Thanks, Lana. Well, we have been talking about whether we understand each other? Leonard Seeff this morning said he has been saying the same thing over years and years. Bob Temple has been saying the same thing. He points to the 2009 guidance. He has said it very clearly; it is all there. We keep saying the same thing, but people don't seem to hear it.

Thinking that maybe speech isn't the best way to communicate, maybe writing is more important. Write it down, and maybe we can get it better understood. So, I thought I would do a little experiment.
Lana said the theme of the conference is really about understanding each other. When we write something, we take trouble to try to write it carefully. Also, if we are going to get it published, it goes out and it is reviewed by our colleagues, who give it a tough review and they will criticize it. They won't accept it if it doesn't make sense. Then, it is also subject to editorial commentary and review. So, by the time it gets printed, it has been through a lot of critique. So, we try to write it carefully. It gets looked at carefully before it gets published.
Okay. Once it gets published, it is in the literature. Well, that's nice. About two years ago I was asked to write a chapter for a new book on antitargets. Now what is an antitarget? An antitarget is a site, a receptor, that is affected by a drug that is not intended to be affected. So, it is what is causing the adverse effects. The target is the therapeutic effect. The antitarget is the unwanted adverse effect, which is very unpredictable. So, this is a book on antitargets from all aspects. I was asked to write about the clinical aspects of liver injury from antitarget effect, from effect on receptors not intended when the drug was being developed and is being used for its therapeutic value.

An old idea *(paraphrased by many)*...

“Those who cannot remember the past are condemned to repeat it.”

*The Life of Reason, vol. 1; 1905*  
*George Santayana (1863 – 1952)*

“Those that fail to learn from history are doomed to repeat it.”

*House of Commons, 16 November 1948*  
*Winston Churchill (1874 – 1965)*
So, I figured that we want to look at the past so we don't repeat the same old mistakes over and over again.

To test this point, I did a little exercise, a little experiment on communication of written ideas in the literature...

About two years ago, I was asked to write a chapter for the second edition of a book on “Anti-Targets II,” to focus on development of ideas concerning drug-induced liver injury, I was not inclined to accept but finally did when they promised to make my chapter publicly available at no cost...
I drafted a chapter entitled “DRUG-INDUCED LIVER INJURY: CLINICAL AND DIAGNOSTIC ASPECTS”

--- In it I cited 52 references published from 1763 to 2014, many of whose authors were no longer living, but for 19 of the papers with a total of 92 listed authors, I searched out their e-mail addresses;

--- I also ferreted out pdf copies of those papers, aided by the FDA medical librarians;

--- to the authors whose email addresses I could find, I sent, about two months ago, an unapproved proof copy of my paper and a full copy of their published paper.

So, what I did was a little experiment. I wrote the paper and I went through a number of revisions. I cited 52 references, but I took the trouble of getting a copy not only of the abstract, not only the title, but each full paper. I got the full paper PDF using our nifty FDA library. I got all 52 citations word for word and went over them one more time. And then, I sent the paper to the person whom I cited and along with what I had said about them and said, "Did what I say correspond to what you wrote, what you intended me to understand? Did I understand you and did I get it right?"

So, I sent them out. I couldn't find email addresses for everybody. Many of the people I cited are not with us anymore. I was only able to get 19 email addresses of the 52 from authors who have published more recently.
And so, this is what I said to them in an email back in January: "We would like to do this little experiment. I send you a copy of what you wrote some years ago; I want you to look at it one more time, and see if what I said correctly corresponded to what you intended me to get from your message." So, it was aimed at understanding each other about what we write.
I said, if we don't get any responses, we will call it a zero. If we get a response from the author of the paper, "Right on, you got it right; you understand," that is a one, and so on down. Two, no objection. Three, maybe I didn't quite understand it. Four, you're absolutely dead wrong. Five, maybe we should have explained it more clearly, and other comments.

<table>
<thead>
<tr>
<th>Scoring Scale for Responses</th>
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<tbody>
<tr>
<td>0)  No response</td>
</tr>
<tr>
<td>1)  Right on; you got it right, understood what we meant</td>
</tr>
<tr>
<td>2)  No objection; close enough</td>
</tr>
<tr>
<td>3)  Not quite right; you didn't fully grasp what we meant</td>
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<tr>
<td>4)  Wrong! You missed the point, misquoted us</td>
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<tr>
<td>5)  Perhaps we should have explained it more clearly</td>
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<tr>
<td>6)  Other comment or non-answer</td>
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Here are the results of the January mailing. More than half didn’t respond at all. Oh, dear. Only four people out of 19, or about 20 percent, said, "You understood what I said." I didn’t really learn much.

### RESULTS – 1 (to January mailing)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Responses</th>
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<tbody>
<tr>
<td>0</td>
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<td>1</td>
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<td>2</td>
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<td>6</td>
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</table>

| Total | 19 |

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Complete table:
The response rate was rather poor, as indicated above. Appreciating that people are busy, and may be disinclined to respond to survey-like questions,

.... I tried again a month ago in February, giving the partial results, more specific request (please use the rating scale), and found 10 more email addresses...

So, I said, this was a waste of time, but I will try again. I dug out 10 more email addresses, to bring the total to 29 of the 52. So, after that poor response, I decided I would try again in February, a month ago. I didn't send it to people who had already responded, but to about 20-some more different people.
And this time, out of the 29, we got 10 people who said, "Yes, you understand what we are saying. You got it right." But we still didn't get responses from a lot of people.
CONCLUSION

So my little experiment was a bust. It really didn’t work. But I learned a lot from doing it — the careful review of what others had written, the close attention and effort to summarize that and then to try to express it clearly and in logical sequence.

I don’t think ‘I’ll do it again that way, but maybe in some other way. But I learned that:
1) it was good to get in the habit of obtaining full copies of papers others had written and published,
2) and read them carefully before citing them.

So, the conclusion was this was a bust.
(Laughter.)
This was not a good idea. And I said, well, I haven't failed, but I have just found a lot of things that don't work, as Thomas Edison had said. So, even the brilliant minds of our scientific world have made mistakes.

“I have not failed. I've just found 10,000 ways that don’t work.”
Thomas A. Edison (1847-1931),

“Brilliant Blunders: Colossal Mistakes by Great Scientists That Changed Our Understanding of Life and the Universe.”
(... Darwin, Kelvin, Pauling, Hoyle, Einstein)
Mario Livio, 2013
The messages of this exercise I take as: Even though we keep trying to learn from and remember, and to avoid, mistakes made by others in the past . . .

... that may not be enough.

It is almost certain, at least very likely, that we shall make new mistakes and have to learn new lessons. We should not expect necessarily to get everything right the first time, or the second, ... or the nth...

There is to be lots of room for humility in the broken path to new, better scientific understanding, as we stumble forward and keep trying.

We can are making new mistakes; not just repeat old mistakes. There are lots of opportunities to make mistakes in this world. So, I don't think I will do this again. (Laughter.)

It was an experiment, but it was a lot of work. A lot of people, frankly, are too damned busy, but. I only heared from one person who said, "I won't respond to you because I'm too busy." (Laughter.)

The rest were good people, just didn't respond at all. Nevertheless, I have a message: It is a good idea to read papers carefully; It is a good idea to be careful what you write; It is even a better idea to do that before you send it in for publication.

There's lots of room for mistakes. We all make mistakes, and we shouldn't expect always to get everything right the first time.
I close with an example of patient, repeated effort to seek the truth, to keep asking, about the challenging question of what processes are the most frequent causes of acute liver failure, at least in adults in the United States ... from Dr. Will Lee, of Dallas, who today is on service and unable to be here with us.
And so, I close with an example of what Lana has just shown you, an example of a group that is called the Acute Liver Failure Study Group, headed by Will Lee in Dallas. Looking year by year, now for about 15 years he has been looking patiently at the incidence of acute liver failure, and he keeps getting the same results.