

**Corporate and Economic Pressures on Academic Freedom**  
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**Presentation Made at Academic Freedom Forum**  
**June 11, 2003**

Most of my work has involved conflicts of interest and the financial ties of investigators, both personal and through their research. First, I want to clarify what types of economic pressures we need to be thinking about. There is funding for individual investigator research in the form of contracts and grants; there are personal financial ties to companies—having stock options, receiving consulting fees, having a personal contract with a company outside the university; and there are institutional financial ties, between corporations and departments for instance. To give you an idea about why this is important (*slide 3*) shows data over a 20-year period at UCSF on the total number of disclosed personal financial ties. The red line shows all faculty up to 2000. It's gone up a little bit since then. The blue line is clinical faculty. When you submit a grant you have to make certain disclosures depending on whether it's a federal grant or privately funded. Federal rules say you must disclose any personal income that might be related to your research, and it's up to the investigator to decide whether it's related or not. Income is defined as something you would pay taxes on. So if they give you a check made out to you and you use it to buy an instrument, you would have to disclose it. But if they write the check to UC Regents for you to buy the instrument, it doesn't fall under this. The point is that personal financial ties like honoraria and stock options have been increasing for all faculty at UCSF, and these data are not unique to San Francisco. Personal financial ties are increasing all over the country among all sorts of academics. If we convert this to the percentage of faculty at UCSF who are actually serving as PIs, it comes out to about 30% of the faculty who have personal financial ties over the last two-year period.

I have looked at a lot of the definitions of academic freedom and it boils down to freedom of inquiry, exploration, investigation, research, expression, publication and dissemination. I'm focusing on corporate and economic ties, so my version is *No Strings Attached*. If you are receiving money, there should be no strings attached that can get in the way of any of those things. In the rest of my talk I'm going to speak about the strings that *are* attached. First, why do people care? No one would care if we thought there was no bias associated with private support for research. I did a study on researchers who were funded to do meta-analysis or systematic reviews of the health effects of secondhand smoke. We looked at all of the factors that might be associated with the outcome of a review. The quality of the review; whether or not it was peer reviewed; what the topic was—for example, second hand smoke might be associated with lung cancer but not pancreatic cancer; the year of publication (as more evidence accumulates you might expect the results of a review to change); and finally, you might expect the sponsor to be associated with the outcome of the review.

(*Slide 5*) shows the odds of any of these factors being associated with the conclusion that secondhand smoke is not harmful. If the odds cross "1," it means there is no association. So you see the only thing that is associated with the outcome of these reviews is whether or not they were associated with the Tobacco Industry. If the Tobacco Industry funded the study, it was ninety times more likely to conclude that secondhand smoke is not harmful.

I've also done these types of studies on drug company research. (*Slide 6*) shows a meta-analysis I recently published in the British Medical Journal about pharmaceutical studies. If there were no association between pharmaceutical company funding with the outcome of drug trials, all of the

studies would be crossing this line. We put together all of the studies that looked at whether drug company funding was associated with outcome. The summary odds ratio is four, so drug company funded studies, when controlling for everything else, are four times more likely to conclude that the company's drug is either more beneficial or less harmful than the comparison. This suggests some bias because funding is always associated with outcome.

Why is this? It can have to do with the questions asked; the design of the study; how the study is conducted; whether the results of the study are published or not published and the use of the study results. The main concerns includes whether research funding is driving the agenda, and whether the questions are beneficial to the companies asking them but not others. There have been six studies looking at the comparators used in drug studies. They have found that in industry-funded studies, if the sponsor's drug is being compared to another drug on the basis of efficacy, the sponsor uses a higher than normal dosage, and the competitor's drug is a lower than normal dosage. Their drug ends up looking more effective since they're given a bigger dose. If the question is whether the new product is less harmful than a competitor's, they use a lower than normal dose and compare it to a higher than normal dose of the competitor. In addition, there are research organizations funded by Industry that can have control over the questions asked.

I have done extensive studies on the Center for Indoor Air Research (CIAR), which was funded by five tobacco companies and which doesn't exist anymore. Their mission was to fund research on indoor air quality and environmental tobacco smoke. Two years after its founding, environmental tobacco smoke was removed from the mission statement. The mission changed to just funding research on indoor air. Why was that? The types of projects that CIAR funded fell into two categories: One was specially reviewed by Tobacco Industry executives and lawyers. The other was peer-reviewed by a scientific committee. The ones that were specially reviewed were more likely to be on secondhand smoke. The ones peer-reviewed by scientists were more likely to be on other indoor air contaminants. They had more control over the studies that were actually on secondhand smoke, because the lawyers and executives were selecting them. We looked at how the data from these projects were used for everything they ended up funding. The specially reviewed projects were less likely to result in peer-reviewed publications and more likely to result in testimony at regulatory hearings than peer-reviewed projects. They were being used for policy purposes, not to generate new knowledge. If an investigator at our university received a grant from CIAR, it didn't say this is specially reviewed or this is peer reviewed. It just said this is a grant from CIAR. The peer review it went through and who selected the grant for funding was not known.

Concerns about conduct and design can also extend to supply of materials. For example, people doing tobacco-related research have often gotten cigarettes from drug companies for testing. A UCSF colleague received these company-produced cigarettes and was getting results he thought were a little odd. He sent the cigarettes out for an independent analysis that found they weren't the composition they were supposed to be.

There are also examples of sponsor involvement in data collection and analysis. The most common examples deal with selection of study sites. For a lot of the CIAR studies someone would submit a grant to study, for instance, five communities. CIAR would say we are going to fund your grant, but we want you to study these places instead. Another example, particularly with drug companies is statistical analysis. Someone independently collects all the data, but it is sent off to the company for statistical analysis. The company hires an independent statistician, and it's out of your control. One thing we have with the tobacco industry is the internal

documents that were released in 1998 as part of the settlement agreement. These documents give us insight into how this industry worked and made decisions. There is a book written by David Rosner called *Deceit and Denial*, which is about the asbestos, lead and plastics industries and how they fund research, which is based on internal documents too.

The Hirayama study in 1981 was very influential for tobacco control. It showed an association of secondhand smoke and lung cancer, and has since been the most frequently cited study in regulatory hearings on indoor air regulation. The study found that women who didn't smoke but who were married to smokers got lung cancer at a greater rate. The tobacco industry has always argued that the Hirayama study is invalid because the non-smoking women were misclassified and that they were really smoking women. It created a study to support its arguments. These are quotes from internal documents showing how they did it.

The tobacco industry gave a grant to two Japanese academics to do a study on misclassification bias. They say, "There are two Japanese listed as co-principal investigators. But Chris Proctor [a tobacco industry scientist] would be a "behind-the-scenes" study director..." It goes on to say that they think this study is going to produce results that show the Hirayama study is invalid. So is it a Japanese study? The Senior Vice President of Philip Morris received a memo from the R&D department saying, "Also, I am of the opinion that Dr. Chris Proctor might supervise this work but his presence should be low key and not appear in any of the publications, particularly since this is a Japanese study. Proctor (and his fee) may be necessary to help get this done. But this should be a Japanese study. Proctor should not be a coauthor on any publication that comes out of it." So Chris Proctor, not the Japanese academics, are actually doing this study. They had a huge debate over who should fund it. "This is NOT a project that should be funded by CIAR, although there MAY be (I'm not convinced yet) a reason to say it was sponsored by CIAR so as to "hide" industry involvement... One may wish to use a CIAR cover for this project. I believe it is very important that this be done with all due haste." They decided not to fund it through CIAR but directly from a tobacco company. The whole idea here is hiding involvement. This outlines what is really happening: "Project management would be undertaken by Covington and Burling [a law firm]. The project managers would remain remote from any scientific publications. Two Japanese scientists will be the principal investigators. Mr. Peter Lee [a tobacco industry consultant] also will be asked to assist in reviewing the study design and in interpreting the data. It is not anticipated, however, that Mr. Lee will serve as a co-author of any of the publications..."

(Slide 17) shows a progress report on the study, which is on Covington and Burling stationary. There are seven drafts of the paper written and you can see gradual changes in authorship. Eventually the Japanese investigators are no longer authors on the paper. "...we feel it is time to recommend that Mr. Peter Lee be asked to submit the Japanese spousal study research for publication in the British Medical Journal. We spoke with Mr. Lee earlier today, and he has agreed with this course of action, but will await final approval. We suggest that some acknowledgement, as a footnote to the paper, be given to Dr. Yano's contribution to this research." The Japanese investigators got the grant, but the final publication is coming and they're not on it. Peter Lee is the only author on the final publication. The acknowledgement discloses financial support from the tobacco industry, but I would argue that this disclosure does not tell you enough about what really went on behind the scenes with that study. That example is just one many to show some of the threats of this kind of sponsorship. The sponsor was involved in the questions asked, the design, data collection and publication—everything.

Some main concerns about publication related to academic freedom are suppression of data, review of manuscripts by the sponsor and selective data publication. My UCSF colleague Betty Dong was involved in a classic case of data suppression. Betty had funding from a pharmaceuticals company to compare generic thyroid preparations to their brand name counterpart. She found that the generics were as good as the brand name. The company didn't like that. They wanted to find that their brand name was better. So they sued her personally, they sued the university, and they said she couldn't publish. She submitted the paper to the Journal of the American Medical Association, which accepted it for publication but pulled it at the last minute because they were also threatened with a lawsuit. The Journal stood up for her and wrote an editorial called "Thyroid Storm" that lays out the whole story. This is a huge fear that people have about academic freedom—that I'll do something and my sponsor won't let me publish.

I also want to point out that there are other, more subtle things happening with publications. With the tobacco industry, you've seen lawyers and executives involved in actually writing publications. We also have the example of advertising companies being contracted by pharmaceutical companies to write scientific papers. They either write it based on data from the investigators or they ghost write it and later find an academic to put his name on it. The pharmaceutical company funds your study, and as part of that funding agreement claims access to your data. They get the data and send it to the advertising company who writes it up.

There is also selective publication, which is a tricky problem. There was a drug called Sulfinpyrazone back in the 1970's. The company that made it funded a randomized control trial to compare it to a placebo. They gave it to people after a heart attack to see if they had more or less occurrence of cardiac death. They also measured total mortality in these studies. The investigators submitted their publication to the New England Journal of Medicine; it was accepted and published. What their study showed was that Sulfinpyrazone compared to placebo decreased sudden cardiac death. After it was published, the FDA saw the publication, wrote to the Journal and said we think you have a serious problem because when you look at total mortality, Sulfinpyrazone actually increases total mortality. We're not going to approve this drug because it is actually more likely to kill people. The problem was they were a peer review journal and when you get a paper to review it's only as good as the data that are given to you. They trusted the investigators. They thought they were getting the whole story and they weren't. This was in the 1970's, but is it still happening? A study on serotonin uptake inhibitors, an anti-depressant, was published last week. The investigators looked at 42 studies that were submitted to a regulatory agency in Sweden to get the drug approved for treatment. They found that only 19 of these had been published in the medical literature, and all showed the drug was effective compared to competitors. The ones that didn't show the drug was effective had never been published. Of the 19 that did get published, only two of them presented all the analyses. There's something called an intention-to-treat analysis, which will always make your effect look a little more conservative. Only two of them published the intention-to-treat analysis, which they did submit to the regulatory agency.

In the university we talk about the goal of gaining new knowledge. Is that why corporations are funding research? In my view, in these instances they are funding research to control the research agenda, promote a product, generate controversy so they are protected from regulation or litigation, and finally, to improve their image. Regents' Regulation 5 on Academic Freedom states, "The University assumes the right to prevent exploitation of its prestige by unqualified persons or by those who would use it as a platform for propaganda." In many of these studies,

the purpose of generating the data is to use it in a regulatory proceeding or to use it for promotion for the company. It is not to generate new knowledge in peer-reviewed publications.

There are a lot of examples from the pharmaceutical and tobacco industries of data generated strictly for promotional purposes. Also known as the “credibility criteria.” Philip Morris had something called the Worldwide Scientific Affairs Program. (Slide 28) shows a checklist for a proposal before it gets submitted. There are four boxes at the top and that last box says “credibility.” These are the reasons that Philip Morris might fund this project: it’s a product change; it helps them for regulatory reasons; it’s about health and safety; or it enhances their credibility. In a document selecting people to do tobacco industry funded research, the head of Philip Morris Scientific Affairs says, “I generally support the concept of collaborative investigation with selected scientists if they’re qualified, they’ve demonstrated significant objectivity in the past, and they collaborate and not just take the money.” This is the tobacco industry criteria for funding somebody—that they not just take the money. To me, no strings attached means you just take the money.

There was a study published a few weeks ago in the British Medical Journal, which caused a huge uproar. It showed that environmental tobacco smoke was not associated with lung cancer mortality. It was a tobacco industry study and there were a lot of strings attached. We’re writing a paper about it. The grant actually went to a UCLA investigator. The tobacco companies talked about the most appropriate means to fund the study and they decided to use an unrestricted gift that would minimize university restrictions. I think this is really important. The company wanted to fund the investigator in the way that would minimize university restrictions, which theoretically might protect academic freedom. A copy of the check that went to this investigator amazed me. There’s a warning on it that says, “This is Tobacco Money.” I think that every corporate check an investigator gets should have a warning label like that. It gives us something to think about...why is there that warning? I think we have to be really cautious about this money.

**Question:** *In the British Medical Journal article you mentioned that said there wasn’t an effect of secondhand smoke; did the authors have to disclose that their funding was from tobacco? Do you know if the Journal has a policy that disclosure is all that is necessary and reader beware?*

**Lisa Bero:** Yes, and that article had the longest financial disclosure I have ever seen. It does say the study was funded by the Center for Indoor Air Research, but our research suggests this isn’t enough because you don’t really know what went on behind that study. It doesn’t reveal that Philip Morris funded it; and as you see, the check is from Philip Morris. So this study actually had funding from two sources, only one of which was disclosed. The British Medical Journal has been in the forefront of asking for financial disclosure. They did a randomized control trial of their peer reviewers. They sent out the same research article and made up a disclosure for some of them saying it was industry sponsored. The study showed that the peer reviewers were more critical of the ones that said they were industry sponsored. The New England Journal has a policy against disclosure, but it is up to the editor to decide. The author has to disclose to the editorial team, who may or may not decide to publish it. They have occasionally gotten into trouble. Recently, the NEJ published a very influential review of a drug and although they knew it, they didn’t disclose that the author worked for the drug company.

*Do you have any data indicating why a credible scientist would accept a grant from an organization that put those kinds of stipulations on publications or data review?*

**Lisa Bero:** Some of the tobacco industry documents are sad because they talk about investigators and say, he didn't get tenure, she didn't get her last grant. So they actually prey on people who are hurting for money. We interviewed clinical investigators at UCSF and Stanford and asked them how they felt about restrictions on clinical trials and personal financial income. They usually say, "If I'm in conflict I know it and I can handle it." Most investigators believe if there is a problem they will handle it and that their publication won't be restricted or they won't be sued. I think raising awareness about this is very important.

*What were the restrictions put on the UCLA study that guided the results?*

**Lisa Bero:** There is a particular data set called CPS1, which comes from the American Cancer Society that was the subject of this study. However, the American Cancer Society had said this was an inappropriate data set to use for this question. This investigator submitted a proposal that wanted to look at four data sets, one of which was CPS1. The other three were more appropriate to the research question, but the tobacco company only funded him to look at CPS1. So he went ahead and did the study this way and it got published. I can't speak to people's motivations, especially when you've come so far and someone is editing your manuscript. You really want to get it published.

*What was the reaction from his colleagues? How has the School of Public Health reacted to this? There is an issue on tobacco funding that your Chair is bringing forward to Council about what the Systemwide Senate ought to say on behalf of academic freedom.*

**Lisa Bero:** I don't know what has happened at UCLA, but the international response to this article has been huge. People have written online critiques of the study—asking how it ever got published, who peer reviewed it, saying it should never have been accepted. I think the key here is whether it is ok to take money from anybody if there are strings attached. The other side is that we should have the freedom to take money from any source, but I think the full question should be: do we have the freedom to take money from any source if there are strings attached?