Secret Ties to Industry and Conflicting Interests in Cancer Research

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Background  Recently it was reported that a Swedish professor in environmental health has for decades worked as a consultant for Philip Morris without reporting his employment to his academic employer or declaring conflicts of interest in his research. The potential for distorting the epidemiological assessments of hazard and risk through paid consultants, pretending to be independent, is not exclusive to the tobacco industry.

Methods  Documentation is drawn from peer reviewed publications, websites, documents from the Environmental Protection Agency, University reports, Wellcome Library Special Collections and the Washington Post.

Results  Some consulting firms employ university researchers for industry work thereby disguising industry links in the income of large departments. If the industry affiliation is concealed by the scientist, biases from conflicting interests in risk assessments cannot be evaluated and dealt with properly. Furthermore, there is reason to suspect that editors and journal staff may suppress publication of scientific results that are adverse to industry owing to internal conflict of interest between editorial integrity and business needs.

Conclusions  Examples of these problems from Sweden, UK, and USA are presented. The shortfalls cited in this article illustrate the need for improved transparency, regulations that will help curb abuses as well as instruments for control and enforcement against abuses.  Am. J. Ind. Med. 2006.

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A RECENT DISCLOSURE: RYLANDER AND PHILIP MORRIS

Recently it was revealed that the Swedish professor in environmental health at the Gothenburg University, Dr. Ragnar Rylander, had worked for decades as a contracted consultant for Philip Morris without reporting this outside commission to his employer or declaring conflicts of interest in his research [Diethelm et al., 2005; Editorial, 2006]. His consultancy generated substantial amounts of money both for research and as consultant fees from the tobacco industry. The scientific integrity of his publications has been questioned [Diethelm et al., 2005]. Swedish law requires that public servants, including academic researchers report...
outside commissions, and it is the responsibility of the employer to decide whether the outside commission is acceptable, or if there is an unacceptable conflict of interest. If the commission is considered a case of conflict of interest it should be denied.

For 30 years Rylander kept his commission as a contracted consultant with Philip Morris secret from his employers (the Swedish EPA, the University of Gothenburg and the University of Geneva), while at the same time he discussed all his tobacco related research at the universities with Philip Morris and their lawyers. Industry knew what the universities and the public did not know. His correspondence shed light on this loyalty to Philip Morris [e.g., Rylander, 1987]. When the first systematic description of Rylander’s relations with Philip Morris were published in Sweden 2002, he stated: “I have never been a consultant for PM” [Tallmo, 2002]. Two months in 2002 the contract was made public after being found in the Philip Morris Archives [Philip Morris Incorporated, 1972].

While there is increased scientific and public sensitivity to the scientific validity and public health implications of work funded by the tobacco industry, there is evidence to indicate that other industries such as the chemical industry are still distorting epidemiological research, especially in the field of cancer. Our hypothesis is that the case of Professor Rylander is a seminal event for a far more widespread practice of non-disclosure and concealment of ties to industry, and as well the influence on editorial decisions as to what to publish and not to publish.

**EXONENT, INC., DIOXIN, CANCER, AND ADAMI**

In the fall of 2001 a group of Swedish scientists at the Karolinska Institute (KI), Hans-Olov Adami, Anders Ekbom, Magnus Ingelman-Sundberg, Anders Ahlbom, and one researcher in Lund, Lars Hagmar, initiated an attack in a leading Swedish daily newspaper on other researchers who had been reporting on the association between cancer and exposure to various toxic and physical agents [Walhjalt, 2002a,b]. Studies which suggested findings of an association between cellular telephones and brain tumors [Hardell et al., 2001a], dioxin pollutants in mother’s milk and the risk for childhood malignancies [Hardell and Dreifaldt, 2001], as well as cancer risks from alcohol [Hardell et al., 2000] and dioxins [Hardell et al., 1995a,b, 2001b; Hardell and Eriksson, 1999]. This work by Hardell et al. was criticized as lacking academic rigor without any regard for research method. Hardell rebutted in a peer-reviewed journal [Hardell, 2004].

Thereafter, one of the authors of the original newspaper article, Professor Hans-Olov Adami, together with Jack Mandel, an epidemiologist working for the U.S. consultancy firm Exponent, Inc., and Dimitrios Trichopoulos, Professor Emeritus of Epidemiology at Harvard, went to the Dioxin 2001 conference in Korea and gave oral presentations. Together they presented the case for the thesis that dioxins are not associated with cancer in humans. The presentations each gave a clean bill of health to dioxin [Adami, 2001; Trichopoulos, 2001; Mandel, 2001a]. Although no new research was presented, statements casting doubt on the carcinogenicity were made as a challenge to the fact that 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) had been classified in 1997 as a human carcinogen of Group I by IARC [IARC, 1997].

Exponent had hired Adami and Trichopoulos and coordinated the presentations on behalf of an unnamed client [Mandel, 2001b]. While Mandel appeared as an employee of Exponent, Adami and Trichopoulos only quoted their academic affiliations, which would infer that they were independent researchers rather than consultants hired by Exponent and paid for by some of Exponent’s clients. The aim of this re-manufacturing of doubt was the ongoing dioxin review process at the US Environmental Protection Agency.

In another article by Adami et al. [2000] the authors state: “There is persuasive evidence that TCDD at low levels is not carcinogenic to human beings and that it may not be carcinogenic even at high levels.” This article was also produced for Exponent. The article, together with another on other endpoints, was delivered to be included in the EPA review, for which the Vice President of Exponent, Dennis Paustenbach, was on the Science Advisory Board. Exponent’s activities on dioxin at the time included a number of other consultants from Exponent giving oral and poster presentations which sowed doubt about health effects from dioxins at the Dioxin 2001 conference [Connor and Finley, 2001; Fehling et al., 2001; Hays and Aylward, 2001; Hays et al., 2001; Paustenbach, 2001; Sun et al., 2001].

Paustenbach [2002, 2005] also conducted work during this time for Dow Chemical on dioxin in soils from their production plant in Midland. He recommended a cleanup level nine times above the level stated by Michigan state regulations which would save Dow a lot of money. Dow reached an agreement with the State governor based on Paustenbach’s conclusions. The EPA objected to the agreement [EPA, 2002]. Paustenbach was later a member of the panel to set the standards for clean up after Agent Orange negotiated between the US and Vietnam [Memorandum of Understanding, 2002]. Corporate and government interests coincided and Exponent was on the market filling the needs.

**MONSANTO, ROUNDUP, NON-HODGKIN’S LYMPHOMA, AND ADAMI**

Recently litigation on health risks from herbicides in Israel led one of the co-authors of this article to a Monsanto website on Roundup [Monsanto, 2002] which cited Adami.
Via a telephone number on the Monsanto website, we traced “unpublished references” in Monsanto’s possession in which Adami and his associate Professor Trichopoulos stated that “errors in exposure assessment, or chance...are likely explanations for the weak glyphosate/NHL association” [Adami and Trichopoulos, 1999]. This statement, posted on the above web reference, re-emerged, as a word-for word download, without attribution of the source, as a major part of an expert opinion by the Chief Toxicologist of the Israeli Minister of Health to the Israeli Supreme Court. For more details see ED Richter, Expert Opinion, Feb 11 2004; for Physicians for Human Rights vs. Government of Israel [Dallal, 2004].

The Swedish Cancer Society has for a long time funded Adami’s appointment as a cancer researcher. Adami’s research team has gained substantial amounts in grants from the Swedish Cancer Society over the years. The main source of this money comes from gifts from the Swedish population. The aim of funds held by the Swedish Cancer Society is to make research on different risk factors and improve the possibilities to prevent cancer. Adami’s activities, however, seem to have cast doubt on certain environmental cancer risks. The Swedish Cancer Society has made no move to require Professor Adami to publicly disclose his potential conflicts of interest.

Monsanto, Asbestos, Herbicides, and Doll

It has also been revealed that Professor Sir Richard Doll, a long time epidemiologist for what was until recently the Imperial Cancer Research Fund in England, had failed to disclose his funding from Monsanto [Walker, 2005]. Apart from his relationship with Turner and Newall, the asbestos manufacturers [Tweedale, 2000; Castleman, 2001], the other long-term relationship that Sir Richard Doll had with industry between 1970 and 1990 appears to have been with Monsanto.

During the later part of the 1990s, Sir Richard Doll made depositions as an expert witness on behalf of chemical companies, which were being sued in North America and Italy. Coincidentally, the law firm acting for Dow Chemicals, which took Doll’s depositions, Covington and Burling, was previously counsel for the Tobacco Institute and played a decisive role in organizing campaigns for Philip Morris [Covington and Burling, 2005].

Doll presented evidence to rebut claims brought by workers and ex-workers that they had contracted cancer from exposures to vinyl chloride. Doll’s statement was only used in the North American case of Ross, in which the plaintiffs, whose deceased husbands had contracted brain tumors after working with vinyl chloride, won massive damages.

Doll [1988] became an expert witness in these cases by virtue of his authorship of the article Effects of Exposure to Vinyl Chloride. The article made no declaration of vested interests or payments in relation to chemical companies. Doll’s 1988 review of mainly industry-organized studies reported that there was no significant carcinogenicity associated with vinyl chloride other than in the liver. He gave the seal of approval to the safety of the chemical and its productive process, even though by 1979, a decade earlier, vinyl chloride was classified by IARC as a Group I human carcinogen with target organs liver, brain, lung, and hematopoietic system [IARC, 1979].

Doll’s article remained the gold standard for more than a decade, and served as the basis for the following statement in 2001, by the American Chemical Council (previously called the Chemical Manufacturers Association). “The world’s leading researchers have studied vinyl chloride and brain cancer and concluded that the evidence does not support a link between brain cancer and exposure to vinyl chloride” [American Chemistry Council, 2001]. In fact, in his review, like other researchers, Doll had found an association between brain cancer and working with the production of vinyl chloride but dismissed this association as not significant or unlikely to be caused by occupation. Apart from these broader defences of vinyl chloride production, Doll’s paper [Doll, 1988] was specifically responsible for the US Environmental Protection Agency dismissing the significance of non-liver cancers in vinyl-exposed workers, as critically discussed elsewhere [Prince, 2005; Sass et al., 2005].

Doll agreed to write his review after being approached by the ICI Medical Advisor, Brian Bennett [Doll and Bennett, 2005]. Bennett had cleared his suggestion to approach Doll for the work with the US Chemical Manufacturers Association (CMA), the trade organization for chemical manufacture of which Monsanto was an important member.

In 2002 Sir Richard Doll deposited a number of boxes of articles at the Wellcome Institute (see PP/DOL, Sir Richard Doll (b. 1912) Epidemiologist. Wellcome Library for the History and Understanding of Medicine). In these articles there is a letter from the epidemiologist at Monsanto, William Gaffey, renewing Doll’s contract to act as a consultant for the company at the billable rate of £1,000 a day. Doll replied to this letter [Doll, 1986]. “I greatly appreciate the offer to extend my consulting agreement and for the increased fee, and I have signed and am returning one contract note.” Gaffey was a mathematician, brought in by Monsanto specifically to “clean up” the public image of dioxin.

Furthermore, these articles reveal that Bennett and Doll agreed that any article written by Doll would be “peer reviewed” by Julian Peto, Doll’s closest colleague and by Geoffrey Paddle and Ted Torkelson (Dow), medical advisers of two chemical companies. The cost of the review was settled at £15,000 plus expenses [Wellcome, 1984, 1986a,b]. One of the first letters which Doll wrote, in March 1986, on beginning the review was to Gaffey, asking for his advice and it was Gaffey who also managed Doll’s—at that time
secret—consultative contract with Monsanto [Wellcome, 1986a,b].

In February 1988, Doll sent the finished review of vinyl chloride on Bennett’s advice, to the editor of the Scandinavian Journal of Work, Environment and Health, which accepted it for publication [Doll, 1988].

The £15,000 fee for the review was paid for by the CMA, partly by ICI, the biggest producer of vinyl chloride in the UK, and partly by Dow, another big producer of vinyl chloride. However, in the years 1987 and 1988 when Doll was finishing the review he was also separately receiving consultancy funding from Monsanto, also one of the other biggest producers of vinyl chloride in North America and an important member of the CMA. None of this funding was declared in the published article.

In January 2000, Doll was cross-examined by Ross’s lawyers on the expert evidence he had given for Dow Chemicals and others. The lawyers cross-examined Doll on his review and the absence of acknowledgements for its funding from the chemical industry. Doll told lawyers that he had written asking Bennett’s advice about acknowledging payment for the review from the CMA and Bennett had advised him that there was no need for him to acknowledge the source of his funding. On the matter of his consultancy payments from Monsanto at the time he was writing the review, which involved a Monsanto product, Sir Richard (Doll) said simply that he did not know he should disclose these sources of income [Doll, 2000].

In December 1985, just prior to writing to Gaffey at Monsanto for his advice about his review of vinyl chloride studies, Doll had appeared to add his authority to the campaign that Gaffey was running to counteract the image of dioxin as a highly toxic agent. On December 4, 1985, Doll wrote to Justice Phillip Evatt, who had presided over the Australian Royal Commission that had enquired into the effects of Agent Orange and dioxin on Australian personnel during the Vietnam War [Doll, 1985; Hardell et al., 1998; Hardell and Eriksson, 2003; Hardell, 2004].

The Commission’s conclusion was that there was no evidence that exposure to Agent Orange including TCDD was a health hazard. However, it was later revealed that part of this ruling including a review of the scientific evidence, was an almost verbatim account of a Monsanto submission on the issue. As discussed elsewhere [Hardell et al., 1998; Hardell, 2004], the scientific evidence was distorted and manipulated in the Commission’s (or rather Monsanto) document.

Doll’s unsolicited letter to Evatt, however, supported the Commission’s views. In his letter Doll stated:

\[\ldots\mathrm{relating\ to\ 2,4-D\ and\ 2,4,5-T\ (the\ phenoxy\ herbicides\ in\ question)\ that\ there\ is\ no\ reason\ to\ suppose\ that\ they\ are\ carcinogenic\ in\ laboratory\ animals\ and\ that\ even\ TCDD\ (dioxin),\ which\ has\ been\ postulated\ to\ be\ a\ dangerous\ contaminant\ of\ the\ herbicides,\ is\ at\ the\ most,\ only\ weakly\ and\ inconsistently\ carcinogenic\ in\ animal\ experiments\ \ldots I\ am\ sure,\ however,\ that\ it\ [your\ review]\ will\ be\ widely\ quoted\ and\ that\ it\ will\ come\ to\ be\ regarded\ as\ the\ definitive\ work\ of\ the\ subject\ [Doll, 1985].\]

Doll’s letter also attempted to question the veracity and validity of the work by Dr. Hardell and his colleagues, and for that matter, its very legitimacy as a scientific work as discussed in later publications [Hardell et al., 1998; Hardell and Eriksson, 2003; Hardell, 2004].

“Your Review of Hardell’s work, with the additional evidence obtained directly from him at interview, shows that many of his published statements were exaggerated or not supportable and that there were many opportunities for bias to have been introduced in the collection of his data. His conclusions cannot be sustained and in my opinion, his work should no longer be cited as scientific evidence. [Authors italics] [Doll, 1985].”

In spite of receiving copies of articles that revealed the manipulations of scientific facts in the Monsanto submission [Monsanto Australia Limited, 1985] and a rebuttal of the Commission’s findings [Axelson, 1986] Doll never changed his position. The questions to be asked are first, whether the now disclosed facts that he was at that time secretly a highly paid Monsanto consultant perhaps influenced his statements. Second, how did Doll’s hidden consultancies influence his other work?

MOTOROLA, THE SWEDISH RADIATION PROTECTION AGENCY, INTERNATIONAL EPIDEMIOLOGY INSTITUTE, BOICE, AND MCLAUGHLIN

Another example of industry ties to research, but not one where there was a failure to disclose, involves the potential association between cellular phones and brain tumors. In 2002 the Swedish Radiation Protection Authority (SSI) hired two US epidemiologists to review published epidemiological studies on the relationship between the use of cellular telephones and cancer risk. They were Dr. John D. Boice, Jr. and Dr. Joseph K. McLaughlin from the private company International Epidemiology Institute (IEI). In their review [Boice and McLaughlin, 2002], they claimed that no consistent evidence was observed for increased risk of brain cancer, including meningioma, acoustic neurinoma, ocular melanoma, or salivary gland cancer, and mobile phone use. Featured in their review was an article by Hardell et al. [2002] of an association between cellular telephones and certain brain tumors. The review heavily criticized this article.

However, Boice and McLaughlin were co-authors of some of the studies in their “independent” review. The very positive words by Boice and McLaughlin about their own studies, which showed no association between cellular telephones and certain tumor types, should be viewed while...
INDUSTRIAL TIES: THE NEED FOR RULES

We note that relationships between corporations and “independent” researchers appear to be prevalent across most areas of medical research and not be restricted to reviews but also affect original research. In 2001, a study of 1,396 highly ranked scientific and biomedical journals by Krimsky and Rothenberg [2001], reported that only 16% had conflict of interest policies.

A recent study found that one-third of all original research articles published in the New England Journal of Medicine and the Journal of the American Medical Association were funded by for-profit healthcare companies [Friedman and Richter, 2004]. Furthermore, one in four original research articles published in these journals had one or more authors with corporate financial relationships and conflicts of interest. The authors with conflicts of interest were two times more likely to report results supporting their sponsor’s products [Friedman and Richter, 2004]. For obvious reasons these numbers are biased. Only those with known conflicts of interests are recognized. Those with hidden ties are not found in the correct column.

There have also been cases in which editors and journal staff have suppressed publication in the peer-reviewed literature [Egilman, 2005; Friedman and Richter, 2005]. In 2004, an editorial questioning the benefits of increased doses of EpoGen® (epoetin alfa) in patients with renal disease was rejected because it “went beyond what (the) marketing department (was) willing to accommodate.” In fact, the executive editor initially accepted the manuscript but was “overruled” by the marketing department, providing a clear example of an internal conflict of interest between editorial integrity and business needs [Vedantam, 2004].

Financial relationships between industry, researchers and academic institutions are becoming increasingly complex [Tuchet et al., 2005]. Funding from industrial sources for research itself should be a good thing, because, in theory, it should provide access to resources and information no longer readily available from public sources and can catalyze highly creative interactions to advance knowledge to promote and protect health. But the few examples we give show that it invites abuse when it is secret, concealed, disguised or non-disclosed, and as other research suggests, these examples are not isolated. Conflict of interest in itself is widespread, but its potential for generating misinformation is greatly increased when it is undeclared.

Whatever the rights and wrongs of particular cases there are clear lessons to be drawn from the abuses which have until recently compromised the integrity of epidemiological research on environmental hazard and risk. Unfortunately, powerful industrial interests are undermining independent research on hazard and risk in Europe and North America.

The case studies are troublesome, because they involved some of the world’s leading epidemiologists. It is highly likely that there were delays in addressing the carcinogenic risks that these epidemiologists minimized in the interests of their clients. These case studies illustrate the need for rigorous policies and practices to prevent the abuses of this kind by requiring open declaration of direct and indirect support, professional codes of practice that will help curb abuses, enforcement of these codes and evaluation of the efficacy of enforcement.

We call for swift, immediate and forceful policies and action by the independent academic community and, no less important, editors of scientific journals to protect scientific integrity, openness, and fairness. Such policies and actions are needed to ensure credibility and restore the essential role of the medical epidemiologist in protecting the public health.

ACKNOWLEDGMENTS

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Wellcome. 1986a. Doll Papers. PP/DOL/B/5/3. B. Gaffey to R. Doll 01/05/86. Once again I enclose two copies of a letter extending your consultation agreement with Monsanto. We have changed the fee from $1,000 per day to $1,500 per day.