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Conflict of Interest in Biomedical Research

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CONFLICT OF INTEREST IN BIOMEDICAL RESEARCH

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I HAVE BEEN DOING RESEARCH on academic and industry relationships for about 20 years. I got into it when I was a young faculty member at the Kennedy School of Government at the time. I was still actively seeing patients at Massachusetts General Hospital, which concluded an agreement with the Hoechst AG Company to do a long-term research collaboration, including setting up a whole new Department of Genetics, which in those days was pretty farsighted.

After this agreement was announced, a little known Congressman, who chaired a government oversight subcommittee of the House Commerce Committee, invited the president of Mass. General down to talk about this new relationship, because he was concerned that we were selling our birthright, our scientific birthright, to the Germans. I was interested in what, in fact, these kinds of relationships meant. That began what subsequently became a twenty-year course of investigation. That Congressman was Al Gore. So, I like to attribute my interest in this topic to Al Gore.

I would like to talk about the role of the university in biotechnology Research & Development. I will review the topic broadly and get to conflicts of interest later on. I guess there are four R's in my agenda. First of all, I am going to go briefly through the reason for these relationships. Then I am going to talk a little bit about the record and what, in fact, has transpired and what the consequences of these relationships have been for both of the parties—universities and industries. Then I would like to talk about the rub—the problems—especially conflict of interest as a problem, and how we might approach those conflicts from the standpoint of resolving them.

We have heard of the Bayh-Dole Act; we have heard about public support of research and expectation of return as reasons

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for the involvement of universities and industries. I think that some of these rationales often go unstated, but they are worth recalling, especially when we get into the pros and cons of some of these relationships.

I like Abraham Lincoln's quote that the reason for intellectual property law was to add the fuel of greed to the fire of genius. That gets right at the bargain that we are making with intellectual property law and the university-industry interaction.

We should recall that this process does have its basis, to some degree, in changing norms in the university. These kinds of relationships were not always sanctioned and there are, of course, changing norms of all kinds prevalent in the medical profession generally, which come into play when you start talking about clinical research. One has to start thinking more broadly about the norms that underlie professionalism generally when discussing academic-industry relationships..

In terms of the record concerning academic-industry relationships (AIRs), including their prevalence and magnitude, I would like to talk just very briefly about the data sources upon which I base my discussion.

I have been in this work a long time now. We have done, over the last twenty years, four national surveys of life science faculty, conducted at various times with various emphases, starting in the mid-1980s. We just came out of the field with the last survey that was done in the 1999-2000 period.

Over this period we have also done two surveys of industry executives on their relationships with universities, one in 1985, one in 1995. We actually did a survey of students and trainees on their relationships with industries in the mid-1980s. I will be sharing with you information from several of these sources.

There is a common assumption and perception that the number of academic-industry relationships has exploded and that every other faculty member today and probably tomorrow, every faculty member, will have a deal with a company. Our data does not support this impression.

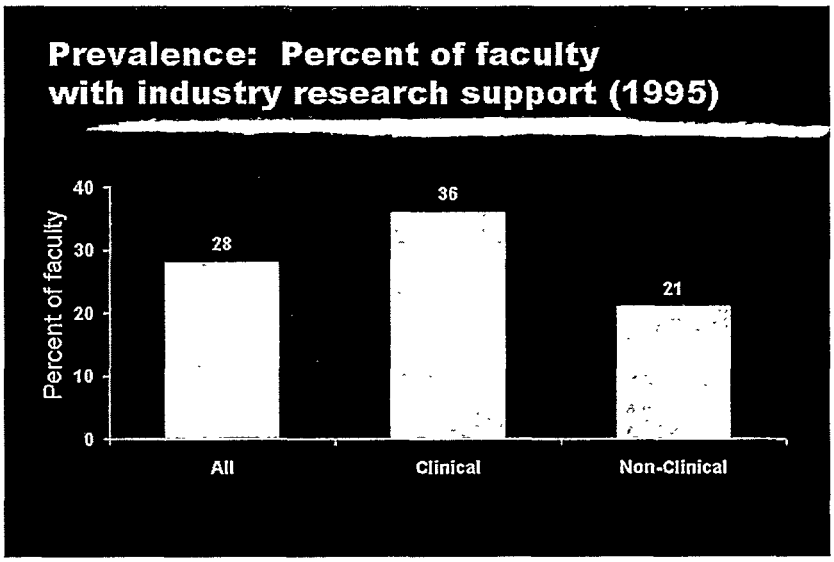
We have looked at the prevalence of faculty members' receipt of industry funding at four different points in time over the last two decades. Basically, we find the prevalence has not changed much. Somewhere between twenty-one and twenty-eight percent of faculty, depending on how you define the term "faculty member," have research support from industry.

In the mid-1980s, about twenty percent of students had some research relationship with a company, if you included the support of scholarships and fellowships from industrial sources.

The other thing that has not changed much is the prevalence of faculty members holding equity in related companies. Equity holding is a particularly sensitive topic. We found that in the mid-1980s, about seven to eight percent of faculty reported that they held equity in a company related to their research; and in our 1999-2000 study, we have found basically the same thing: about seven to eight percent of faculty report that they have equity in a related company.

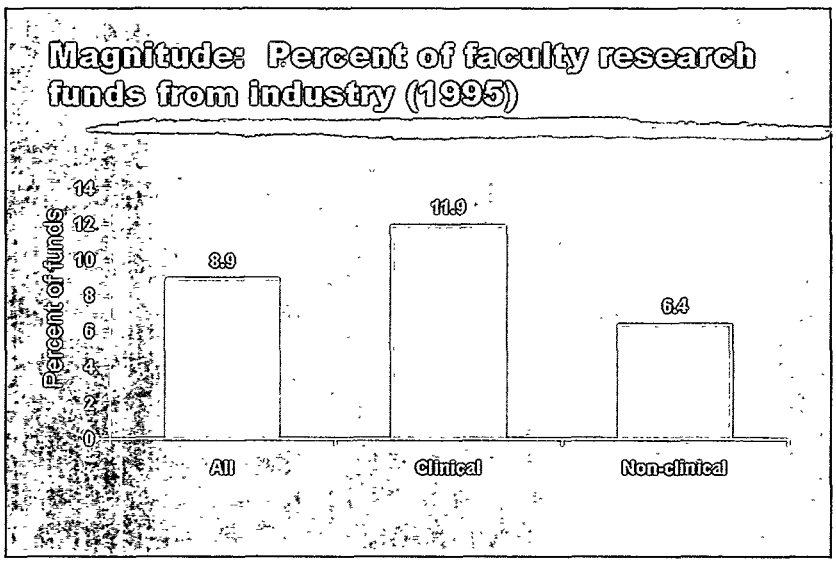
About half of faculty act as consultants for a company. So, these relationships are prevalent, but they are not exploding, at least not based on the data that we have collected.

There is some variation in rates of industrial involvement among faculty of different types. For example, clinical faculty tend to report higher rates of relationships than non-clinical. The 1995 survey shows about twenty-eight percent of faculty reported that they got support from industry for their research, but the number for clinical faculty was a little more than a third, while for non-clinical faculty it was about twenty-one percent.



Clinical-non-clinical distinctions are critically important in talking about conflict of interest.

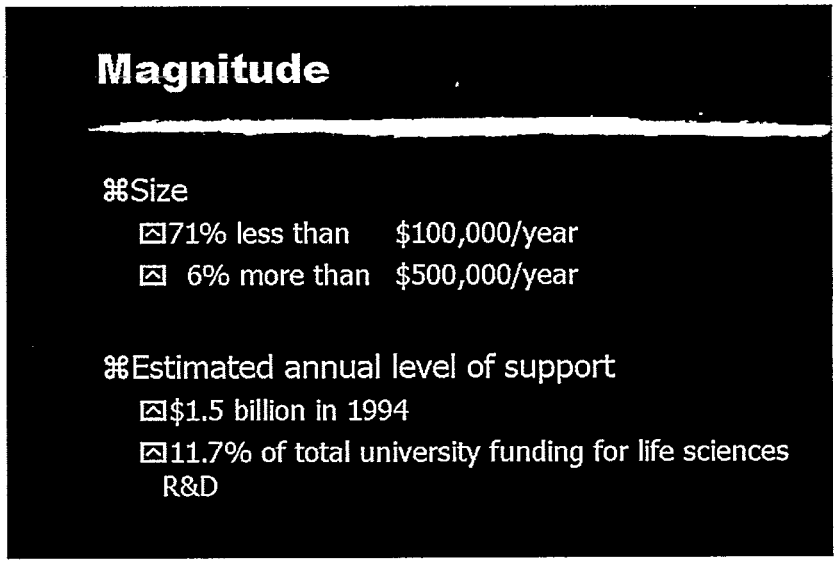
Again, the impression is that industry research is ubiquitous and that industry funding is a major source of support. If you look at the numbers as reported by faculty concerning the proportion of their budgets derived from industry, one finds that the numbers are modest: about nine percent of direct costs of research, on average, across the major research institutions in the United States, twelve percent for clinical faculty, and six percent for non-clinical faculty.



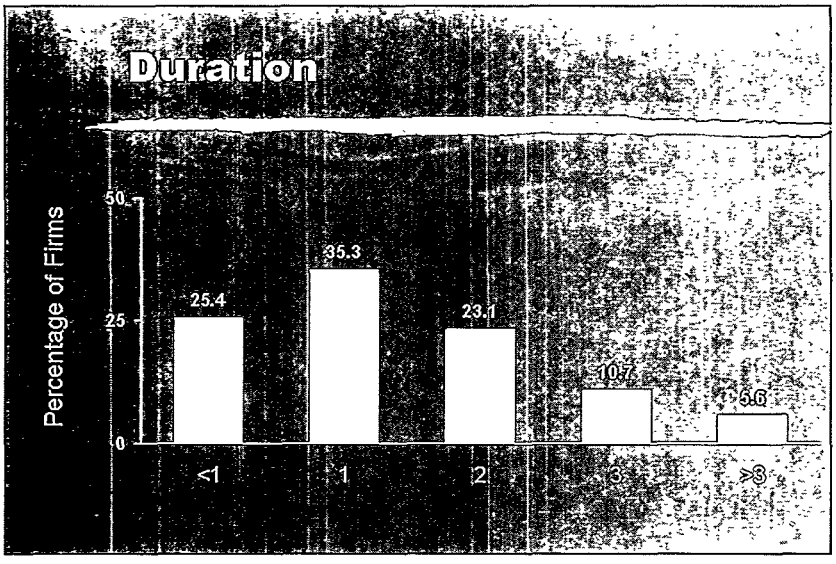
Industrial research relationships with universities also tend to be small. We hear in the newspaper about megarelationships, about multi-million dollar, multi-year arrangements that raise concerns about the university being bought lock stock and barrel. But, in fact, for most faculty members, relationships are small and, as we will see, they are short-term.

According to 1995 data, only about six percent of relationships were in excess of $500,000 a year, seventy-one percent were less than $100,000 a year. We estimated from this data in the mid-1990s that at that time about ten to fifteen percent of total university funding for life sciences research and development came from industrial sources as opposed to perhaps sev-

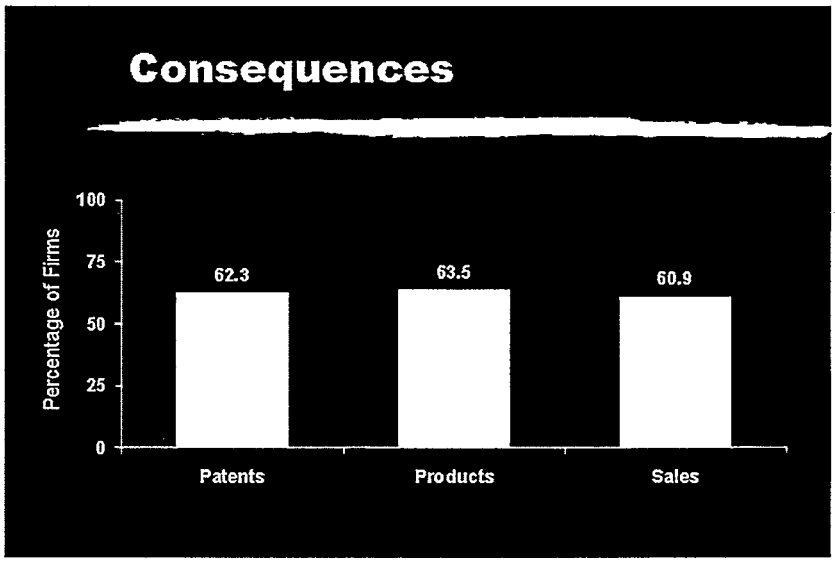
enty to eighty percent from public sources, like the National Institutes of Health.



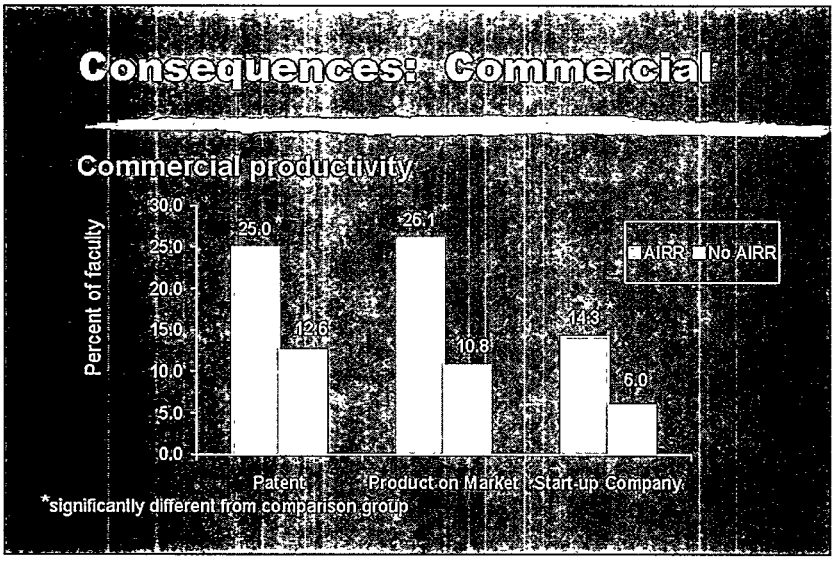
Most relationships are short. The great majority are less than two years in duration and only a tiny minority are more than three years in duration. So technology transfer officers are all in pursuit of the big long deal, but the big long deal is a rare event.



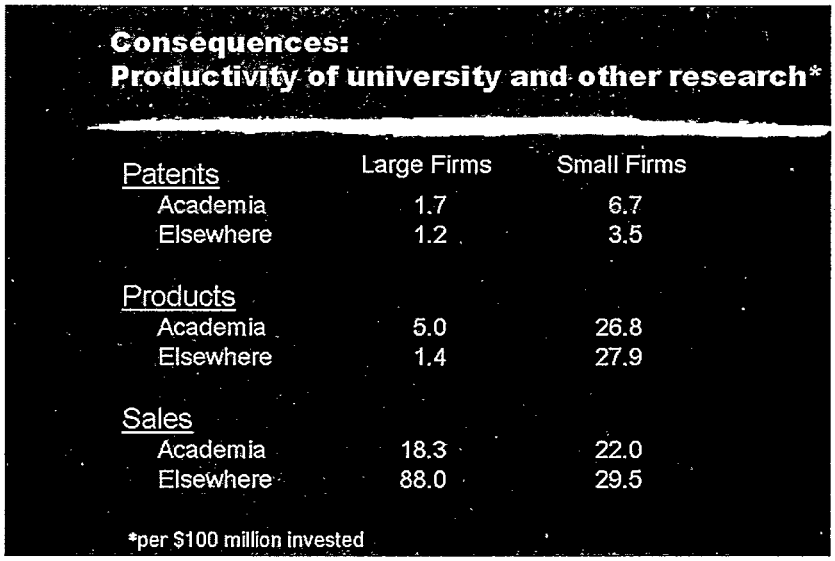
Let us talk about some of the commercial benefits. In the mid-1980s, we surveyed industry executives and asked them what they had gotten from their dealings with universities, especially their research support universities. Close to two-thirds, over sixty percent, had gotten some return from their investment in the form of patents, actual products, or products that had sales. So, there was something coming in concretely in return for their relationships with universities.



We have data comparing faculty who have support from industry for their research with faculty who do not have support from industry, in terms of some measures of commercial productivity. Not surprisingly, people who get industry support are more likely to report that they have patented, that they have a product on the market, or that they have a start-up company. Whether this relationship is in any way causal, we cannot tell from our data, but it seems reasonable to believe that there is a tendency for people with industry money to focus a little bit more on the commercial results of their work than those who do not have industry money.



Based on mid-1990s data, we attempted to look at the productivity of research at universities and other sites based on patents, sales, and products resulting from that research. Just to summarize, we found that the return on investment in academic institutions was at least as high or higher than on investments in research in other sites. Investing in universities did not seem to be something that companies had to apologize for doing.



Consequences:
Productivity of university and other research*

	Large Firms	Small Firms
Patents		
Academia	1.7	6.7
Elsewhere	1.2	3.5
Products		
Academia	5.0	26.8
Elsewhere	1.4	27.9
Sales		
Academia	18.3	22.0
Elsewhere	88.0	29.5

*per $100 million invested

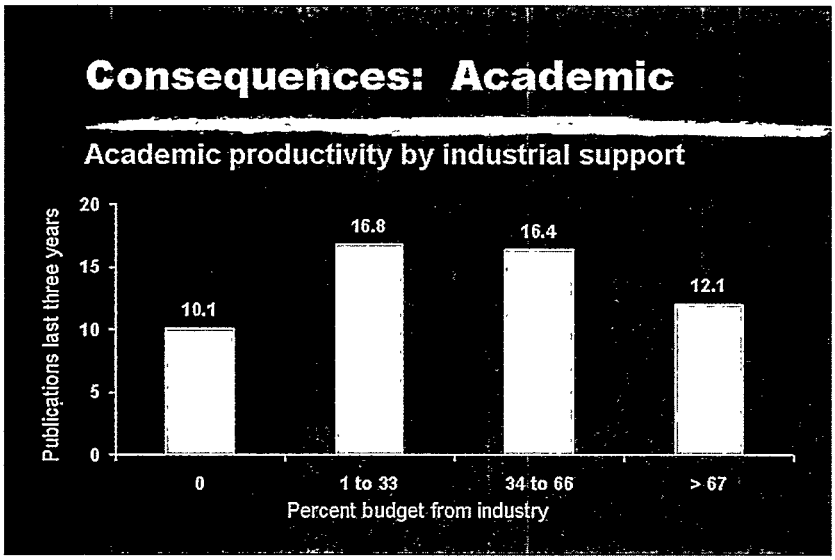
There are also more highly visible and intuitive benefits, such as the Silicon Valley, Route 128, and the Research Triangle Park phenomena

Based on studies by the National Bureau of Economic Research, we know that academics participated in founding twenty-four Fortune 500 companies and over 600 non-Fortune 500 life science firms during the 1980s and early 1990s. These numbers are probably higher now.

And there also are studies showing that if you quantify the number of star scientists (these are scientists that in the life sciences have extraordinary records of productivity in publishing and grant getting) and then correlate that with the presence of new biotechnology entities—new biotechnology start-up companies—there is a relationship between the academic bench strength in a region and the number of new companies in that region.

We published data in the mid-1990s based on a mid-1990 survey that looked at the productivity of academics in their own coin of the realm: their rates of publication in terms of their level of industrial research support. The faculty members who produced the fewest number of publications in the three years prior to the time that we queried them were those who had no industry support; and that those with moderate amounts of in-

dustry support tended to be the most productive faculty members as judged by rates of publication in peer review journals.



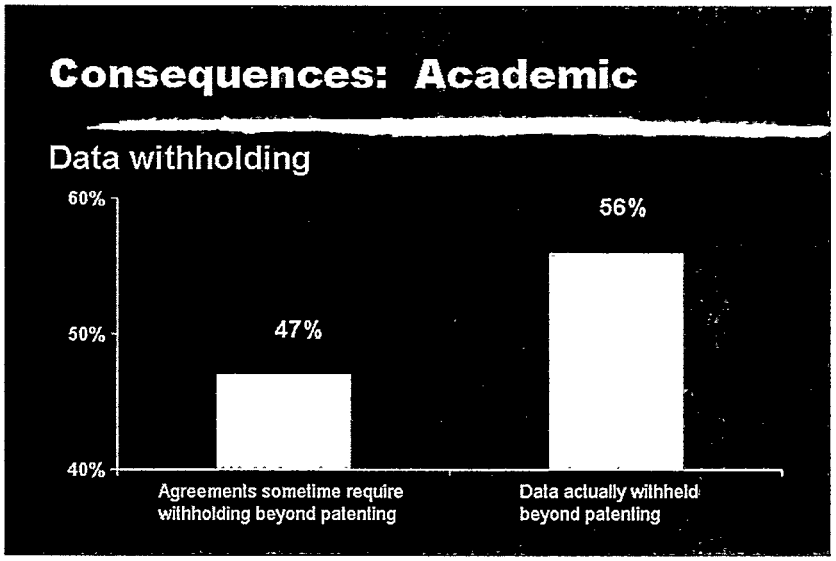
Now, there tended to be a decline in publication rates as the amount of industry funding exceeded two-thirds of the faculty member's total. And when we looked at the citation adjusted influence of the publications by faculty with more than two-thirds of their support from industry, we found that they published in less influential journals than their peers, including their peers who had no industry support.

So, there may be an effect or at least a relationship between quality of publication and the extent of involvement in academic-industry relationships. But there is no adverse effect on the numbers of publications.

There are some other effects, though, that in academic environments we need to be attentive to. One of them is data withholding, which is our euphemism for secrecy. When we asked companies in the mid-1990s about whether they required, as a part of their agreements with the universities, some secrecy or withholding of data that went beyond what we might think of as the normal pre-patent review, many will admit that they do.

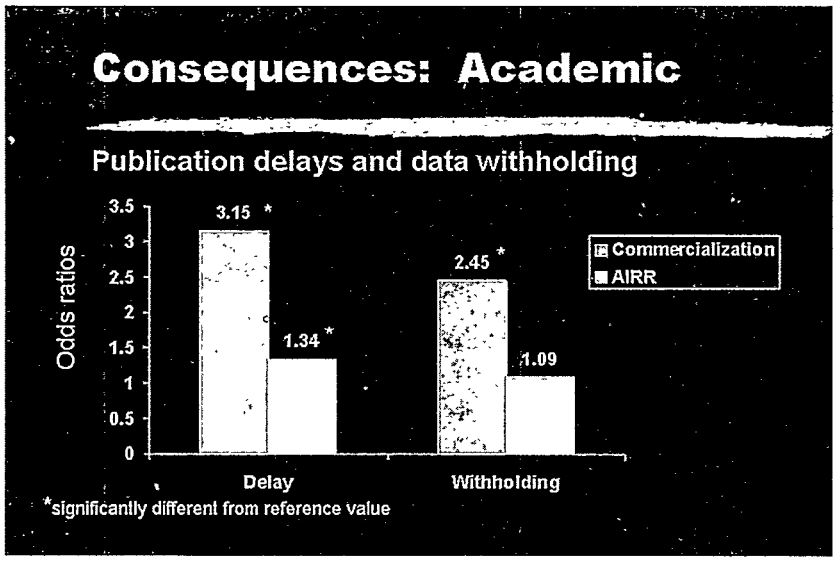
Forty-seven percent said that their agreements sometimes require withholding of data beyond the time required to file a patent and fifty-six percent of those said that this agreement had

actually been implemented at some point. That is, they have actually insisted on data being withheld beyond the time required to patent the finding.



If you look at faculty members' behavior as reported in our surveys, you will also find a difference in their reported data withholding behaviors depending on whether they have industry support, or whether they are involved in commercializing their own research.

Faculty members are more likely to say that they delayed publications for more than six months in order to honor an industrial request if they have industry support for their research than if they do not. They are also more likely to say, by a substantial margin, that trade secrets have resulted from their research. We define trade secrets as information kept secret to protect its proprietary value. The same pattern is observed among faculty who report engaging in commercialization of research results, independent of whether they had research support from industry.



Now, what does it mean when people withhold data? That is one of the questions we got interested in. We were recently funded by the National Human Genome Research Institute to look at precisely this question for geneticists and other life scientists.

We asked geneticists in particular what the consequences were when they were denied access to requested data from an investigator who had published his research findings. Among the reported consequences were: ability by requesting scientist to confirm published results (twenty-eight percent); delay in their own publications (twenty-four percent); and a series of other effects.

Academic-industry interactions are not the only reason why data is withheld. When you ask people why they withheld data, you find that there are other reasons that are much more important than a commercial relationship. A lot of people just say it was too much effort.

Other people will say they were protecting their ability to publish their next paper or were protecting one of the junior colleagues. Forty-four percent cite the financial costs. Twenty-seven percent say that they were honoring, or thought they were honoring, an industry requirement; about twenty-one percent say that they were preserving the commercial value of their work.

The faculty members who have relationships with industries are more likely to direct their research consciously in a commercial direction. That should not surprise anybody. I guess that is the reason why we promote these relationships: to tap the university intellects for commercial purposes. Nevertheless, there is a possible change in the direction of research.

One thing we need to be aware of when we enter the clinical realm is the evidence that has accumulated of bias in clinical research reporting associated with industry support. There is accumulating evidence that clinical studies supported by industry or conducted by scientists with financial relationships are more likely to favor industrial interests.

A study by Stelfox and colleagues in the New England Journal of Medicine in 1998 found that ninety-six percent of those who published reviews supportive of calcium channel blockers in the treatment of hypertension had a relationship with the manufacturer that made calcium channel blockers, as opposed to thirty-seven percent of those who published critical articles.

Ninety-nine percent of industry trials of nonsteroidal anti-inflammatory agents found that those agents were equal to or superior to competing drugs. That is probably above the random chance. Five percent of industry sponsored trials reported unfavorable findings for cancer drugs compared to thirty-eight percent of non-industry supported trials.

There is the question of whether industry relationships can involve threats to patients. The most celebrated case of this was the Gelsinger case, a gene therapy trial at the University of Pennsylvania in 1999. There was a series of interlocking relationships between the investigators and a company in which they held equity and in which the University held equity. This led to a cascading series of public involvements in rethinking the conflict of interest rules that pertain to publicly funded research. It is not yet resolved, I would point out.

Now, I do not know of any definitive evidence that a conflict of interest has ever directly injured a patient, but the Gelsinger case and a number of others have certainly created the suspicion or appearance of that eventuality.

There are situations of complex overlapping conflicts of interest in academic clinical research that are certainly public. Perhaps the best example of that is Boston University, in which

the president of the University and the investigator doing the clinical research all held equity in the start-up company that the university had partly funded.

So what is the rub? I have begun to hint at it already. One of the rubs is conflict of interest. There are a series of rubs, but I think they can be collected under this general concept of conflict of interest.

A conflict of interest occurs when two interests collide; pretty straight forward. Interests are things of value to somebody or something. Usually it means that pursuit of one interest detracts or has the potential to detract from the other interest; otherwise there would not be a real conflict. Now, sometimes we can manage our way out of conflicts. And when we talk about managing conflicts of interest, it is usually with that in mind, the hope that some clever device can be created that will reduce the possibility of conflict to such a low level that it becomes unimportant.

The Institutional Review Board mechanism was designed and has functioned to balance the conflict of interest between the investigator and his or her research subject, and correctly or incorrectly, was perceived to have mitigated this conflict until recently.

Not all conflicts can be managed that effectively, of course. In beginning to think about choices, we need to recognize that not all interests are equal. In effect, we, in our daily work and thinking are always creating hierarchies of interest; some interests trump other interests. We assign them a rank in making decisions among them. These are some of the tradeoffs that we are implicitly weighing when we consider the conflicts of interest created by academic-industry interactions.

One notable conflict pits the interest of science in some large sense against the interests of a researcher. And the conflict that we are battling there is whether the financial interest of the researcher might hurt the progress of science, the scientific enterprise, because of concerns about bias or secrecy or diminished quality of research.

Another set of conflicts that we are always managing is the interests of patients versus the interests of researchers. This is uniquely true in research that involves living human subjects. There we are concerned with whether the financial interests of

researchers may cause or appear to cause harm to patients. This really becomes an issue of patient protection.

I have often had disagreements with some of my research colleagues over what was at stake over managing conflicts of interest. They want to focus on the bias issues and I think that in many ways the critical issue is patient protection.

Still another conflict pits the interest of research faculty against their students and post-doctoral trainees. Recently, the Harvard community just created a new regulation that provides students a way of finding impartial review of their situations outside of their own laboratories if they were concerned that their professor's financial interest may be compromising their educational experience.

All of these might be less troubling if it were not for the fact that we have a collective interest in commercializing research because of its benefits to the economy and public health. So, in some way the public health and the economy are weighed against, or could at times be in conflict with, the interests of patients, science, researchers, and students—at least potentially.

Now, what should we do about all of this? My own view, and the one I think increasingly accepted in the scientific community, is that conflicts of interest, real or apparent, that threaten patient well-being are not acceptable. Therefore, conflicts of interest that directly affect patients in clinical trials need to be carefully regulated and perhaps prohibited.

Conflicts of interest that may cause damage to science in some generic sense are much more difficult to assess and I think need to be weighed against all of the harms and benefits that result from these relationships.

Since I am a researcher, I want to call for more research on this topic, exploring the benefits and risks. I do not think we fully understand them at this point. We also need to explore the effects of alternative policy interventions in managing conflicts of interest.

I think there is a rationale for prohibition of one type of conflict of interest, and that is financial conflict of interest involving research on living human subjects. I also think that it is probably appropriate to ban certain collections of conflicts of interest because they distract the university from any effective supervision of its faculty. Those are the kind I mentioned with respect to Boston University, in which the web of institutional

interests is so dense that it is not clear who is supervising the interests of the university.

But for the management of other kinds of relationships, I think that we can agree that disclosure of all relationships, including institutional equity, is necessary, and that there may be a role for certain kinds of limitations in gains; for example, those associated with the sale of equity in companies supporting faculty research.

This is an area of continuing interest. I hope that it is one where we will continue to be sensitive, not only to the benefits of academic-industry interactions, but also to their harms. I think that in the long-term, it is in the best interests of all parties involved.