The Dunlop-Dottridge Lecture

Presented at the 2002 Annual Meeting of the Canadian Rheumatology Association in Lake Louise, Canada, February 23, 2003

Medical Publication Ethics

***Sir Humphrey*: I need to know everything! How else can I judge whether or not I need to know it?**
***Bernard Woolley*: So that means you need to know things even when you don't need to know...and if you don't need to know you still need to know, so that you know there is no need to know.**

In the BBC television series "Yes, Minister," when Sir Humphrey Appleby tells his deputy, Woolley, "I need to know everything!," you might ask how much should we rheumatologists know about medical publication ethics. Certainly, we do not need to know everything, but we should be aware that publications like *The Journal of Rheumatology* are an integral part of the medical discovery cycle (Figure 1)[1]. As such we participate in a process with ethical implications. Thus, we need to ensure that what we publish does the right thing. We owe this to our patients and to society.

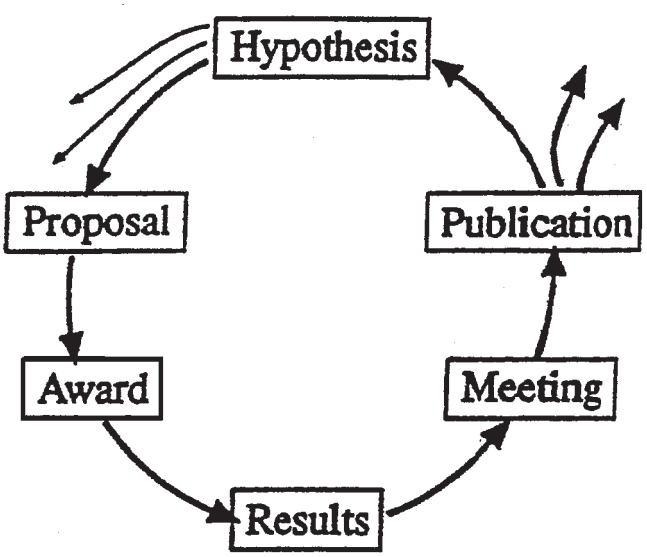

Figure 1. The medical discovery cycle. From Gordon DA, Tokyo: Churchill-Livingston; 1992:457-60[1], with permission.

About 2 decades ago Arthur Hailey in his book *Strong Medicine*[2] told a story dealing with ethical issues related to the role of academic medicine and the pharmaceutical industry in the discovery of life-saving medicines, their side effects, and a description of misconduct on the part of the scientific, corporate, and regulatory world. The dilemma of the story arises when the plucky heroine, a veteran pharmaceutical executive, resigns rather than approving a drug whose safety she questions. A self-serving medical director, however, wins approval for its use by blackmailing a US FDA official. As she feared, the drug proves dangerous, a political scandal erupts, and she is invited to return as company president. At a time when industry was not such a dominant research player the story resolves as she establishes company guidelines for a more ethical climate to approve and market safer medication. Today Hailey's book could serve as a model for analysis of medical publication ethics, complete with a prologue, a broad cast of characters, perspectives on their behavior, and an epilogue.

THE PROLOGUE

In the words of George Lundberg, former editor of *JAMA,* the purpose of medical publications is to "shed light, give heat, and take heat."[3] Because society is becoming more dependent on technology, we need more transparency in the conduct, sponsorship, and publication of scientific advances. If the public is to trust us, we need to keep earning that trust by how we behave, and are seen to behave.

THE CHARACTERS

In 1978, a small group of general medical journal editors, now the International Committee of Medical Journal Editors (ICMJE), met informally in Vancouver and established a uniform set of requirements for manuscripts submitted to journals like *The Journal of Rheumatology*[4]. These guidelines describe manuscript submission criteria, including a uniform format for bibliographic references, as well as issues ranging from authorship to conflict of interest and duplicate publication.

Authorship. In the past decade the number of authors of any paper has increased dramatically. It is not uncommon for editors to see a single case report listing many authors. And examples of ghost writing by pharmaceutical company writers along with "guest authorship" is suspect[5]. Because of these concerns the Vancouver group, now known as the ICMJE, in their update of May 2000, addressed authorship accountability[6]. They stated that credit should only apply to:

(1) Substantial contribution to conception, design, or acquisition of data or analysis and interpretation of it; (2) drafting the article or revising it for important intellectual content, and (3) approval of the final version. Conditions 1, 2 and 3 all had to be met, while the acquisition of funding, collection of data, and general supervision of the research group in itself was not considered sufficient to justify authorship[6]. These latter contributions are best recognized in the Acknowledgments section of the manuscript. While we ask corresponding authors to ensure their colleagues meet criteria for authorship, many journals now ask authors to state their precise role in the preparation of their manuscript in accordance with the ICMJE. How this requirement affects the overall quality of the manuscript and whether it will inhibit questionable authorship is uncertain.

In 1984 *The New England Journal of Medicine* (NEJM) became the first major medical journal to require authors to disclose financial ties with industry relating to products studied in submitted manuscripts. With closer relationships between academia and the pharmaceutical industry over time, it was suggested in some quarters that academic medicine had become a saleable commodity[7]. Thus, in response to these increasing tensions at the academic-industrial interface, the Vancouver group noted in 2001 that because the publication of clinical research findings in peer-reviewed journals was fundamental for most treatment decisions, authors should disclose details of their own and their sponsor's role in any study[8]. The idea was to improve scientific objectivity with reduced commercial interference.

The implementation of these regulations will see authors not only describe their role, but disclose their financial ties as well. It is interesting to speculate how well these guidelines will be followed and how they might affect authors' competition with scientific and commercial rivals. Ideally they should provide the public with more transparency in understanding research and publication biases.

In response to these new regulations, Allan Holmer, representing pharmaceutical manufacturers, commented that, while the integrity of industry was questioned by the Vancouver group, that of academic investigators was taken for granted[9]. This despite the fact that sponsors of trials did most of the real work. The distinguished former editor of the NEJM, Arnold Relman, however, replied that these new regulations were not strong enough because authors should always have complete control over the conduct and interpretation of any clinical trial data, independent of the sponsor[10]. In his view a minimal requirement was "that the authors of a paper about a sponsored clinical trial have the same responsibility for the work as the authors of any other published research." Such a statement was missing from the updated requirements of 2001[10].

John Geddes of the University of Oxford added that "rather than being targeted primarily at meeting the demands of the regulatory authorities, sponsored studies should aim to produce above all reliable, clinically useful estimates of the effects of the treatments."[11] In other words, investigations with a commercial motive should be counterbalanced by more research support from government agencies and independent private groups.

Stimulated by these issues, a Canadian group in their essay "Dancing with the Porcupine" expressed the view that research based on academic expectations was to "seek truth," whereas for industry, the prime motive "is to make money for their shareholders."[12] Their oversimplification served as the basis for a proposed set of rules for governing university-industrial relationships. These were devised in the form of a contract that would enshrine rights such as immediate disclosure of harmful clinical effects by investigators, guidelines to determine the "intellectual originality" of the research, and a certification and rating system with binding agreements. The contract would also include registration of all trials and require a written debriefing at the conclusion of every agreement.

The introduction of new biologic therapies in rheumatology has also presented ethical challenges for which Doig and Kinsella in their *Journal* editorial provided a framework[13]. They noted that the physician-patient relationship is always biased in favor of the physician. The shortcomings of informed consent for short term trials were one thing, but longer trials presented greater challenges to institutional review boards. These authors also anticipated that commercial interests might lead sponsors to attempt withholding information to patients about adverse drug effects. They also cited cases of researchers being intimidated by a variety of special interest groups leading to unwarranted interference[14]. And they called for better mechanisms for independent monitoring. Like the Vancouver group they envisioned the protective effect of research ethics as part of any trials process.

With the growth of new drugs, the pharmaceutical industry has difficulty finding enough patients for clinical trials and has to seek the help of marketing professionals to find patients. Traditionally, clinicians have recruited patients from their own and colleagues' practices, but now the complexities of conducting trials to meet regulatory requirements have led to the development of contract research organizations, and with them, more ethical challenges.

The development of clinical practice guidelines is another example of the relationship between authors of these guidelines and the pharmaceutical industry. Choudhry, *et al* reported that 87% of authors of these guidelines had some form of interaction with industry, 58% had received financial support to perform research, and 38% had served as employees or consultants for industry[15]. Moreover, 55% of these authors were involved in establishing practice guidelines without any disclosure process in place. Detsky said that these conflicts should be discussed before guidelines were developed, and he also proposed that authors

should be forbidden from holding an equity position in the sponsor company. Nevertheless, conflict appears to be inescapable because most of the best qualified investigators are the ones with the most trial experience.

The NEJM recently stated that it could not find enough experts without financial ties to industry to write editorials or review articles[16]. For this reason they have relaxed their conflict of interest rules to no longer exclude such authors. However, Kassirer feels that "readers must be able to trust that authors' opinions … are not unduly tainted."[17] These concerns were echoed by Relman, who writes that "Editors are on safer ground when they prohibit such conflicts of interest altogether, rather than attempt to manage them by establishing flexible guidelines and negotiating with authors."[18]

In 2001 Krimsky and Rothenberg reported that while almost 50% of American medical journals had conflict of interest policies and many now ask for a conflict of interest disclosure statement, the rates of disclosure were very low, reflecting either poor compliance or a low rate of financial conflicts[19]. The former possibility seems more likely, particularly if authors are reluctant to reveal their sources of support to their academic and commercial rivals.

Recently, Levinsky has drawn attention to non-financial conflict of interest by investigators related to safety of research subjects[20]. Here academic self-interest and career ambition of the investigator has endangered lives. The management of this misconduct is not a publication issue *per se*, but something for the ethics committees of research institutions to deal with *before* publication. To quote Levinsky: "Ultimately, however, the covenant with research subjects and with society relies on the ethical attitudes of individual investigators with the support of standards set by institutional leaders and by government."

On occasion authors have submitted the same material to different journals, so-called duplicate publication. For example, 3 papers from one center with the same authors reported effectiveness of a new agent using data from the same control group as if each was a separate study[5]. At *The Journal of Rheumatology*, our editorial board has also experienced occasions where the reviewers, whom we frequently share with other rheumatology journals, drew attention to duplicate publication. In each case these irregularities were dealt with in collaboration with the editors of our colleague journals and the papers were rejected.

The editor of the *British Medical Journal,* Richard Smith, however, has expressed the view that there was no problem with duplicate publication as long as it was openly acknowledged and the author's permission obtained[21].

BEHAVIOR OF THE CHARACTERS

Peer review. This process is as fallible as it is human, but like democracy, it's the best we have. The selection of manuscript reviewers obviously depends on the topic of the manuscript. In the case of *The Journal of Rheumatology,* reviewers are drawn from members of our editorial board, and the authors cited in the bibliographic reference list are almost always considered. In our case authors are encouraged to suggest the names of 3 or 4 persons who might be considered suitable reviewers of their work. At the same time it is not unusual for authors to provide the names of certain reviewers whom they do not consider suitable because of conflict of interest. The final decision on selecting reviewers, however, rests with our editorial committee.

Generally speaking, an anonymous peer-review system seems best at present. This allows for a more candid assessment. However, one study showed that blinding reviewers' names to the authors or revealing their identity made no significant difference in the quality of recommendations or time taken to review[22].

Misconduct. As with authors, the question of conflict of interest on the part of reviewers is real and they are asked to decline participating if they feel uncomfortable doing so. This occurs when the reviewer or editor has professional, commercial, or personal ties that could influence his or her judgment. Examples of conflict include financial ones with industry, or those with friends and relatives. More often conflict is related to scholarly passion or rivalry with other groups. Reviewers are always asked to respect the confidentiality of the review process. In some instances reviewers have delayed their review for competitive reasons or plagiarized material. In one famous example an assistant professor of medicine was asked by his superior to review a manuscript sent to the NEJM[23]. Subsequently, the reviewer and his chief published an article on the same topic plagiarizing parts of the manuscript previously reviewed.

Examples of misconduct can be categorized as what might be referred to as "soft" as opposed to "hard" fraud. The former includes publications containing duplicate material without disclosure. A famous example of the latter type involves the case of an immunologist in New York who faked a demonstration of tolerance of skin grafting from a black mouse onto a white one by darkening transplanted skin patches in white mice with a black felt tip pen[23]. Another spectacular example of persistent cheating involved cardiology researcher John Darsee who published over 100 papers based on extensive fabrication and falsification of data while working at 3 different institutions until he was exposed while working at Harvard[23].

These examples illustrate Stephen Lock's words that "Fraud and misconduct in medical research arises when behavior by a researcher, intentional or not, falls short of good ethical and scientific standards."[23]

In 1997 a committee on publication ethics (COPE) was formed by a group of European editors struggling with cases of publication misconduct[23,24]. There was dissatisfaction with the usual response of rejecting a manuscript when there

was clear evidence of bad behavior. Examples of a Scandinavian experience outlined misconduct in Danish scientific publications from 1993 to 1997 (Table 1)[25]. Based on this experience the question of sanctions arose, but because reputations were at stake, there was need for due process before cases could be dealt with fairly. Based on this misconduct, guidelines were proposed that extended from simple rejection of the paper to notification of the institution where the work was performed and forbidding the authors from publishing for a defined period (Table 2)[26].

Table 1. Issues of misconduct in Danish scientific publications[24].

	Year					
	93	94	95	96	97	Total
Cases	15	5	2	10	9	41
Authorship issues						10
Suppression of unwanted data						4
Unauthorized use of data						4
Plagiarism						3
False descriptions of method						3
Distorted statistics/conclusion						2
Theft of data						2
Construction of data						2

Table 2. Proposed duplicate submission/publication guidelines[25].

Process
Notify the editor of the other involved journal
Send both manuscripts to the same reviewers to assess whether they are essentially the same, if the duplication is discovered during the review process
Contact the authors and ask them to explain
Penalty
Reject both manuscripts
Disallow any of the authors from submitting any manuscript to either journal for 3–5 years
Notify the Chair of the Department or Dean of the involved institution of this unethical behavior
If a published article is later found to be redundant, publish a notice to that effect in the journal and follow the same guidelines for punishment

Although COPE was set up to deal with breaches of research and publication ethics, The Office of Research Integrity in the Public Health and Science, US Department of Health and Human Services also provided guidance for editors in January 2000[27]. Their recommended first response to scientific misconduct was to publish a retraction. However, the view was expressed that editors were not ultimately responsible for conducting a full investigation or deciding whether scientific misconduct had occurred. Those responsibilities rest with the institution where the work was conducted or with the funding agency. However none of these processes appear foolproof because we have seen recent examples of institutions turning a blind eye to misconduct[28].

Other possibilities for dealing with misconduct include correction and retraction, and Richard Horton editor of *The Lancet* has proposed a category he termed "withdrawal of aegis." By this he meant an erasure of the publication after it has been determined that the published material was proven erroneous. Another concern arises when physicians who have committed crimes are honored by having their names applied to clinical syndromes. An example is the eponymous distinction of Reiter's syndrome given to a war criminal[29].

Editorial process. Ultimately manuscript review depends on good will and responsible behavior in arriving at fair judgment of manuscripts. In the case of *The Journal of Rheumatology* editorial decisions are based on the results of reviewers' comments and deliberations by an editorial committee. The decisions can involve outright acceptance or rejection, acceptance with revision, or reconsideration after re-review. The latter category is most problematic because it implies either a tentative acceptance or rejection. In every case these manuscripts are sent back to reviewers for at least a second look before a final decision is made.

Copy editing is a valuable editorial function that serves to eliminate "word bloat," or the use of words like "methodology" for "methods"[30]. Sometimes copy editors make changes that cloud rather than clarify meanings. For this reason authors should review their page proofs carefully to detect any uncalled-for alterations from their original intent.

Editorial independence. Other editorial problems arise when medicine and politics are mingled. A good example related to the Clinton presidency was a January 1999 article in *JAMA* from the Kinsey Institute of Indiana University, which reported that undergraduate populations of students attending a state university in Midwest America held widely divergent opinions about what behaviors do and do not constitute having "had sex"[31]. In this case Dr. E.R. Anderson, the Executive Vice-President of the American Medical Association, took action to remove Dr. George Lundberg, the distinguished longtime editor of JAMA, not because he objected to the content of the paper, but because its accelerated publication "focused on sensationalism here, not Science."[32]

The response of Dr. John Hoey and colleagues at the CMAJ recalled the ICMJE documentation that editorial freedom meant "full authority for determining the editorial content of the journal without presuming to define the scope of legitimate content. To do so would be to put shackles on free inquiry. Medical journals are not the repository of absolute truth, but when they foster curiosity and debate they have some hope of approaching it."[33] Dr. Floyd Bloom, Editor of *Science*, noted that editors must be "free to navigate the editorial path … without editorial independence there will be little content worthy of distillation into new knowledge."[34]

The subsequent departure of Dr. Jerry Kassirer as Editor of *The NEJM* represents another example of editorial jeop-

ardy after conflict with the proprietors of the journal. As press critic A.J. Liebling once asked: "Why should freedom of the press belong only to those who own one?" Surely ethical medical journalism depends on the free flow of ideas, disagreement, and debate.

THE EPILOGUE

Despite an awareness of the medical publication ethics story, the question arises whether better guidelines for publications such as *The Journal of Rheumatology* are feasible. Just as our manuscript review process has all the frailty of a human exercise, so too does the entire challenge of ensuring best practice of publication ethics. Without an awareness of several outstanding issues, however, it is impossible to suggest improvements (Table 3).

Table 3. Outstanding issues.

• Universal conflict
• Integrity of disclosure
• Transparency of process
• Bureaucratic barriers

The issues involving all of us in medical publication relate to conflict of interest, disclosure, and the credibility of our review process. All of the characters in our story — authors, reviewers, editors, sponsors, and readers alike — face conflict of interest from their own competing interests. As such, we all wear many hats and hold different biases that are inescapable, whether conscious or not. Full disclosure of these conflicts is fundamental to earning public trust. Too often, however, the presence of conflict is unseen because it is not actively sought from our editorial community. Related to this is transparency of the trial design process that is compounded by the complexity of the statistical examination of data.

Because of intrinsic imperfections in this process institutions, sponsors, regulatory bodies, and medical journals have established guidelines to ensure greater integrity[35]. Proposals to define rules governing the university-industrial relationship have been embodied in a standard contract that would define the relationship between authors, institutions, and sponsors to determine what is legitimate "academic activity."[12] This would also include mandatory certification for participants, and a rating system to ensure accountability. At the University of Toronto, David Naylor, Dean of the Faculty of Medicine, and a working group have approached these challenges by establishing 4 principles to guide negotiation of research contracts[36]. First, to forbid censorship and confidentiality restrictions by the sponsors. Second, to ensure that investigators are free to submit work for publication within 6 months of sharing their findings with a sponsor. Third, to guarantee researchers the right to disclose immediately any safety concerns that arise during the study. And finally, to establish a mechanism for dispute resolution of issues between investigator and sponsors.

Attention has also been drawn to serious concern for the safety of clinical trial subjects. In one case the death of an 18-year-old in a gene transfer trial of the University of Pennsylvania involved substantial financial interest for the university and the institution[37]. The deaths of 3 other research volunteers at Johns Hopkins did not involve financial conflicts, but several research institutions have adopted proactive policies that restrict the conduct of clinical research by faculty with financial ties to the sponsor[38]. All of these concerns and their possible solutions constitute work in progress, which at present we seem to be dealing with in piecemeal fashion.

Whether it will ever be possible to solve these questions comprehensively is debatable. Above all, however, we need to foster more open discussion to promote and explain our journal policies while providing a forum for sharing collective observations and experiences. In our efforts to improve things we should try to avoid bureaucratic strait-jackets, keeping in mind the words of communication theorist Marshall McLuhan: "We shape our tools and thereafter our tools shape us."

DUNCAN A. GORDON, MD,
Editor, *The Journal of Rheumatology*,
920 Yonge Street, Ste. 115,
Toronto, Canada M4W 3C7

Address reprint requests to The Journal of Rheumatology.

ACKNOWLEDGMENT

The author thanks Robert Inman, John Hoey, Yvonne Pigott, and Murray Urowitz for help in the preparation of this report.

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