in managing the relationship to best provide for full disclosure by all parties regarding the nature of relationships.

Transparency of conduct is an attainable goal even though there will be opposition from the high roaders and from the low roaders, albeit for different reasons. To declare the nature of one's interaction with any entity that can influence scientific conduct may be too much of a paper-pusher's paradise to contemplate. Yet it is necessary to attain the transparency that is vital.

We must acknowledge the perspective of commercial entities and we must be sensitive to the fact that some excellent sponsor-supported research has propelled our discipline forward. If the alternative to sponsor-supported research is minimal research or no research at all, we must accept the responsibility to work with sponsors to find that middle road where their goals and our goals are met. As I referred to earlier on, we, as the clinicians, are ultimately responsible for the care we provide our patients. We owe it to our patients and to ourselves to be diligent yet pragmatic. The optimist in me is confident that we can resolve these issues ethically, while the pessimist in me fears this is not only desirable, but obligatory.

Disclosure: Dr Koka has no potential conflicts of interest to disclose.

Presented at the International College of Prosthodontists Scientific Session, September 7, 2007, Fukuoka, Japan.

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