

**A Special Interview with Dr. Beatrice Golomb
By Dr. Mercola**

DG: Beatrice Golomb

DM: Dr. Joseph Mercola, DO

INTRODUCTION: Welcome everyone. I'm really honored to have with us today a world class expert in helping you and all others understand some of the interactions that drug companies have on the scientific method. Dr. Golomb agreed to join us today and share some of the information she has uncovered over the last number of years.

Dr. Golomb, thank you for joining and I'm wondering if you could tell our listeners what your training is. How did you get interested in this field?

DG: I'm an MD and a PhD. I'm an Associate Professor of Medicine and an Associate Professor of Family and Preventive Medicine at the University of California at San Diego. I have been interested in this issue prior to the work as I was doing research on statin cholesterol-lowering drugs, in which I was initially perplexed between the disparities that I saw between the published evidence, review papers, guidelines and follow-on papers after trials were published.

I was perplexed about how these data could draw people to certain conclusions that they appear to be coming to. I would ask my colleagues how could they have read this paper and have come to this conclusion.

Over time as I began examining the evidence relating to conflict of interest and published results, I began to see that there were forces at play that both lead to disparities between the evidence that was published relative to the "truth" of the evidence that was procured. There are also disparities between the secondary representations of that evidence and the evidence that was published.

There is actually widespread evidence even within the medical literature which shows that these forces can lead to qualitative differences in the conclusions relative to the fact.

For example, FDA analysts now have access to clinical trials whether or not they are published because of clinical trial registries that some journals now require. They require that a trial be registered in one of these registries and its conclusion be allowed to get published in a major journal.

Now, that doesn't actually require that those results then be published but at least now there is an opportunity for the FDA to get access to the existence of those studies and sometimes to have access to the evidence from the studies.

So, the FDA conducted an analysis of antidepressant drug trials and found that out of 38 trials for which the evidence appeared favorable, 37 had been published, whereas out of 36 trials for which the evidence were unfavorable toward antidepressant drugs, 22 weren't published at all and 11 were published in a way that misleadingly conveyed the outcome as though it were favorable.

Therefore, research that goes to the published evidence would result to over 90% of publications which were favorable relative to the truth, or at least 50% as determined by the FDA analysts.

So, essentially, the difference between unanimity and a coin toss with readers of the literature is that they appear to see that the results were consistently favorable relative to actual trials. They show that they were about as likely not to show favorable outcomes just to show favorable outcomes.

So that's an example of how the evidence we see can be dramatically different from the evidence that was procured and there are actually a number of mechanisms that lead the procured evidence to already have disparities that generally favor treatment benefits relative to truth.

Those rely in part on factors like how subjects were selected for participation in clinical trials, which often end up leading to people who are non-representatively unlikely to experience adverse effects and sometimes more likely to reap benefits. Often, for very noble reasons like protection of subject against harms, etcetera in clinical trials, and cost efficiency by selecting those subjects that show the biggest benefit etcetera, the result is that the findings of the clinical trials are not representative of the more general population to whom the treatment will then be given.

DM: Before we go on to another example, I just like to frame this into perspective. When I graduated from medical school in 1982, one of my motivations for going to school was to actually learn about health and wellness and not necessarily to treat disease.

But during the course of my training and like you, I'm a family physician and I did my residency and family practice, yet I don't have a PhD as you did have additional research, but my perspective was really altered and shifted to the point where I began to think in simplistic terms. I was really brainwashed, manipulated and really convinced in almost every type of educational interaction and intervention that I received, I was convinced that the drug model was the primary method to treat almost every single illness. If there was an illness, there was usually a prescription that would follow.

Through some long, hard efforts and time, I was gradually convinced. I mean, you mentioned antidepressants – I had put thousands of people on antidepressants

because I was so convinced about the data that they had presented. But through time, effort, energy, and independent study, I came to realize that this was not correct.

And why I'm really so excited about your research and what you're uncovering because many of our critics claim that we are abandoning the scientific method and I think nothing can be further from the truth. I just have enormous respect for the scientific method and I think when it is done properly, it can clearly provide us with an amazing discovery of the truth and help us; it can really guide and direct our treatment protocols.

But the problem and what many people, the vast majority of the public from my perspective, and I am interested to hear your thoughts on it too is that these critics fail to appreciate that much of this research has been really influenced with tremendous conflict of interest that you carefully detailed. I'm wondering how you came to that process. It was through the statin drugs. Do you have any epiphanies or what catapulted that whole process for you?

DG: Well, I think the specific thing (inaudible 7:02). There was a trial called the Prosper trial, which is the first randomized trial of statin use in elderly patients. It took patients who were not just elderly which already gives them high of heart disease but they had in addition to either have heart disease which is a group that in general shows greater benefit with these drugs or have additional high risk factors for developing heart disease.

So, she looked at their rate of death from heart disease, it actually matched the rate of deaths from heart disease of the second highest risk study that had been done with statins in middle age. And in that study in middle aged men, statins actually lead to life prolongation at least in the clinical trial samples that was selected for study.

But in the Prosper trial, all (inaudible 7:44) mortality was absolutely neutral. No hint of a trend towards benefit. And all (inaudible 7:48) morbidity was similarly completely neutral. No hints of a trend toward benefit. Stroke risk was neutral and there was a 25% increase in new cancer that was statistically significant in the statin group compared to the control group.

But if you read the abstracts of the paper, the abstract for this drug company funded trial stated that this trial extends to the elderly the treatment strategy used in middle age. I was stunned by that. I thought well, okay, so the trial that drug companies funded and that may explain how they choose to interpret the findings so favorably but surely the follow on literature will recognize this and draw strikingly different conclusions.

But instead I saw articles with titles like, Elderly under Treated and Drug Extends Treatment to Elderly. I kept thinking, do these people actually read this article. And then (inaudible 8:42) as I became aware of the literature on ghost writings...

DM: I'm really curious as to...sorry to keep on pestering for this, but you know, the vast majority of physicians are reading the same literature you read and they're not

motivated to pursue this at a deeper level. I'm wondering what variable, factor or epiphany motivated you to study this so carefully and to draw out these details that so many physicians for whatever reason choose to ignore.

DG: The problem is I really can't read the mind of other physicians but the challenge to me is not that I am concerned about this but that everybody else has not been summarily concerned about this.

DM: Well, you recognize that's the case. We are talking 99.9% of physicians who do not make the same criticisms or do the careful analysis that you've done. Maybe it's not 99.9...

DG: Not only that...

DM: It's a huge majority and perhaps as high as 99%.

DG: I would certainly imagine that it is as high as that. I think they often haven't been...perhaps they haven't encountered an issue that they have looked at deeply enough to recognize these disparities or perhaps there are other factors. But I will say that it really wasn't just statins either.

A number of projects were around in which again, I seem to see these systematic disparities generally in favor of treatment in representations of the evidence and in guidelines relative to the published evidence. But it wasn't really even just the statin issue.

DM: Well, you have an MD and a PhD but prior to...some of our listeners might begin to appreciate some of the motivation behind this is that, weren't you the scientific director for the Department of Veterinary Affairs and Research and Advisory Committee on the Gulf War Veteran's illnesses?

So, you've had formal training on this area that may predispose you to be more sensitive to the specifics that many other physicians are just not attuned to.

DG: Well, I would perhaps phrase it the other way. I think part of the reason I got interested in the Gulf War area was that I was already concerned at that point about the way the inferences were drawn about that condition. I was approached by the head of the RAND health program to ask if I wanted to be involved in the set of reports related to Gulf War illness and I had seen the conclusions of the Institute of Medicine and the Presidential Advisory committee reports relevant to Gulf War illness at that time.

This time was the 1990's and those reports essentially rephrase what they said, to make clearer the way the inferences were drawn. Inferences were basically absences of proof of a connection between organic factors and illness, which is interpreted as proof of absence of a connection between organic factors and illness and since no one had

looked and therefore, no one had proved that the exposures they had received were related to their illness.

These then concluded that there couldn't be a relationship. But you couldn't conclude that there was no relationship because there was no evidence. Nobody had looked or even asked if it was biologically possible and therefore, it merited more inquiry.

So I jumped at the chance to participate not because I had any conclusion either direction about whether Gulf War veterans were ill or whether it was related to exposures that they had experienced but because I felt that an honest inquiry hadn't really taken place and I wanted to make sure that one was. And when closer inquiry didn't take place, it was clear that some of the exposures that Gulf War veterans had strong biological plausibility as precipitants for their illness and I outlined in one of my reports a research plan that would help to evaluate whether or not, there was a cause of relationship.

And now, a number of those studies have been done including my suggestion that we look at the genetic variants of the enzymes that detoxify some of the chemicals they were exposed to on grounds that if these chemicals were causally linked to illness in people who have sluggish variants of these detoxifying chemicals should more likely be ill and sure enough, they are. People who had higher levels of exposure to these chemicals would more likely be ill and sure enough, they are.

In animal studies exposing animals to these chemicals, I suggested that we should look at long-term effects, which might differ not only in amount but in direction from short term effects and sure enough those long term studies have shown that if you look long after exposure, you'll identify new abnormalities that weren't present immediately after exposure. So, in that case, I think it wasn't just the fact that I was involved that conditioned me to be concerned about the evidence but it was also the concern about evidence that conditioned me to be involved.

DM: Well, thank you for that clarification. I believe the largest drug companies earn about 500 billion, that's half a trillion dollars annually and that's certainly quite a bit of revenue that one can use for a variety of reasons. From your investigation, how much percentage of studies that are currently being published in the medical-clinical area is actually being funded by the drug companies either directly or indirectly?

DG: I've never looked at that question and it would very much depend on how you ask the question. Certainly in the case of statin (inaudible 14:09) are the areas that I'm probably most closely familiar with, all of the large randomized control trials are drug-company funded. All of them.

DM: All of them not just the majority. Your review and this is your area of expertise, and you've carefully looked at this and your conclusion is that all of them are funded by the drug companies. Is that correct?

DG: That's correct.

DM: Wow, that's quite a statement.

DG: Yeah, all of the large randomized control trials are drug-company funded right.

DM: That is just profound.

DG: Right. It's very expensive to do those studies. The only other source of funding for reasonable sized studies is the NIH and we approached the NIH actually to conduct a study and see whether coenzyme Q10 might mitigate muscle side effects of statins. We were told by NIH officers that they wouldn't even consider a lot of requests to do the study unless we ask the drug company to supply the statin that was used in the study.

And so I contacted the NIH and I said, "I'm really trying to have a career free of drug company conflict of interest, would it be such a problem to have one study that doesn't have a drug company involved in it?" And they said somewhat reasonably that their interest is in leveraging their funding and therefore, "no they would not consider an application as we asked the drug company to supply the drug," which of course already set some level of conflict of interest.

The problem is there are finite funds available for research and the NIH, which is the only other source of sizeable funds, generally not quite as sizeable as they are required for the really large drug studies, it also has an interest in leveraging its resources and providing funding to a larger number of trials, which then motivate further conflict of interest issues associated with (inaudible 16:02) participation.

DM: Let me just interject here for those listeners who aren't familiar with the NIH, that's an acronym for the National Institutes of Health and is really the government-sponsored and funded health agency and as you mentioned, next to the drug companies, NIH is the largest single source of funding for these studies and when one independent objective, truth-oriented researcher seeks to go and do these conflict of interest retrials, you're obviously going to need funds to do that.

When you go to the only other option really that's available, the NIH, the people from NIH are refusing to do it because they want to "leverage their ties with the drug companies," which is just extraordinary.

DG: Well, they want to leverage their money and one of the ways to do that has the unfortunate side effect of producing ties to industry. And so I will say that there maybe others but I am the only researcher of drugs that I am aware of who actually has tried or has so far not had drug company conflicts of interest.

DM: I'm particularly curious too about the coenzyme Q10 issue that you mentioned, is it true that in Europe, which is clearly a whole different scenario, it doesn't necessarily have the same guidelines or conflicts of interest that we have in this country? I would

be interested in your comments on that. Have they done trials or is it professionally a standard of care to actually recommend coenzyme Q10 when they're administered in the statin drug? That was my understanding that it's almost a malpractice not to co-administer them when they're giving a statin drug in Europe.

DG: I'm not actually familiar of any standard of that kind. I have heard that and I would actually need to look this up to verify it but I've heard that in Canada, the labeling on statins mentions that statins lower coenzyme Q10 and I know certainly that in Japan coenzyme Q10 is approved for treatment of heart failure but I'm not actually aware one way or another of whether there are those propensities in Europe. I certainly haven't heard of that.

DM: From your experience, are the funding challenges somewhat similar for objective researchers like yourself in Europe, do they still have the same challenge when they're seeking government funding to do a trial – that there is this connection to the drug companies – or is it more objective?

DG: That's very interesting and I 'm actually going to answer your question a little bit indirectly. It's my perception that this is changing in the untoward direction but some years ago, I was involved in a panel reviewing a set of responses to a contact put out by the NIH.

The NIH was interested in people who perform studies to evaluate whether more intensive drug treatment for diabetics was the superior standard of care, where more intensive drug treatment was for both blood sugar levels and blood pressure as well as blood cholesterol. And what I found fascinating is a number of people then proposed to science to do this study and submitted them to the NIH and this review group was evaluating those studies.

And what was fascinating to me was with perhaps 30 reviewers in the room, there were three of us who viewed this as a two-sided question meaning that more intensive therapy might either be better or it might be worse and it was me and the two reviewers who were not from the United States.

One was from Canada and one was from Sweden. Out of the 40 or so applications that came in, there was one that treated it as a two-sided hypothesis, meaning it didn't presume that more intensive treatment would be better and that was the one application that was not from the United States, it came from Canada, but my colleagues in Europe are telling me that the drug company involvements are actually becoming more extensive now outside of the United States and that they're beginning to experience some of the (inaudible 20:01) challenges that we have here.

DM: Well, thank you for explaining that. Now, I'm wondering if you can go into some of the other details that you've uncovered with respect to the actual publication process, which many of our listeners are not familiar with. You've mentioned clearly the initial part of the process, which is the funding for the actual trial but once one actually

collected the data, then there is a whole other set of variables with respect to submitting them to peer-reviewed journals and so. If you can go into that, you will uncover some amazing details there.

DG: Right, so we've already alluded to as you pointed out that there are funding disparities and that less favorable studies, which drug company funded are less likely to be submitted for publication. Then, there are actually issues at the level of the journal and it would be nice to think of medical journals as these bastions of truth and light and that they have no bias but in fact, they're businesses and they make their money through many cases, from drug company advertisement and also from sales of the glossy reprints of the drug and favorable articles to industry.

Interestingly, several former editors-in-chief of major medical journals such as Richard Smith of the BMJ (British Medical Journal), Richard Horton of the Lancet, and also a couple of former editors-in-chief of the New England Journal of Medicine, have actually each written books and opined heavily on the favorable impact of drug company influence on medical publishing, where there are strong conflicts by the journal to publish favorable articles for the drug company in order to reap those hundred thousand dollars or so in reprint sales for the favorable articles and also to keep the drug companies happy so that they continue to get drug company advertising.

DM: But before we gloss over that, it's an important point because many of our listeners may not know that there is an occupation, which is called and many people have heard of the detail man or woman whose actual sole responsibility is to go and educate "physicians" about these new drugs and in the process of doing that, one of their tools is to provide this reprint of a favorable study and that is not something that they go to their home office and photocopy because that would be copyright infringement.

What they need to do is they actually have to pay for that reprint from the journal and that's exactly what you're referring to. These reprints, in many cases, cost six figure amounts, and generate a hundred thousand dollars extra additional revenue over and above the advertisements that are being paid by the drug company. The drugs company then gives this which to the journal for publishing the study. It's another perk for them.

DG: That's correct and as Richard Smith, the former editor-in-chief of BMJ, cites that the publisher can either publish the shoddy quality drugs favorable (inaudible 22:53) and reap the one hundred thousand dollars in revenue in order to meet their end of the year profit goals or they can even fire the editor who declined to publish it and has set up striking conflict of interest.

Also, as a New York Times article noted, several editors of major medical journals who were willing to give information if granted anonymity pointed out that journals not long ago counted their profits and in the tens of thousand of dollars now make profits in the

range of millions of dollars. So, the amounts of money that are at stake are not small and the evidence, that in fact this has had an impact, comes from several sources.

One was the Annals of Internal Medicine. Some years ago, it published an article on the impact of drug company advertising on physician behavior and also how accurate drug company advertising was to physicians. And the article was not flattering to drug company advertising. Somebody taxed the impact on the Annals' revenues with regards to publishing that article. He/She tracked what the trajectory of revenues was before the article was published and after the article was printed.

You can look at that and of course make some comparison to how other journals are doing. The researcher estimated that they lost 1 to 1.5 million dollars in advertising revenue over the ensuing several years as an apparent consequence of having published that unflattering article. As I was told by someone who was cautioning me against going into the issue of looking at drug risks and benefits, every one of the major medical journals sat up and took notice.

And there is direct evidence now as well of drug companies rejecting unfavorable articles, which are articles unfavorable to industry based on factors other than article quality. An example of this was...

DM: Before we go there, let me just finish up this one area, an important question to help put things in perspective. How many clinically significant medical journals are there? There are hundreds, thousands, tens of thousands, so what's the total basic universe that...I mean, just the proximate...

DG: It totally depends on how you define clinical significance.

DM: Well, from your perspective. I mean, that's obviously subjective but from your perspective, would you say there are thousands, ten thousand? What's the range?

DG: Again, I don't know what you mean by clinical significance. I'm not really sure how to even begin to address that question. Certainly, there are, at a minimum, hundreds of medical journals that, you know, if you count the different sub domains of medicine, general medicine, infectious disease, cancer...

DM: So, let's say there are a thousand top journals. Let's say there is a thousand just for the basis of discussion. You outlined some very significant criticisms of this whole process. So, of these thousand top journals, what percentage in your experience would you say are really affected significantly by them? Would you say that it is the majority? would you say it is 90%? Do you have any idea from your impression and experience in this field?

DG: I try whenever possible to avoid drawing inferences beyond evidence and what I will say is that for the published ones that have high "impact" factors, meaning that people look at them a lot and cite them a lot, certainly most of the top, well-read medical

journals, perhaps with the exception of some of the recent online journals, involved drug company advertising.

DM: Thank you for allowing me to ask that question. So you can continue with some of the other challenges that you've uncovered that really contributed to this perversion of the truth and promoted in a non-conflict of interest way. So tell us what you've learned.

DG: So, I'm going to sort of finish up on this one a little bit to give an example of why we know that sometimes unfavorable articles are rejected and there is a substance that people may have heard of, it's called erythropoietin that's used for example by athletes to increase the number of red blood cells that carry oxygen but it is also used in end-stage renal disease.

Erythropoietin is a strongly marketed drug and somebody wrote an article to a reputable kidney journal pointing out the evidence for "mortality" benefit with this drug in end-stage kidney disease and therefore the guidelines that recommended their use were based on flat analyses.

And in this particular case, all three of the peer reviewers favor the publication of the article and the editor was actually either honest or stupid enough to put in writing to the author that whereas he and all three of the reviewers favor the publication of the article, he was overruled by the marketing department for the journal. And this was put in writing.

This author then forwarded this to Richard Smith, the former editor-in-chief of the BMJ who has become an activist in this area. We have no idea whether this happens frequently. Certainly, I think most editors would not put that in writing and the more likely scenario would be that the author would receive a letter saying this is not of interest to our journal. But we know at least that there exists some cases in which that happens and we really have no idea how widespread that is.

Another issue that has come to light particularly when there has been litigation against companies for factors like, for example, pushing off label indications in Neurontin. With the Vioxx litigation, what has come out in the discovery process during this is that drug companies often go straight to "scientific" articles.

That is to say they write a review article or a primary article and submit to a scientific journal but what they do is either they write it or they hire what are called MECCs (Medical Education and Communication Companies) which are for-profit companies that essentially are purely funded by pharma to do these kinds of activities.

They' will either write an article themselves or have MECC write an article that favorably spins their drug and they will then find an academic who is willing to be the listed as an author of that article. So that there will be no apparent connection between the drug company and the MECC in many cases related to this article.

And they will then essentially flood the literature with favorable (inaudible 29:25) on ghost-written articles putting their drug in a favorable light. To me, this helps explain these findings on why the secondary articles after the Prosper trial were so favorable and so inconsistent with the actual findings and the study. Now that I understand this ghost writing process, that makes far more sense to me.

And another issue that has been uncovered is the issue of duplicate publication. So, it is considered unethical to republish the same clinical trial multiple times. It's just considered an ethical breach. In fact, one set of authors looked at a particular drug called Ondansetron that's used as an anti-nausea, anti-vomiting agent.

They did an extremely careful review of the literature and it was very difficult. They identified that a high fraction or substantial fraction of the clinical trials related to that drug were published not just once but several times over in a way that hid the fact that it was the same study being republished to changes in the author list and changes in the methodological details.

The studies that were more favorable to the drug were more likely to be published. And so that if one data what's called a meta-analysis or aggregate analysis of the effect of different multiple clinical trials, this process of plural publication and by the way, the same study was published as many as five times which led to a considerable over estimate of the efficacy of the drug and the authors noted that no other reviewers in this field had actually detected that it was the same studies being republished by sometimes as many as five times.

So, that's another way in which there is a sort of further perpetuation of the disparity between published evidence and the truth. And then, once you have all this published body of evidence and the unfavorable trials are less likely to be submitted and published and favorable trials being more likely to be submitted and published in duplicate, have favorably spend review articles published upon them...

DM: Before you go over it, I mean you established one statement but I think that's a huge one and I think it will bypass most of our listeners' appreciation. These favorable reviews, can you go through the process?

Let's say this heavily funded study that was influenced by the drug company and then additionally influenced by the editor to publish this for their marketing department. The next step is that these favorable reviews are published by experts. Can you describe that process a little bit?

I think it's a bit similar to the ghost writing process but it's also quite different.

DG: It is different, right. So we have information on this process, wherein during a certain period of time, a specific subclass of drug could actually work for a time. The most widely prescribed drugs, a subclass of what are called calcium channel blockers (and I won't go into what the subclass is), but they were widely used as blood pressure

lowering drugs and then somebody did some analysis that suggested that they may increase the risk of bad (inaudible 32:38) events.

And there was a period during which this was a subject of intense debate in the medical literature and an analysis was done on whether published statements about calcium channel blockers were more likely to be favorable, neutral or unfavorable as a function of whether the authors of those statements had drug company conflict of interest. It was either a calcium channel blocker manufacturer or with drug companies overall.

There were two striking findings: one was that in general, there were very high levels of conflict of interest, so even among those who published unfavorable statements, I think it was in the order of 40% (inaudible 33:21) drug company conflict but then it was on the order of 60% for people who publish usual statements and in the high 90's for people who published favorable statements when in fact, in about a hundred percent of the studies with favorable statements, the authors had conflict of interest with some drug company.

So, one way that one could interpret these findings during this period and state the evidence of making favorable statements about those drugs was with the drug company conflict of interest. These conflicts of interest are so very widespread. (inaudible 33:58) provide these enormous pushes toward favorable spinning of information related to drugs in the medical literature.

DM: Don't the major journals have specific policies regarding conflict of interest and require the submitting author to declare their conflicts? How does that work? How do they get around this and are able to still publish these findings?

DG: Let me say first that that's a moving target and it's not always a case but many of the major medical journals have these policies particularly for editorials. But unfortunately, it was sort of discovered that it was virtually impossible to find or that was the claim of people who make choices out of editorials who didn't have drug company conflicts. Somebody actually did an analysis of editorials in one of these journals and I don't have the exact figures at my fingertips.

He/She did one analysis about the top medical journals and found out that these journals actually have such a policy. It was actually found that despite this policy, the majority of the editorials written actually involved people who did have drug company conflict of interest.

Of course, there is also the issue that even when there are these policies for disclosure, what a colleague of mine told me is that initially, for example, if I give a talk with the American Heart Association, they just have a disclosure slide at the beginning and that initially, people actually took that seriously and gave their disclosures.

Then the speakers discovered that people sometimes looked more askance at their findings. People became perhaps a little bit less careful about doing those disclosures.

And I did a debate some years ago at the American Heart Association, the original title of which was supposed to be, "Should statins be put on the water supply?" And I was told that originally they thought they would find nobody to take the no position, which tells you how sort of strongly spun that area is.

But the night before the debate, I was at a dinner in which there were a number of people including the person I was going to debate the next day with. He apparently forgot that I was sitting across from him at the dinner table and told the person next to him that if I were really to disclose all my conflicts of interest, it would take four slides to which that prominent researcher said, "if there is anyone I'm not on the take from, come on over." So, that also gives you a sense of how convoluted the attitude is toward these conflicts of interest in medical research.

Actually, there was a case recently, a year or so ago, in which somebody wrote an article on one of the major medical journals that purported to find the benefit of a psychiatric drug treatment over a non-drug therapy for psychiatric condition. And the author read a letter to the editor saying, "Gee, even the data in the study didn't really appear to support that conclusion" and that letter to the editor was published.

But then this individual, Jonathan Leo, did a quick Google search and found that the authors of that article actually had conflicts of interest with the company and that made the drug they were touting in conflict with what they hadn't disclosed. And so then, Jonathan Leo attempted to contact the editors of the journal with this information and they sort of said they would follow up and over the next several months, he tried contacting them to find out what had come of this and didn't seem to be getting any replies.

So he wrote a letter to BMJ Online describing this and actually instead of the authors of the journal reaping the negative consequences of this, they were played out on him. I guess the deputy editor called him and essentially according to him, the editor told him that unless he retracted this letter to BMJ, not that there was anything factually incorrect on it, he would be sorry.

His students would be sorry. He would be barred from life for the major medical journal, which I will not name. And the editor-in-chief called his dean in an apparent effort to put pressure on him to withdraw the letter. These issues are complicated and it's quite clear that these conflicts of interest are not always disclosed.

DM: What you described really sounds like a devastating collapse of the whole system. It just really doesn't work and it has been modified, morphed, and changed into really nothing more in many cases, perhaps if not most, a marketing arm of the drug companies.

DG: I think that's a serious concern - that there is a large number of unequal partnerships with industry, partnerships by academics, partnerships by journals, and partnerships by patient advocacy groups that often functionally end up rendering each

marketing arm of industry or at least certainly swaying them toward that direction relative to where they would have been had not been these unequal partnerships where money is received from industry. And it really does often lead to the question, “how do we ascertain the truth from the evidence that’s out there” and all these body of evidence makes it very clear that that’s extremely difficult to do.

DM: I’m personally curious how you were able to insulate yourself from this conflict of interest. I mean its obviously some strong personal motivation that you had. So what motivated you and then how were you on a logistical level able to do that because it takes funding to get these studies published? I mean, did you do it philanthropically out of your own funds or were you able to find an organization to fund your trials, studies and research?

DG: I would say some of both. My income definitely goes toward my research and we did actually have one sizeable NIH randomized (inaudible 39:50) that was funded without a drug company, sizeable but not on the scale of multiple thousands but it did have a thousand individuals. I got a small award from Robert Wood Johnson General Physician Faculty Scholar award that none of which went to my own income but rather to support a project that I thought was important although it was intended to go to me.

We now have a small study, funded by the Department of Defense, which looks at coenzyme Q10 in Gulf War veterans. So we’ve had funding from a few different sources over time and are desperately looking for other ways to get funding. We’ve also had small donations from some subjects who had adverse effects from statins who we felt have been helped by our work and that’s been really nice. The amounts of money are quite small.

DM: The details you have been able to uncover are quite fascinating. Have you come to any conclusions, ideas, and suggestions, if there is any hope about this whole system? Is it recoverable? Is it modifiable? I mean, we’ve got these policies in place but are really in name only. Clearly, from the examples you’ve given, these policies are just really ignored and more than ignored, they’re also violently not implemented. So, can the system change or is it permanently broken?

How to Resolve Drug Company Influence in the Medical Field

DG: I think there are a number of things that could be done that would mitigate the problems and since there are already these clinical trial registries, why not add something else to that? So right now, federally funded studies in principle, meaning large enough NIH-funded studies for example, are supposed to be willing to make their data public access or publicly available after some time that the study is completed.

Why not demand as part of entering your trial internal registry, that you make those data publicly available at a certain time? Now, you know, this doesn’t completely protect against willful manipulation of data but if people are not willfully manipulating the evidence, then at least those data will become available whether or not the drug

companies choose to publish them themselves. So that's one thing I think that should happen.

DM: And the reason for this is that as a committed clinician, academic clinician who is seeking to identify the truth, for people like you who are in this position, it is virtually impossible to do that because when you read the scientific paper, many of our listeners have never done that because it's a different language for them. It's basically impossible to analyze it because they don't include the data sets. Is that the reason you're suggesting this?

DG: That's right and there is extremely strong evidence that they're doing some form of selecting the favorable outcomes or something like it. We have very good evidence for this from head to head trials of different classes of drugs. There is one article that was very cleverly entitled, "Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine:

An Analysis of Head-to-Head Trials of Second Generation Antipsychotics." Basically, the article noted that these drugs are basically in the same class and have approximately the same likelihood of benefit. Whoever funded the study had its drug come out on top or about 90% of the time. And there was this similar analysis of head to head trials of statin drugs in which the odds for the results being favorable toward whichever company funded the study were 20 to 1 and the odds for the conclusions being favorable were 35 to 1.

So this makes it extremely clear that if you have two drugs that are approximately equal you can make either one look better either by selecting your outcomes or by whatever other processes and this poses an extremely frightening question, "if you can create odds so high favoring a drug over one that it is inherently not superior to, what implications do that have if that other drug is called placebo?"

DM: Yes, indeed. You've done a masterful job in uncovering the process that is typically used to promote these drugs. However, I'm wondering that the beginning of the process starts when physicians are educated in medical school. That's when they start the brainwashing from my experience.

I'm wondering if you found or what have you uncovered in that perspective?

How are the medical students typically initiated in this process and oriented to this perspective?

DG: There are several issues involved. One is that most of the physicians who are doing the training are all conditioned by the existing literature and the existing "expertise" which is influenced by all the factors that we've just mentioned.

So, they legitimately believe the benefits of these drugs often to a degree that's not even supported by the published randomized trial evidence because it will be supported

by the follow-on review papers, commentary expertise and guidelines. But I will say that medical students have actually been on the vanguard of trying to make change and the American Medical Student Association (AMSA) actually developed a policy of trying to rate the impact of conflict of interest in the classroom.

My understanding is that this was motivated initially by a Harvard medical student who had listened actually to their lecture on statins and somebody in the classroom had raised his hand and asked the question about statin adverse effects. It was answered in such a derisive and dismissive way that this other student looked up the lecturer online and discovered that he had all these conflicts of interest with the statin industry.

That ended up prompting the student group to try to take action and you actually had to look more into the details of what that action is but my understanding is that initially Harvard received an (inaudible 45:47) but it was later upgraded. I can't recall to B or an A. I don't really know of the processes that were put in place, how much they do to remedy that situation but at least it's taking a step in the right direction.

And I will say that I certainly had the impression that the lecturers on statins who were there had to be extremely, strongly biased because my husband and I had dinner with a colleague of my husband. His daughter was at Harvard Medical School at the time and he shared with us that the day they had their lecture on statins, his daughter called him up and said, "Dad, make sure the day I turn 30, you call me up and remind me to start statins."

The randomized trial evidence does not support benefit to the patient, that the outcomes balance the benefits and risks like mortality or (inaudible 46:29) morbidity in any group of women, including those with heart disease. It will take a fairly strongly slanted lecturer for her to have come to this conclusion.

So, I think those issues do begin in medical school. I will say that for both medical school and also graduate school, there really is very limited training on how to evaluate evidence. There is very limited training in epidemiology methods, forms of bias confounding, selection of facts and also logical fallacies, which are frankly rife in medical articles.

DM: This is somewhat surprising that you were able to, I guess, garner your expertise because as you mentioned this is really not traditionally thought. You have to acquire in some other fields because they're not going to teach you this in almost every medical school.

To me, this seems one of the most foundational skills to learn because I remember from my medical education, they said that 95% of what you're going to learn in school is going to be outdated by the time you're practicing. So you really do need a skill set to help you evaluate all these new research and yet they aren't giving you the tools and training on how to evaluate the data sets.

DG: I absolutely share that conviction with you. In fact, it's my opinion that it should start in grade school. Like English and Math, it should be one of the key things that is taught and it should be taught and upgraded essentially throughout one's education much less for people who have a career in science or in medicine. I completely agree with you on that.

DM: Another aspect of the medical education is once physicians graduate and actually start practicing, they are exposed to influences outside of the journals and to subsidies given by drug companies for their education such as symposiums and lectures. see (inaudible 48:23) They're getting these seminars.

They're attending seminars that are directly funded and all the freebies of course – the lunches, the sponsorships, and the speaking fees – to the point where I believe it's something like 18 billion dollars, and around 10, 20, or 30,000 dollars per physician every year in the United States.

DG: And my understanding is that that number has actually gone up since that was published. That is a very serious issue. The most striking example: I will say that if I go to a meeting by the American Heart Association (AHA), for example, there is certainly a lot of evidence of industry conflict when I arrive, pay my registration and (inaudible 49:07) get my bag, which has on it giant letters of "Crestor" on it.

This was a couple of years ago. I still have that bag. It will have pens with drug company material and there will be the big rooms with all the drug company freebies and so forth. Those are smaller in scale and scope than they were some years ago. So, there has actually been, as I say, a moving target. There has been some transition in a favorable direction.

And then typically, the drug companies will put on satellite symposia where they'll have a fancy dinner and fancy entertainment, which you can attend for free in turn for hearing the very obviously spun representation of the evidence. But one year, actually at the American Psychiatric Association, the drug companies did something worse. So, in principle, at the main meetings, usually the drug company conflicts are indirect.

The reviewers who choose the articles have drug company conflicts that may influence them to that process but there is no direct drug company involvement usually. But it was actually uncovered by an investigative reporter, who found that at the 2002 American Psychiatric Association meeting, drug companies were actually allowed to choose which topics would be presented, which actually helped shape the presentation., for \$50,000 a session.

When the head of the American Psychiatric Association was approached by the reporter on this, he said, "Well, if we didn't have drug company subsidies for this meeting, physicians would have to pay \$500 or \$600 to come instead of spending a couple of hundred dollars only. If they would pay more, then a lot of them wouldn't be able to

come.” Of course, if they’re spending all these money, the drug companies expect to have some say in what’s put on the seminar.

The counter to that is that if physicians knew that what they were going to do was not sort of a partisan balance representation of evidence but functionally drug company advertising, they wouldn’t be willing to pay any amount of money to go. So yes, there have been extremely overt examples of drug company influence uncovered but usually they’re somewhat more indirect.

DM: It seems like most physicians are aware of these either directly or indirectly but they choose to ignore the potential influence that these has on them.

DG: I think people often feel that they are impervious to the influence and that they themselves can not be affected by it. I think some of the more sort of self honest ones are probably aware that since it is influencing the information that comes to them, it influences their behavior. There was also an analysis by clinical guideline generating committees, which found that most of the committees had members that had drug company conflicts.

It noted that they had, on average, 80% of the members who had such conflicts, and 10.5 industry conflicts on average, and that when they pulled the members of these guideline generating committees, about 20% of them felt that other committee members were influenced by their conflict while a significantly smaller percentage believe that they themselves were influenced by their conflict.

DM: That’s another massively crucial tool that is being used because as you mentioned these expert committees, in many cases, are providing the recommendations for professional societies or even national recommendations from the government such as vaccines . Therefore, many of these committees are basically loaded with experts who have massive conflicts of interest. So, it can’t possibly generate an unbiased objective recommendation.

DG: You know I think that’s exactly right and on my list of “solutions,” which are recommendations to try to at least mitigate this problem, one of the recommendations is that guideline generating committees should be constituted purely of people whose expertise is in epidemiology methods. People whose expertise is in balanced, unbiased analysis of evidence and people who have direct involvement with industry and actually use these drugs should be excluded from participation.

There is a British Columbia Office of Technology assessment review of clinical practice guidelines that found that the more “clinical experts,” who use these drugs and interact with industry are on guideline generating panels, the more the recommendations of these guideline generating committees departed from the evidence.

DM: Well, I applaud that recommendation and I would like to offer my assistance and certainly commit to implementing that because it would seem to me that that’s a very

powerful strategic way to change this whole process and that the sad reality is that the bulk of the majority, if not over 99% of individuals who live in our society, believe that is what is currently in place.

They are absolutely unaware of this massive conflict of interest but in fact if it was substituted like you are recommending then, I think we could solve a lot of these problems. I would definitely like to offer any assistance and help in any way I can to get that process shifted over because I think it's an important shift.

DG: Right.

DM: So, now there are other physicians like yourself who have integrity and honesty and are really seeking to distance themselves from this conflict of interest. I can think of a few but you certainly know others. Can you identify a process that is typically implemented when these physicians stick up because they're typically targeted by the drug companies since they could stand to lose significant revenues from this. So what happens to these physicians?

DG: That's a very interesting question and there is evidence for both the current and the stick process for trying to influence physicians who speak up in unfavorable directions. We have actually from the "Merck neutralize memos" the discovery process for Vioxx.

There is evidence that Merck, which actually had in writing their internal memos, use the words "how do you neutralize problem physicians" to have unfavorable stated opinions about their drugs or favored a competitor's drug and some of the sort of more benign current mechanisms involved when giving them speakerships and offering them grants and so forth in order to essentially try to buy them off. This which shows that at least the drug companies already believe that giving grants and so forth influences physician belief and behavior.

But there is also evidence for less favorable approaches. So, for example, there is a person who later actually became head of the American Diabetes Association. He had presented evidence some years ago suggesting that a diabetes drug, Avandia, much later came out as potentially causing problems like heart failure.

He presented the data back in the late 1990s suggesting that this drug and a related drug class might cause such problems. Then, he received calls from executives in drug companies essentially implying to him that he could be personally liable for billions of dollars in lost market capitalization for the drug as a consequence of his fearless remarks, and they also called his dean and tried to put pressure on his dean to put pressure on him.

Now, obviously, this is an empty threat. If the market and stock for a drug goes down and if the person who made those remarks were responsible for the money, that would mean that anybody who said favorable remarks, which subsequently led to an increase

in market, should gain the positive side which obviously doesn't happen. But still that would be a very frightening phone call to receive.

Another investigator from France who saw my name tag at a Heart Association meeting approached me and asked if I had been the author of an article in the Annals of Internal Medicine on low cholesterol and violence. And he said, "Do you still have funding?" He had been the lead author on...you know, I'll protect his privacy and won't say what the study was, but he authored a study that had shown a large-scale epidemiological study.

The study showed that low cholesterol is linked to increase suicide risk and he had an unrestricted career development award yanked from him as a consequence of having published that. I will (inaudible 57:22) communication, she is studying one of the classic adverse effects of these drugs and it received very small grants from her own university to do laboratory tests associated with this and somebody else from her university who has strong drug company conflicts actually put pressure on the university to yank that from her.

There was a researcher who gave a talk, a researcher from a European country that I won't specify because I haven't been given permission by him to share this story but who had presented some information that was unflattering to this class of drugs. I actually approached him after his talk and asked if he had received any (inaudible 58:02) from this.

And he said that he had received a call from a vice president of one of the major drug companies telling him that if he persisted in presenting this kind of information, they would sue him, that their lawyers were bigger and better than his lawyers and that if he persisted, and that even if he won the case, it would destroy him financially.

And he did something far more savvy than I would have had the brains to do, he said, "I've been taping your call and we're passing the threat out to my lawyer at the end of the call" because that's legal in the country he's in and I didn't ask if he actually did that or if he was just smart enough to say it because I don't want to know. But it was either way a very smart thing for him to do.

I actually was taken aside by a researcher who had shown untoward effects of lowering cholesterol in an animal model. He took me aside after the talk he gave when I was at UCLA because he thought that I should know that they had...the chair of his department had gotten a call from a vice president of one of the major drug companies telling him it would be, and this was represented by him to me, "dangerous for them to continue to pursue this line of research."

So, there are these examples of apparent pushback by industry. Right, they have a lot of money on the line and perhaps it's unreasonable to suppose that you can go to have a publicly traded company where, on the one hand, there is a perceived obligation to stockholders and simultaneously expect them to have patients' best interests at heart. The two are sort of fundamentally incompatible.

DM: That is the basic crux of the problem. I mean, these are corporations whose sole commitment is really not towards public health but towards the bottom line of that corporation. Science evolves and develops and we learn more and more but what many people don't appreciate is the amazing science and it truly is a science of marketing and they have been able to really carefully identify the way to modify, mold and impress upon a vast large percentage of it, if not the vast majority of professional community, how to change and modify their positions on their supported topics.

DG: Right and you could argue to the degree that their stockholders are their obligation, that if you or I were put in charge of those companies and it was our job to improve the bottom line. we too would be putting into place all of these multiple strategies toward improving market share for our drug.

DM: That's true but I'm not sure all of them would do that because there does seem to be some really significant ethical breaches in many of the scenarios you described.

DG: I think there are very serious problems associated with them and again, the expectation is that you can somehow manage the duality of interests with the one being the stockholder and the profit line, which keeps the company alive and vibrant, and the other being the best interest of the patient. Perhaps, the assumption that these two are compatible needs to be reexamined.

DM: I ultimately think that the public needs to know that and many of the details that you've highlighted in this conversation really are commonly known. The end consumer on this is the public.

They are the ones who essentially are going to be the consumers of the drugs in question. Obviously, the physicians are the facilitators of that but ultimately, if there is a significant consumer resistance because they are educated, they understand that yes there are certain times when these drugs are going to be beneficial but is far less than the drug companies who have you believe in.

There are all these other variables that contribute to misinforming the consumers and if these people can understand that and make an informed decision, then they can vote with their economic pocket book and choose to refuse that drug.

DG: Right.

DM: So I think that's the key and that's really what our commitment is – to educate consumers primarily about these specifics and I really thank you for all you have uncovered and have done to help elaborate on the real challenges that we have in the system.

DG: You're welcome.

DM: We definitely would like to facilitate and help, as I said earlier, the transition to these impartial and objective advisory committees. I think that they really should have their expertise grounded in more of the epidemiological and neutral objective science than conflict of interest.

Thank you for all you have done and the best of luck to you in your continued research.

DG: Thank you very much for your time and interest.