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Academic-Industrial Relationships

The Good, the Bad, and the Ugly

The preceding editorial by Dr. David Cullen, Editor-in-Chief of the *Journal of Clinical Anesthesia*, is printed here by invitation. His editorial also appears in the August issue of the *Journal of Clinical Anesthesia*. Such joint and simultaneous publication, although unusual, is not unprecedented,[1-4] and it is prompted by the seriousness of the event described by Dr. Cullen. The ghostwriting of articles submitted to this or any scientific or medical journal is unacceptable and represents an egregious violation of publishing ethics. However, Dr. Cullen's editorial also points to the more important issue that relates to the ethics of the interaction between investigators and corporate sponsors, and between these groups, this journal, and our readers.

Almost every medical editor has commented on the nearly symbiotic relationship that exists between manufacturers and academic researchers. This has been repeated so often that the comment may appear trite. Nevertheless, it is undeniable. On one side of the relationship, industry expends enormous amounts of intellectual and financial capital to develop new and more effective drugs and equipment. On the other side, the specialty provides both the demand for the product (there is no reason to develop a product that no one wants) and the laboratory and clinical investigators who can rigorously evaluate these products. Everyone stands to benefit from this relationship.

Those who claim that any corporate involvement by members of our specialty is unforgivable, who always condemn those anesthesiologists who work closely with companies, or who criticize the journals that publish their work are either naive or disingenuous. Without industry, we would have no modern volatile agents, no neuromuscular blocking drugs, no potent synthetic opioids, no small soft and flexible epidural or pulmonary artery catheters, no forced-air warming blankets, no fiberoptic laryngoscopes, and so forth.* In addition, corporate funding has been central to our specialty in several ways. Young investigators have been trained while participating in corporate-sponsored projects, or by working in the laboratories of sponsored scientists, and many laboratories have been supported by the profits resulting from research contracts. Corporations have also been direct sponsors of basic and applied science and contribute large amounts of money to organizations such as the Foundation for Anesthesia Education and Research. This funding is critical in an era when many topics of interest to anesthesiologists are not supported by agencies such as the National Institutes of Health, and when funds derived from clinical practice are shrinking. Consider that fewer than 20% of the clinical investigations submitted to ANESTHESIOLOGY from US institutions in the past 6 months listed the US government as the source of support. Without commercial support, clinical and, to a lesser extent, laboratory research, in our specialty would be severely compromised.

As long as investigators and sponsors adhere to a set of commonsense guidelines, the relationship should be perfect. To bring a product to market—and to avoid subsequent legal entanglements—the sponsor needs accurate and unbiased data concerning the performance of the product. To obtain these data, laboratory tests and clinical trials need to be conducted. To be of value, these must be well designed and performed (*e.g.*, good analytical chemistry, humane animal use, truly informed consent, fair treatment of participants, appropriate group sizes, randomization, investigator blinding, reasonable control and comparison groups, and so on). None of this can be done without independent investigators; drug companies have limited resources and do not typically control hospitals and operating rooms. However, these investigators, who nearly always work within the academic system, have every reason to expect more than money for their involvement. They should have sufficient control to be certain that the study is executed in an appropriate manner and that the

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* We are aware of the role that physician-inventors had in many practice advances. However, corporate involvement in the refinement of these products, in gaining their approval by the Food and Drug Administration, and in their manufacture and distribution cannot be disputed.

data are appropriately analyzed and interpreted. They should also expect that the results of the trial be publishable in respected peer-reviewed journals. Finally, the journals and their readers need to trust that the described studies are well done, that they report work actually done by the authors, and that they accurately report and interpret the results. How else can the we have confidence that what is being published is of sufficient merit to justify a change in practice?

The problem is that this relationship can be abused or distorted. As the amount of money involved in drug development and marketing increases, the temptation on the part of companies to try to control the process of investigation can be strong. As researchers become more dependent on corporate sponsors to sustain their operations, the tendency to relinquish control or to slant interpretation of results can be just as strong. Contrary to popular belief, this bias is not usually the result of malevolence. A company that has invested hundreds of millions of dollars in a product or a manager who has devoted years of his or her life to its development may be honestly biased in the same way that a parent favors a child—they truly "believe" in their product and want it to succeed. The same can be said of investigators.

These pressures have already changed the corporate-academic-editorial relationship. It used to be that investigators would submit a proposal to a company that would be reviewed and a grant awarded. If a manuscript resulted, it typically included the notation "Supported in part by funds from XYZ." This usually well defined the relationship between the company and the scientist. Companies typically sponsored multiple studies by many independent investigators. Investigator-instigated research still occurs, but less frequently. Companies are now somewhat less interested in laboratory experiments (or perform them in their own facilities) and more interested in large, multiple-center trials, which have a greater potential to yield a definitive answer. These trials are often developed as a result of meetings between the company and the Food and Drug Administration—and the manufacturer approaches the investigator, rather than *vice versa*. In many cases, experienced researchers play a central role in protocol design and completely control the performance of the study, providing the sponsor with "the final product" at approximately the same time that the paper is submitted to a journal. In other cases, the sponsor may be deeply involved in not only design but also data collection, data analysis, interpretation, and even writing the manuscript. In still other cases, the sponsor and the investigator are the same. The physician perhaps is an owner or stockholder of the company or may have received so much funding for so long that their independence is unclear. Whatever the specific situation, the result is that the dividing line between sponsors and researchers is becoming blurred.

This puts a tremendous burden on journals and editors. Our goal is to provide readers with information that is as objective and unbiased as possible. A great deal of time and thought is devoted to this effort. However, while we can sometimes stop the worst examples from appearing, as in the case described by Dr. Cullen, it is virtually impossible for the editor or reviewers to accurately and consistently judge the degree of bias that an investigator might have, or the degree of control that the sponsors exercised over the work. We will also not reject what appears to be a well performed, reported, and interpreted study simply because of possible investigator bias; remember that he or she may be correct. We can reject studies based on flawed experiments and we can eliminate obviously biased statements or slanted conclusions from the manuscript. We can choose not to publish certain types of material altogether (which we specify here). Beyond this, we can only insist on the frank and open disclosure of the working relationships between companies and investigators.

This issue of the journal contains an example of what we mean by "disclosure." The article by Yarmush *et al.*[5] reports the results of a joint university-industry multiple-center project. The authors voluntarily included the statement that "the design and execution of this study, along with data collection and analysis, were performed in cooperation with members of Glaxo-Wellcome Inc., under the direction of Barbara Kirkhardt." Ms. Kirkhardt also appears as the third author of the paper, a position that the authors agreed fairly represented her degree of involvement. A second example is the article by Plattner *et al.*[6] that appeared in the April 1997 issue of ANESTHESIOLOGY. This work was conducted in the Thermoregulation Research Laboratory directed by Dr. Sessler, which as been supported by the US Public Health Service (National Institutes of Health) and by several companies. The article in question is clearly "basic clinical research." Nevertheless, the authors provided the editorial office with a complete list of private funding sources and the following statement, "Major corporate funding for the Thermoregulation Research Laboratory is provided by Abbott Inc., Augustine Medical, Inc., Apotheus Laboratories,

and Fairfield Medical Optics, Inc.," even though none of these companies directly supported the study or obviously benefited from it.

Based on these issues, we believe it is time for ANESTHESIOLOGY to reexamine its policies with respect to corporate-sponsored work. Specifically, we wish to present the following guidelines.

Sponsored Symposia

Much has been written about the problems associated with publishing the results of single-product symposia paid for directly or indirectly (*via* an educational grant) by the company that produces the product.[7-9] The problems far outweigh any possible advantages and the journal will maintain its policy of refusing to publish such sponsored single-drug symposia.

Authorship

The Guide for Authors contains the following statement: "Manuscripts are received with the understanding that they have been written by the authors; manuscripts drafted by anyone other than the listed authors are unacceptable." Further, "Manuscripts are also received with the understanding that all listed authors have participated in the design, execution, and/or analysis of the work presented and that all authors attest to the accuracy and validity of the contents. All persons or organizations involved in data collection or processing must be listed as authors or otherwise be clearly acknowledged." These statements do not mean that a paper cannot be prepared with the help of a nonauthor colleague (although this person should be acknowledged), nor does it mean that every author must have examined and personally redone the statistical analysis of the data from every patient. It does mean, however, that ghostwriters or unlisted "editorial assistants" are unacceptable. It also means that all authors have read the final manuscript in detail and that they have had the opportunity to examine, comment on, and edit it. It also means that the "raw" data have been made available to all authors well in advance of their seeing the final paper and that they have had a realistic chance to examine and question that material.

Corporate Sponsorship

The Guide for Authors now states "Authors must clearly define any funding sources supporting the submitted work. This must include all corporate sponsors, even if their support is indirect, *e.g.*, a local foundation that supported the project. The authors must disclose any commercial associations that might pose a conflict of interest in connection with the work submitted. Other associations such a consultancies, equity interests, or patent licensing arrangements should be noted at the time of submission." In a future Guide for Authors, this request for information will be further formalized.

Two comments are needed. First, departmental and private foundations are created for clear and sensible reasons, but they should not be used to conceal the relationship between an investigator and a sponsor(s). If a company provides large amounts of money to a foundation, which in turn supports an investigator's salary (or the salary of other involved personnel), purchases equipment used on a range of experiments, or simply pays the light bills in the laboratory for several years, then that company's contribution to that foundation should be noted, even if they are not the obvious, direct sponsors of a particular project. Companies making recent large contributions should also be noted. Second, the exact role of the sponsor should be defined. In many cases, the role may be nothing more than "supported in part by A." In others, such as that noted earlier, involvement is greater and should be accurately described.

Reviewers

Our editors and invited reviewers are subject to the same potential conflicts of interest and biases as our authors. It would be tempting to establish a policy saying that no submitted paper would be reviewed by anyone with any kind of conflict, real or potential. Unfortunately, this is impossible and unwise. There are rarely more than a handful of true experts in any particular area, and the best have been involved in sponsored research (because companies, like editors, try to seek out the best). If they were eliminated, we would be forced to turn to reviewers without the needed expertise—which would hardly benefit the journal or its readers. Nevertheless, we strive to avoid obvious conflicts. All of our editors have submitted formal conflict of interest statements to the editorial office. All reviewers are asked to answer a series of "conflict" questions that accompany each manuscript sent for review, and our office is compiling a database of the responses.

Reviewers receiving corporate sponsorship will continue as reviewers (unless it is discovered that they have failed to disclose their conflicts), but the editor-in-chief will consider their potential biases before any editorial decisions are made. The present editor-in-chief will also make every effort to avoid any personal form of corporate involvement that might influence (or appear to influence) his judgment.

This journal does not wish to discourage the working relationship between researchers and manufacturers. Both play an indispensable role in bringing new drugs and devices into practice. Neither can function without the other. However, great mischief can result from the relationship.[10] The "rules" just noted cannot solve all of our problems and obviously cannot prevent authors or sponsors from intentionally concealing important relationships (although we will try to remain vigilant). But we believe that editors, reviewers, and, most importantly, our readers have a right to know about the relationships that may influence the conduct or interpretation of important research. ANESTHESIOLOGY will do its best to provide this information. From that point forward, it is up to our readers to critically evaluate what they read and to draw their own conclusions.

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The Pharmacokinetics of Intravenous Fluids

This original research publication presents a new and innovative application of pharmacokinetic data analysis, usually applied to drug disposition, to the physiologic effects of parenteral intravenous fluid administration. In classical pharmacokinetic data analysis, a drug is administered, blood is sampled, and drug concentrations are measured over time. Pharmacokinetic models, usually mamillary with first-order kinetics, are fit to the measured drug concentrations using nonlinear least-squares regression. The data analysis estimates drug volumes and clearances that characterize the extent of drug distribution into body tissues and the rate of drug movement between tissues and removal from the body. Drs. Svensen and Hahn have examined the pharmacokinetics of the intravenous administration of Ringer's acetate, 6% dextran, and 7.5% NaCl using the dilution of three markers in blood, blood hemoglobin, blood water, and plasma albumin, analogous to the measurement

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