SCIENTIFIC JOURNALS AND THEIR AUTHORS' FINANCIAL INTERESTS

A Pilot Study

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1. INTRODUCTION

As post World War II science has flourished it was accompanied by an exponential growth in journals. In recent years, the credibility of scientific publications, particularly in the biomedical fields, has been challenged by the perception of financial conflicts of interest involving both scientists and their academic institutions. Woolf, a sociologist of science, has summarized the problem:

> In modern science the disinterestedness of scientists has been linked to their objectivity and thus to the reliability of their research. Although most people recognize that scientists are unlikely to be completely neutral with respect to their studies, they are skeptical about scientists who appear as advocates for certain positions rather than as objective presenters of fact [citation]. In several allegations of research misconduct, there have been charges that apparent financial conflicts of interest have distorted the knowledge base on which other decisions depend (Woolf 1994, 90)

Many of the financial interests thought to be in conflict with investigator objectivity appear to have been catalyzed by increasing relationships between univer-

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sities and industry, particularly biotechnology firms. In the United States, at least, several studies (Blumenthal 1986; Blumenthal 1996; Krimsky 1991) have documented the increasing importance of such relationships for both groups, and that a significant number of faculty working in the life sciences at leading US universities are involved. This phenomenon has also been noted in European, especially British, universities (Spier 1995).

In a nonbinding decision, the International Committee of Medical Journal Editors (ICMJE), a small, voluntary nonrepresentative group of medical journal editors with no invested authority, has twice recommended that editors and authors address these issues: first in a resolution that urged authors to acknowledge any financial relationships that "may pose a conflict of interest" (International Committee of Medical Journal Editors 1993); and later in a resolution addressed to editors which suggested that "[p]ublished articles and letters should include a description of all financial support and any conflict of interest that, in the editors' judgment, readers should know about" (International Committee of Medical Journal Editors 1997).

In an effort to discern the scale of the problem of author financial interest in publications and the degree to which leading biomedical and scientific journals were following the ICMJE recommendations for disclosure of relevant financial interests of authors, we undertook a pilot study.

2. PILOT STUDY

The purpose of this pilot study was to measure the frequency of one set of verifiable "financial interests" (as defined for this study) in the subject matter of the articles published in 14 scientific journals that are linked to the principal authors of those articles. The objectives of the study were: (1) to select a set of published articles and observe the degree to which a sample of authors hold a financial interest in areas related to their research that are reportable under current standards; and (2) to examine the hypothesis that significant numbers of authors of articles in life science and biomedical journals have verifiable financial interests that might be important for journal editors, reviewers and readers to know.

These objectives were applied to a pilot study of academic scientists in the state of Massachusetts, USA, who were cited as first or last author in at least one article published during 1992 in 14 leading journals of cell and molecular biology and medicine. The State of Massachusetts was chosen for the pilot study because it has significant biomedical activity, is the home of many new biotechnology start-up companies, and has strong academic institutions (including Harvard University and the Massachusetts Institute of Technology) with faculty that are likely to be involved with the biotechnology industry.

To achieve these objectives we first adopted an indicator of "possessing a financial interest" (based on recent US policy guidelines) that applies to scientific authors. Second, we constructed a database of every article published in 1992 by 14 leading life science and biomedical journals (n = 10,148) that had a first or last author whose affiliated institution was located in Massachusetts (n = 811). Third, we applied the indicator to determine the frequency in which authors and articles satisfied the condition of "possessing a financial interest." Fourth, we examined the articles for any disclosure of financial interest.

2.1. Indicator of Possessing a Financial Interest

For this study a scientific author is said to possess a financial interest in his/her published work if he/she meets one of the following conditions. (1) holds a membership on a scientific advisory board of a company that develops products related to the scientist's expertise; (2) is listed as an inventor on a patent or patent application for a product or process closely related to the scientist's publication under review; (3) serves as an officer, director, or major shareholder in a for-profit corporation involved in commercial activities related to the scientist's field of expertise. This indicator is not meant to exhaust the meanings of "possessing a financial interest." Other possible criteria include personal and familial investment holdings, consultantships, and honoraria. We took these criteria from those adopted in regulations by the US Public Health Service in 1995 to address conflicts of interest in governmentally-funded research, including that of the National Institutes of Health (US Department of Health and Human Services 1995). Note that many scientists have consulting relationships with biotechnology firms which are not in the form of membership on scientific advisory boards, but because we did not have data to independently verify these relationships, these financial interests were not included as indicators in this pilot study.

2.2. Scientists as Advisers to Companies

We utilized two data sets: 1) Massachusetts biotechnology firms including their officers and scientific advisory boards (SABs), and 2) scientists listed as inventors on patents or patent applications registered in the World Intellectual Property Organization (WIPO). The methodology for developing an inventory of scientific advisory boards (SAB) for a population of companies was adapted from Krimsky *et al.* (Krimsky 1991).

An inventory of Massachusetts biotechnology firms was developed in two stages. First, a comprehensive list of firms was derived from the following sources: (1) Krimsky *et al.* (Krimsky 1991) data base; (2) the 1994 Massachusetts Biotechnology Council membership list; (3) The Genetic Engineering News Guide to Biotechnology Companies (Genetic Engineering News 1994), and (4) an inventory of Massachusetts biotechnology companies prepared in June 1993 by Lyndon Lien for the Biotechnology Center of Excellence Corporation, Boston, Massachusetts. We found a total of 149 biotechnology companies (i.e., the comprehensive list with a Massachusetts address derived from the four sources).

Second, a subset of the comprehensive list (i.e., the dedicated list) was compiled by selecting from the comprehensive list those companies that utilize genetic or cellular techniques to manipulate genes or organisms, that work with genes or proteins, or that use cells to clone genes or reagents. Excluded from the dedicated list were those firms that are primarily instrument manufacturers or that engage in large scale fermentation from source materials provided by another company. The list of dedicated Massachusetts biotechnology companies (DMBC) consists of 84 entries. SABs and company officers were obtained from DMBCs through a variety of sources including corporate annual reports and governmentally-mandated financial disclosure statements of public companies. Corporations that are not required to file periodic reports with the US Securities and Exchange Commission were surveyed by letter and phone. Using this method we compiled a list of 370 unique scientists on SABs of Massachusetts firms.

2.3. Author Data Base

To select our study population of journal authors against which to apply our indicator "possessing a financial interest," we chose a base year of 1992 and 14 leading journals in cellular and molecular biology, and medicine. We chose 1992 because it was the most recent year for which complete patent information could be obtained from the WIPO (the information becomes public 18 months after filing), it coincided with available information on SABs and it was a year that saw considerable commercial activity in biotechnology and a heightened discussion about conflict of interest.

The 14 English-language scientific journals were chosen as a representative sample of the leading biologically-oriented science and biomedical journals based on the 1993 journal impact factors calculated by the Institute for Scientific Information (ISI) (Institute for Scientific Information 1993). The 'journal impact factor' has been defined by the ISI as 'a measure of the frequency with which the "average article" has been cited in a particular year.' We sought journals that were publishing articles of potential commercial interest to biotechnology and biopharmaceutical firms, both in the clinical and basic sciences.

The journals selected (and their ISI impact factors) represented the subject categories of the general sciences: Nature (22.139), Science (20.967), and the Proceedings of the National Academy of Sciences (10.480); biochemistry and molecular biology: Cell (33.617), EMBO Journal (12.634), Journal of Cell Biology (11.118), Molecular and Cellular Biology (8.291), Journal of Biological Chemistry (6.733), and Plant Cell (6.342); genetics and heredity: Genes & Development (14.270) and American Journal of Human Genetics (9.076); and general and internal medicine: New England Journal of Medicine (24.455) and Lancet (15.940). A new genetics journal, which only began publishing in 1992 and produced only 9 issues that year, Nature Genetics, was not rated by ISI but was included on the basis of its subsequent reputation.

From the original research articles appearing in these journals in the subject areas of cellular and molecular biology and genetics (n = 10,148) we selected a subset of those articles on the criteria that either the first or last author was affiliated with a Massachusetts nonprofit academic or research institution (812 articles or 8.0% of the original set).

We chose first and last authors to set boundaries on the size of the author database while insuring that it included the significant contributors to the research publications. We assumed that one or both of these authors would likely have had primary authorship responsibility, as is the common practice in the biological sciences for multiple-authored papers. The number of unique Massachusetts-based authors derived from the screening criteria was 1,150. The total number of authors on all articles screened is likely 5–6 times larger than that figure of 1,150. As expected, many of these authors were listed on multiple papers. In our analysis we deleted from the reference group 45 authors who listed a Massachusetts biotechnology company as their address since that constitutes a disclosure of financial affiliation. This left 1,105 authors who gave as their affiliation a nonprofit academic or research institution identified with 789 articles.

2.4. Patent Applications and Patents Issued

One of the objectives of the study was to determine the percentage of authors who were listed as inventors on patent applications or were issued patents on products or processes that closely resemble the content of their scientific papers. In this respect, the inventorship status on a patent/patent application meets one of the criteria for possess-

ing a financial interest. Patent applications filed in the US Patent and Trade-mark Office in Washington remain confidential until the date they are issued as patents, a process which can take 2–3 years or longer. Thus, at the time of the study, the patent application system in the United States was essentially a secret one, and there were no industry or academic databases containing information on filed US patent applications. Therefore, we chose to review the patent applications of US origin filed under the Patent Cooperation Treaty (PCT), which was signed in 1970 and came into effect in June 1978 under the supervision of the World Intellectual Property Organization (WIPO) in Geneva. Under the terms of the treaty, WIPO is required to publish the patent applications it receives exactly 18 months following the date of their submission to the US Patent and Trademark Office. Using the PCT filings, we were able to identify the patent applications of US origin on which authors were listed as inventors, which are otherwise required by law to be treated as confidential information by the Patent Office.

We matched the list of authors selected from the 14 journals with WIPO-listed patents and patent applications for the base year 1992. The WIPO information was available on PCT Patent Search, a CD-Rom available from MicroPatent in East Haven, Connecticut and Cambridge, England.

We checked every author in the author database against the names of inventors on patent applications and patents listed on PCT Patent Search. Then we screened for those patent applications listing the relevant author's name as an inventor that had a close relationship with the author's journal article. All 4 members of the study team reviewed the match between the subject matter of the patent and the subject matter of the journal article.

One of these reviewers (G.K.), a scientist with extensive university intellectual property and technology transfer experience, served as the final arbiter of whether the patent application was indeed based on the research article in question. This process relied on the frequent similarity in tables and graphs used in both articles and patent applications, as well as a non-mechanistic visual search for similarity of language in the examples used to describe processes and findings. We reviewed the abstracts of patent applications for a match, and, in certain circumstances, obtained the full text of the applications in order to resolve uncertainties.

2.5. Corporate Officers, Directors or Major Shareholders

To identify authors who are officers, directors or major shareholders of biotechnology companies, we used a database of information on public corporations created by analyzing filings with the US Securities and Exchange Commission (SEC). The database titled Compact D/SEC (1995) is owned by Disclosure, Inc., Bethesda, Maryland, and is updated quarterly from July 1990. About 50 percent of the biotechnology firms in Massachusetts, and the overwhelming majority of biotechnology firms in the United States, are privately held, and therefore are not required to report information to the SEC. For other sources of information on private companies, we used surveys, news reports, and published materials from companies, but this information was very spotty and largely unhelpful.

2.6. Results

From the 1,105 journal authors we found that 112 or 10.1% were listed as inventors on patents or patent applications on file with the WIPO that correlated with

published articles in our study sample. There were 69 authors that were SAB members in Massachusetts biotechnology companies (6.2%). There were 15 authors who serve as company officers, directors or major shareholders (1.4%). The frequency with which an author who does not give a firm affiliation is associated with one or more of the three categories of financial interest is given by the union of the three sets which have overlapping members. This condition is satisfied by 169 authors, which indicates that 15.3% of the author population had at least one financial interest in their published articles.

We also calculated the probability that an article selected from the reference population (n = 789) has one of its lead authors identified with one or more of the three categories of financial interest. Twenty percent have a lead author on a Massachusetts SAB of a biotechnology company (n = 160); 7% have a lead author who served as an officer or major shareholder in a biotechnology company (n = 57); 22% have a lead author who is listed as an inventor in a patent or patent application closely correlated with a publication in our study sample (n = 175). Thirty-four percent of the articles in our study sample (n = 789) meet one of the three criteria satisfying the condition of having at least one lead author with a financial interest (n = 267).

After reviewing the 267 articles identified as having a lead author (first or last) with at least one financial interest closely related to their publication, we could find no statements of disclosure for any of the three indicators of financial interest linked to a lead author who gave an academic affiliation. There was a disclosure of stock ownership in one article in the New England Journal of Medicine but the authors cited were identified as employees of the corporation in which they held stock and were deleted from our analysis.

Patent applications are often filed as an afterthought by universities and research institutions that own the patent rights and require researchers to disclose their inventions in order that these institutions might benefit from successful technology transfer. The US federal and state governments, to the extent that they have research laboratories, are doing exactly the same thing, and the US Congress and state legislatures are encouraging such activities, public and private, to spur economic development.

3. LIMITATIONS OF DATA

3.1. Scientific Advisory Board Membership and Corporate Officers/Significant Shareholders

Our database included active SABs only, but occasionally members do cycle off. Membership data on SABs obtained from company reports and government-mandated documents do not stipulate the dates a person begins or terminates service on the board. Because our SAB data were collected in 1994 for companies founded up until 1992 and because SABs do not change very frequently, we felt it was reasonable to assume that the scientific advisers we identified in 1994 were active in companies that existed in 1992. However, our assumption may not be correct.

Our inventory of SABs was based on Massachusetts companies because we had access to the most complete information on SAB membership in that state. It seems likely that the profile of academic industry ties found in Massachusetts is similar to that in other biotechnology rich states that contain high concentrations of academic researchers such as California, New York, Maryland, New Jersey and perhaps Texas. However,

without a national study of financial interests in publications or other state profiles, it is premature to extrapolate these results to other parts of the United States or to other countries. Because some Massachusetts scientists are on the SABs of out-of-state US companies or international biotechnology companies, our data undercount the corporate SAB affiliation of journal authors. Also, three private companies in Massachusetts declined to report their SAB composition.

A national data set of company officers, directors and major shareholders (beneficial owner of 10% or more of stock issued) was used to identify journal authors who have a university affiliation and fall into one of those categories. However, this database only applies to public corporations, which comprise about 50% of our Massachusetts firm population but a much smaller percentage of all biotechnology companies in the United States. Thus, our sources underestimate the number of academic faculty who are corporate officers, directors or major shareholders. Because the number of such corporate affiliations among academic faculty in our sample is small (n = 15) compared to patent/patent application inventors and SAB members, undercounting in this category is unlikely to impact the outcome significantly.

In general, our data underestimate financial interest because we only considered three factors in measuring it. Other circumstances such as personal or family stock holdings and consulting relationships would drive up the number of authors with financial interests. In addition we were not able to assess financial interest in privately-held biotechnology companies which are not required to report their data to public agencies. Nor did we have access to data that would identify academic consultants to biotechnology companies who are more likely to have technical interactions with client companies than are scientific advisory board members. Furthermore, we were unable to document scientist-authors who received unexercised stock options from biotechnology companies or who purchased company stock in open markets. Finally, we had no way of determining whether the companies on whose SABs any authors in this study were serving intended to exploit commercially the content of the authors' papers. Thus SAB membership, by itself, may not be a useful indicator of financial interest when examining published manuscripts.

3.2. Author Designation

It is possible that some authors listed between the first and the last are scientists who hold financial interests of the type we are seeking to document. By limiting our analysis to first- and last-named authors, we could have underestimated the presence of such interests for any article's set of authors.

3.3. Patent Applications and Patents

Patents or patent applications of US origin but not filed under the PCT would not show up in our data set, and thus patent inventorships among scientists in our study may be underreported.

The degree to which academic scientists are being listed as inventors on patents for biological materials and processes, and becoming eligible for royalties on successfully commercialized products or techniques, introduces an important new source of financial interest among life science and biomedical authors, but this reality must be placed in some context. Under US university policies, faculty scientist-inventors themselves receive only a portion (often one-third) of royalty income from patents on their inventions. For

most authors, the professional status they receive from publications is far more important than any financial interest they may realize from their research results.

3.4. Relevance of Financial Interests to Published Research

Financial interests of some kind may be inescapable to researchers and universities in the late 20th century, and the mere existence of a financial interest in no way establishes a "conflict of interest" or automatically makes questionable the data and conclusions presented. It is the appearance of a potential conflict that the various guidelines mentioned earlier seek to prevent, and the belief that disclosure of such interests to editors, reviewers or readers will eliminate all potential for such a conflict continues to be a hotly-debated topic.

Our results understate the actual financial interests held among members of our study sample. No definitive data are available, but observers in the intellectual property field have speculated that in the early 1980s, more patent applications of US origin were filed under the PCT. With greater financial cost now an issue to both universities and companies, these observers speculate that only the "best" and "most commercially promising" applications are now filed under the PCT.

3.5. Disclosure Policy

The notions of what constitutes a "financial interest" and what is considered a "disclosable financial interest" have been discussed in US agency regulations. The broadest interpretation includes any activity that might give the appearance of impropriety or bias in the published or proposed research. The Public Health Service (PHS) regulations (US Department of Health and Human Services 1995) previously mentioned and those of the US National Science Foundation (National Science Foundation 1995) distinguish between what investigators must consider and what they must disclose. "The investigator must consider all Significant Financial Interests, but need disclose only those that would reasonably appear to be affected by the research proposed for funding by the PHS . . ." (US Department of Health and Human Services 1995, 25812). The PHS lists intellectual property rights under "Significant Financial Interest." It excludes income from service on public or non-profit advisory boards, but not for for-profit advisory boards, although it is unclear whether the monetary threshold applies to SAB membership.

Interpreted narrowly, a "disclosable financial interest" might be limited to actual dollar payments above a threshold in areas related to the published or proposed research. Under this interpretation, holding a patent or patent inventorship that has not generated income or serving on an SAB where the annual compensation is below $10,000 would not be considered a disclosable interest. We have chosen the broader meaning of "financial interest" but leave it to others to determine whether such interests are disclosable under the prevailing standards.

Of the 14 journals in the study sample, four currently require disclosure of financial or other potential conflicts of interest: Science, The New England Journal of Medicine, Lancet, and Proceedings of the National Academy of Sciences. However, Lancet introduced its policy in January 1993, the year following our reference year (Lancet 1993). In 1992, the New England Journal of Medicine and Science (Science instituted its policy on July 31, 1992) required some form of disclosure (Koshland 1992; New England Journal of Medicine 1992). Proceedings of the National Academy of Sciences, as of May 1996,

requires that all authors "disclose any commercial association that might be a conflict of interest in connection with the manuscript" (Proceedings of the National Academy of Sciences 1996). The Journal of Cell Biology introduced its disclosure requirements in October 1997 (Journal of Cell Biology 1997).

Almost all the scientific journals surveyed did not in 1992 and still do not in 1998 require any disclosure to their editors and reviewers of the type of information we have characterized as constituting a financial interest.

We reviewed the 267 articles identified as having a lead author (first or last) with at least one financial interest closely related to their publication. We could find no statements of disclosure for any of the three indicators of financial interest linked to a lead author who gave an academic affiliation. There was a disclosure of stock ownership in one article in the New England Journal of Medicine but the authors cited were identified as employees of the corporation in which they held stock and were deleted from our analysis.

Six articles published in Science after the July 31, 1992, date that mandatory disclosure took effect had a patent application matching the manuscript without a disclosure statement; however, patent inventorship was not required to be disclosed to the editors of Science. We have no way of knowing whether the patent application was disclosed to the journal editors for these or any other articles, and many of the articles may have been reviewed and edited prior to the start date of the disclosure policy. Since the journals, Science and the New England Journal of Medicine, carried a relatively small percentage of the articles in the database (6.7%), and since the requirement in Science only came into effect in mid-1992, the results of our study do not provide a baseline for mandatory disclosure of financial interest.

It should be noted that we had no mechanism with which to examine whether any of the articles of the journals we examined submitted information regarding financial interests to editors of the journals involved, whether required to do so or not. The mere absence of such disclosure to readers of the printed articles does not indicate whether in fact specific disclosure occurred in any given case.

4. RESPONSE TO PILOT STUDY AND SUBSEQUENT RESEARCH

The publication of the pilot study prompted comment in several journals, including an editorial in Nature (Nature 1997), which argued that unless there is evidence that undeclared interests pose serious risks of fraud, deception, or bias, Nature will not ask authors to disclose financial interests. The lead author of the pilot study was invited to attend a congress of medical journal editors in Prague in September 1997. In addition to presenting a summary of the data from the pilot study, Krimsky also presented data from a follow-up study of 235 biomedical journals, of which 23% (n = 53) had some disclosure requirement, including the minimum of citing sources of funding, and 19.5% (n = 46) had disclosure requirements of financial interest that went beyond funding sources.

Data were also presented on a preliminary study of financial disclosures in the journal, Lancet, from July 1993 through December 1996 (a period in which its financial disclosure requirements were in effect), in which only 7 articles (0.5%) out of a total 1,474 research articles published in this period had information about personal financial interests of the authors [unpubl. data].

Further research is needed to discern patterns of behavior by editors of biomed-

ical and science journals with regard to both requiring and disclosing authors' financial interests. At a time when financial interests of investigators are increasingly part of major molecular science and biomedicine research, it remains to be seen what, if any, impact such interests have on the quality and integrity of such published research, but in our view, journal authors, editors and readers all benefit from a clearer understanding of the dynamics of this process and its possible implications.

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