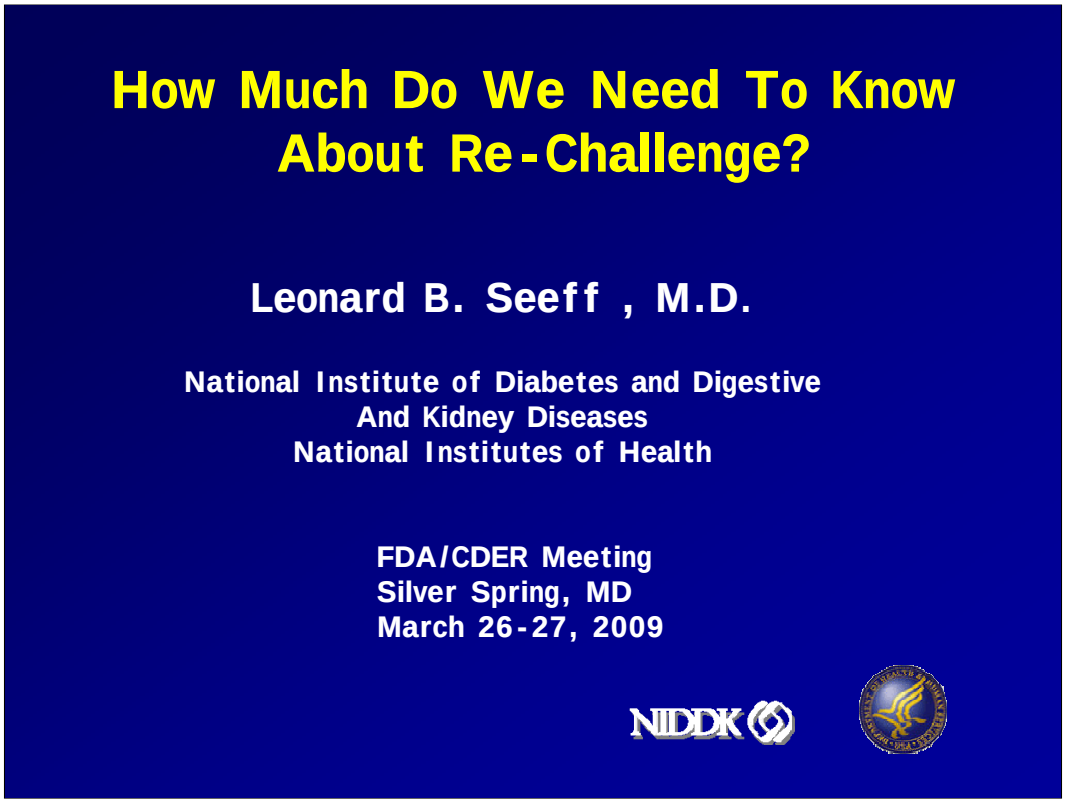
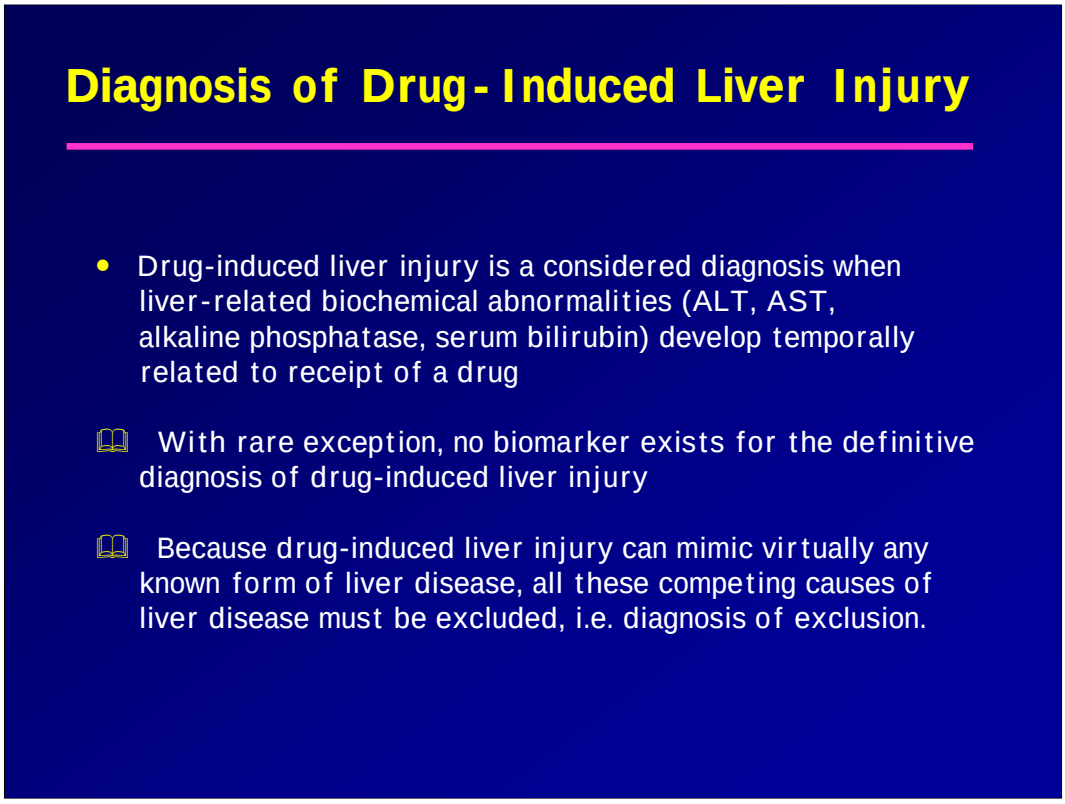


DR. SELIGMAN: Okay. The next speaker is Dr. Leonard Seeff from the NIDDK NIH.

DR. SEEFF: Well, as you heard from all the speakers this morning, the inclination is to begin this talk by thanking our host, Dr. Senior, for inviting us to participate in this very prestigious meeting. Frankly, when he called me and asked me whether I would talk about rechallenge, about which I know virtually nothing, and about which there is not much information in the literature, I decided I couldn't thank him. (Laughter)

In fact, what I'm going to do is to present no answer to the question that he posed but to raise questions. So let's see what we get.

Why is it that the symbols in this slide have changed? I gave a talk yesterday in New York and they changed to wheels and hooks and crosses, and God knows what else.



So anyway, this describes the diagnosis of drug-induced liver injury 101. Drug-induced liver injury has to be considered a potential diagnosis whenever biochemical abnormalities (and I like the term liver-related instead of liver functions, and here's some of the "functions", ALT, AST, alkaline phosphatase, serum bilirubin and so on), develop temporally related to the receipt of a drug. This must be a consideration whether or not the patient already has existing liver disease, but received a drug that may or may not be responsible for the liver injury.

As you know, there is, with the rare exception perhaps of acetaminophen, no existing biomarker for a definitive diagnosis of drug-induced liver injury. Because drug-induced liver injury can mimic virtually any known form of liver disease, as we've heard many times here this morning, all of these competing causes of liver disease have to be excluded, so that DILI is a diagnosis of exclusion.

Diagnosis of Drug-Induced Liver Injury, 2

- Even when all information regarding competing causes of liver disease are available and excluded as the basis for the injury, establishing causality can still be problematic despite evaluation by persons with great expertise in the area of hepatotoxicity
- There is wide belief that re-challenging the affected person with the implicated drug provides the best support for establishing a diagnosis of drug-induced liver disease.

However, even if all the information regarding competing causes of other diseases are available and excluded, establishing causality, as Don has told us this morning, can still be problematic despite evaluations by persons who have great expertise in this area.

So one belief is that there is a possibility that rechallenging the affected person with the implicated drug may provide the best support for establishing a diagnosis of a drug-induced liver injury.

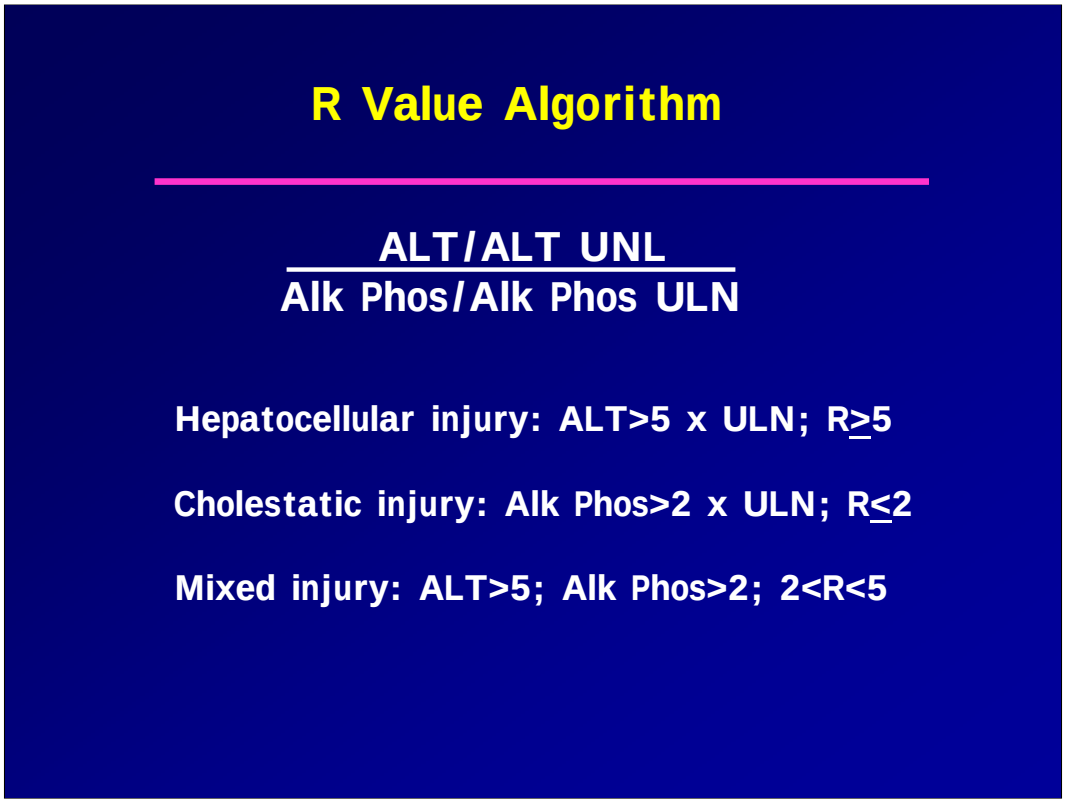
Types of Presentation of Drug-Induced Liver Injury

Broadly speaking, drug-induced liver injury presents as one of 3 categories:

- Acute hepatocellular liver disease, simulating acute viral hepatitis
- Cholestatic liver disease, simulating extrahepatic gallstone obstruction
- Mixed hepatocellular/cholestatic liver disease

The precise distinction among these categories is not well-defined but is generally based on whether the elevation is predominantly that of the ALT or the alkaline phosphatase value. Often, the pattern changes during the course of the illness. Another approach is to utilize the R value algorithm (ALT/ULN ALT ÷AP/ULN AP)

So let me again go back to some basics. Broadly speaking, drug-induced liver injury presents as one of three categories, acute hepatocellular injury that simulates acute viral hepatitis, or cholestatic liver disease which is similar to extrahepatic gallstone obstruction, or sometimes there may be a mixed pattern, mixed hepatocellular/cholestatic liver disease.



The precise distinction among these categories is not well-defined. It's usually based on the height of the ALT or the height of alkaline phosphatase, and we really don't have a number which clearly helps us distinguish between these two. If the ALT seems to be the predominant abnormality, we call it hepatocellular. If the alk phos is seemingly more elevated, we call it cholestatic. So there really is not a distinct way of making that decision. So what we tend to use is what we were told about earlier today, this R value algorithm which is the ratio of the ALT to its upper limit of normal divided by the ratio of the alkaline phosphatase to its upper limit of normal and as you know, you can use these numbers to come up with what is referred to as hepatocellular injury or cholestatic injury or mixed injury.

Importance of Defining Type of Injury

It is generally believed that re-challenging persons with acute hepatocellular injury is more likely to cause serious, potentially life-threatening recurrent liver disease than re-challenging persons with cholestatic liver disease

Concern even greater when the manifestation is that of immuno-allergic liver disease – fever, rash, adenopathy, eosinophilia, lymphocytosis,

So why do we need to know about this when it comes to the rechallenge? Well, because we believe that rechallenging persons with acute hepatocellular injury is more likely to cause serious and even potentially life threatening recurring liver disease than rechallenging persons who have cholestatic liver disease. This is certainly the belief and this is how I grew up, learning from Hy Zimmerman.

The concern is even greater, I believe, when the manifestation is the so-called immuno-allergic form of liver disease, that is the patient who has fever, rash, adenopahty, eosinophilia or lymphocytosis. That patient is potentially threatened if you rechallenge.

How Does Acute Hepatocellular Injury Present?

- Raised alanine aminotransferase (ALT) levels only
- Raised levels of both ALT and serum bilirubin
- Raised levels of ALT and serum bilirubin as well as prolongation of prothrombin time or encephalopathy

These presentations reflect increasing degrees of severity of liver disease

So let's go through the various forms of presentation. The patient may present with acute hepatocellular injury as only a raised ALT level. Secondly, it could be a raised ALT level with a raised serum bilirubin - or the patient may present for the first time with what looks like hepatocellular failure: raised levels of ALT, serum bilirubin as well as prolongation of prothrombin time or encephalopathy. These are manifestations that we as clinicians may have to face when we're called to see a patient who has abnormal biochemical values and has received a drug.

Raised Alanine Aminotransferase Alone

Theoretically this might be an early signal for what ultimately evolves into more serious liver disease as indicated by the later development of increasing levels of hyperbilirubinemia ("Hy's hypothesis")

or

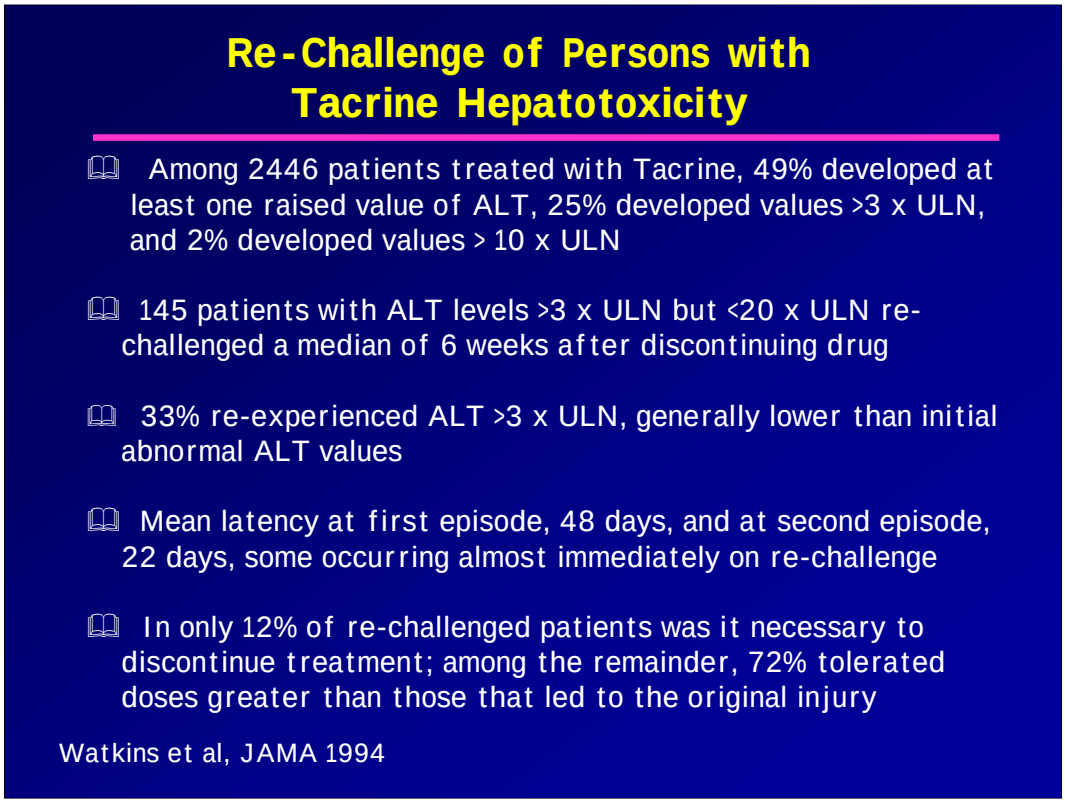
The raised ALT values remain stable or even decline despite continuation of the implicated drug, i.e., not hepatotoxicity but the "adaptation" phenomenon?

Is there a definitive means of distinguishing between these two possibilities? Not to my knowledge!!!

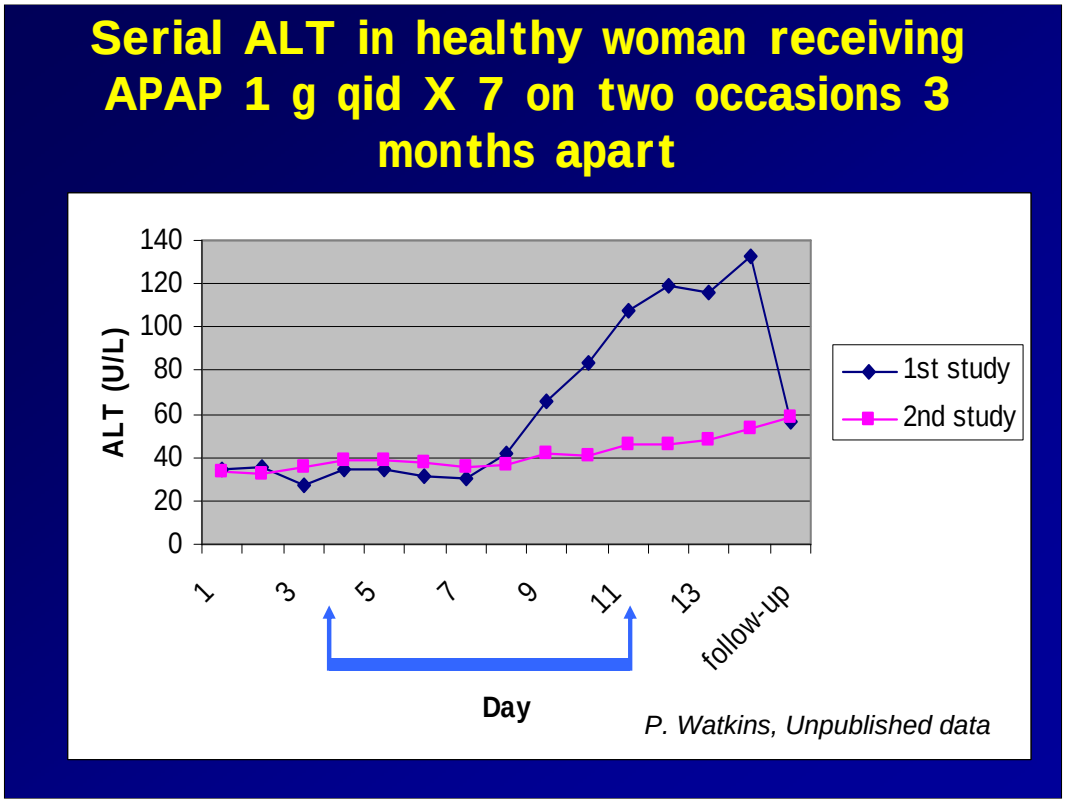
Now how do we respond to each of these? For the person who has just an alanine aminotransferase elevation, theoretically there are two possible scenarios. This may be an early signal for what ultimately evolves into a more serious liver disease, as indicated by the later development of increased levels of hyperbilirubinemia. Like Adrian, who used the term Hy's Hypothesis, (maybe it's a not a law) I've spoken to him recently and he said it was a hypothesis.

Or the raised ALT values may remain stable or even decline despite continuation of the implicated drug, that is it's not hepatotoxicity, but this is the adaptation phenomenon.

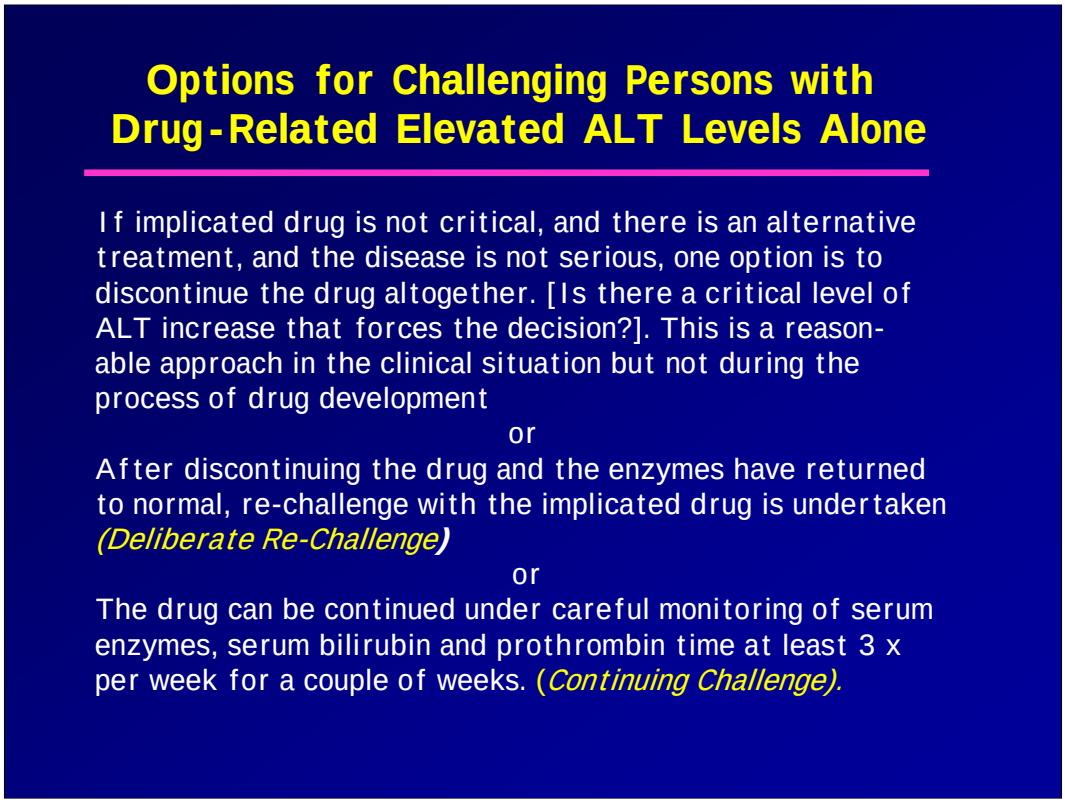
Now as a clinician, I find this distinction the most difficult part of the whole issue. If we're called to see a patient, the patient has been put on a drug, has an abnormal ALT value, the bilirubin is normal, how do we know for certain that this is not something that will eventually progress as we heard earlier today, maybe a month later, the bilirubin goes up and we then have the Hy's issue come up, or whether, in fact, the patient will adapt and this is the adaptation phenomenon. I don't know if there is, in fact, a definitive means of distinguishing between these two possibilities. If anyone here does know, I would like to know so I could use this myself.



As an example, Paul reminded me of and sent me the paper of the tacrine story, the rechallenge of persons with hepatotoxicity. This is a study that many people will know about. This included 2,000, almost 2500 patients who were treated with Tacrine: 49 percent developed at least one raised value of ALT, 25 percent developed values more than 3 times the upper limit of normal and 2 percent developed values greater than 10 times the upper limit of normal. Of these, 145 patients with ALT levels greater than 3 times the upper limit of normal but less than 20 times the upper limit of normal were rechallenged a median of 6 weeks after discontinuing the drug. A third of them re-experienced ALT increases that rose to more than three times the upper limit of normal, but it was generally less than the initial abnormal ALT values that developed the first time around. The mean latency at first episode was 48 days and, as we've heard, there was a second episode, with a shorter latency period of 22 days. And in only 12 percent of the rechallenged patients was it necessary to discontinue treatment. Among the remainder, the rest of the group continued to be treated, and the enzymes went back to normal. So here was an example of what is clearly an adaptation phenomenon.



Here's something else that was sent to me by Paul, this beautiful paper that he published, in which he challenged individuals with acetaminophen 1 g 4 times a day for 1 week and did serum ALTs. In healthy women who were challenged,as you can see, the baseline levels were normal. The challenge began at about 4 days and continued through to about 11 days. The enzymes went up as high as almost 140 and then when the drug was stopped, down went the ALT; when they were rechallenged in the second study, as you can see, the ALT levels, in fact, increased but only slightly. So this is what we're dealing with and this is the difficulty that we face when we wonder about whether the patient is going to end up with more serious liver disease.



So what are the options for challenging persons with drug-related elevated ALT levels alone? As far as I'm concerned, if the implicated drug is not critical and there is an alternative form of treatment, and the disease is not serious, one option is to discontinue the drug altogether, not to use it, if one could replace it with another one.

Now one question I pose here which is being discussed, is there a critical level of ALT increase that forces the decision? I mean if the person's ALT is 8 times elevated, which has already been talked about, that's okay, but what happens if it goes up to 20 times or 30 times the upper limit of normal? Do we cut at that point and run, or do we continue?

If we decide that we're going to continue treatment, this may be a reasonable approach in a clinical situation but, of course, in the situation of drug development, this cannot be done. The other possibility is to continue. And if we decide to discontinue the drug altogether, and we wait for the enzymes to return to normal and rechallenge with the implicated drug, this I refer to as deliberate rechallenge. Or the drug can be continued under careful monitoring of serum enzymes, serum bilirubin and prothrombin time at least three times a week for a couple of weeks. Maybe we need to go on for longer because sometimes it may take four to five weeks for the signal to show an increase; I refer to this as continuing challenge. The patient does not stop taking the drug, continues to use the drug, you know they have an abnormal ALT. It's a continuing challenge.

Uncertain Issues Regarding Re-Challenge Of Persons with Raised ALT Levels Only

How long should the wait be after discontinuing treatment before initiating the re-challenge?

Should the enzymes be completely normal before re-challenge?

What dose and duration of treatment with the implicated drug are required?

Is it necessary to replicate the circumstances of the original injury, i.e., add concomitant drugs used during the original injury?

What represents a positive challenge – "symptoms" in the absence of biochemical dysfunction or is biochemical abnormality essential?

If the re-challenge is negative, does this necessarily preclude an original diagnosis of drug-induced liver injury?

So here are some of my questions. How long should the wait be after discontinuing treatment before we initiate the rechallenge? Should the enzymes be returned completely to normal before the rechallenge? What happens if it's a very important drug and you really need to know something about this? Should we wait until everything is normal? Generally we do. What dose should we use when we rechallenge, and for how long should we rechallenge with the implicated drug? Is it necessary to replicate the circumstances of the original injury, that is, to add concomitant drugs that were used during the original injury because perhaps there was an interaction with a drug that was responsible for this? Is that what we need to do in order to find out whether this drug is really implicated? And what represents a positive challenge? Is it simply symptoms in the absence of biochemical dysfunction or do we need biochemical dysfunction in order to make a diagnosis of a positive rechallenge? But if the rechallenge is negative, does this necessarily preclude the original diagnosis of drug-induced liver injury? And, we know that that may not be the case.

Options for Re-Challenging Persons with Drug-Related Increases in Both ALT and Bilirubin

It is even more important in this circumstance to take into account the importance of the drug, whether it is replaceable by an alternative medication, and the severity of the disease under treatment before considering re-challenge

If re-challenge is performed, monitoring should be more frequent, at least every other day or perhaps daily

Monitoring should include testing for ALT, AST, alkaline phosphatase, serum bilirubin, and the prothrombin time/INR

Unless of life-saving potential, the implicated drug should be discontinued if the serum bilirubin continues to rise or the pro-thrombin time begins to increase

So now we consider options for rechallenging persons who have drug-related increases in both ALT and bilirubin. We're now talking about more serious disease. And I think under these circumstances, it's even more important to take into account the importance of the drug, whether it is replaceable by an alternative medication and the severity of the disease under treatment before considering rechallenge? I think that I would certainly be somewhat reluctant to rechallenge a patient with hyperbilirubinemia despite what I heard this morning, from John about INH. We would need to feel sure that it is important for that drug to continue.

If the rechallenge is performed, because the drug is critical, monitoring should be obviously more frequent, at least every day or every other day. So I think you have to watch that patient very carefully and monitoring should include testing for ALT, AST, alkaline phosphatase, serum bilirubin and the prothrombin time or the INR to make sure that you're not, in fact, inducing what may be a serious liver disease. Unless the drug has a life-saving potential, the implicated drug should be discontinued if the serum bilirubin continues to rise or the prothrombin time begins to increase. There would be no reason I think to continue under those circumstances.

Uncertain Issues Regarding Re-Challenge of Persons with Raised Levels of Both ALT and Bilirubin

The issues raised with respect to re-challenge of persons with raised ALT values only apply equally to this group of persons with an increase in both ALT and bilirubin levels

Is the likelihood of causing harm from re-challenge greater in persons with manifestations of immuno-allergic drug-induced liver injury than those with other forms of idio-syncratic injury and if so, should re-challenge be strictly prohibited for such individuals?

Can one be confident that re-challenge will not set into motion potentially progressive and even ultimately fatal liver disease?

So here again when the patient has both ALT and bilirubin, what are the issues that one needs to consider? First of all, the issues that were raised with patients who have just ALT increases are just as important in these circumstances.

Is the likelihood of causing harm from rechallenge greater in persons with manifestations of immuno-allergic drug-induced liver injury than those who have the so-called idiosyncratic form, and if so, should rechallenge be strictly prohibited for such individuals? Are these people much more likely to run into a serious problem?

And can one be confident that rechallenge will not set into motion potentially progressive and even ultimately fatal liver disease? And this is what we face when we think about this issue, rechallenging patients who have had an initial injury, having, of course, excluded all other causes, and so that is the big problem.

Options for Re-Challenging Persons with Incipient Hepatocellular Failure Due to Drug-Induced Liver Injury

Re-challenge of persons with established or incipient drug-induced hepatocellular failure, as defined by biochemical (raised or rising levels of the prothrombin time or INR and/or increasing levels of serum bilirubin) or clinical (asterixis, overt hepatic encephalopathy) evidence is both ethically and medically inappropriate and unacceptable

Now what about patients who have hepatocellular failure? Can you rechallenge such patients? In my view, it's absolutely prohibited. If anyone has developed what is believed to be a drug-induced liver injury and you've excluded all other causes and the patient had a prolonged prothrombin time or rising bilirubin, I think, unless it's so critical, perhaps indeed for an anti-cancer drug that was talked about earlier today, I would really consider this not a situation in which I would like to do a positive rechallenge experiment because I think this has terrible implications, and may be ethically and morally unacceptable.

Challenging Persons with Drug-Related Cholestatic Liver Disease.

Challenging of persons with cholestatic liver disease is believed to be safer than challenging a person with acute hepatocellular injury. This is particularly so if the liver injury is not accompanied by fever or rash

What about patients who have cholestatic liver disease? Can we rechallenge such patients? By and large, challenging patients with cholestatic liver disease seems to be safer than challenging persons with acute hepatocellular injury, and this is particularly so if the liver injury is not accompanied by fever or rash. So I think if we conclude that one has to rechallenge someone with cholestatic liver disease, one could certainly feel more comfortable about that than individuals who have hepatocellular failure.

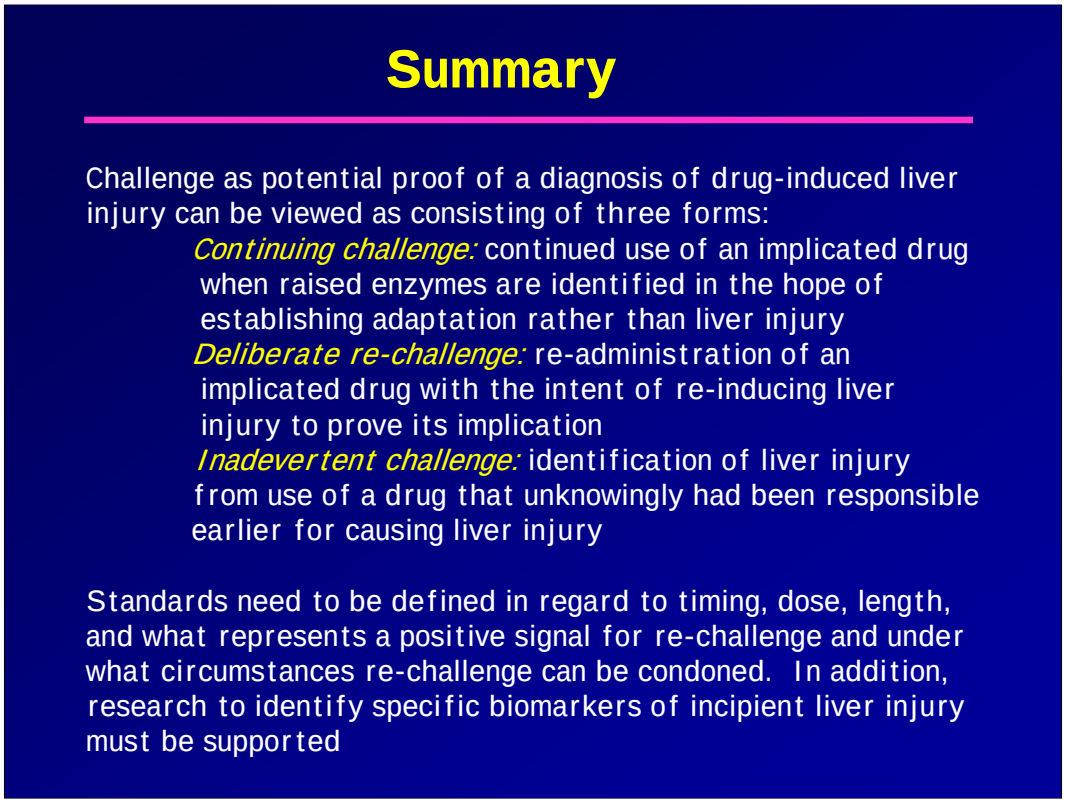
Concluding Thoughts

There is obvious reluctance based on ethical, medical, and medico-legal considerations to undertake and report challenge data and therefore the literature is sparse on this issue. Data must therefore derive from reports of *inadvertent challenge* in which a drug was given to a person who unknowingly had had previous liver injury from the drug, or from large pharmaceutical databases that have collected and analyzed the effect of cautious re-administration of a drug previously implicated in causing liver injury

Precise rules are unavailable on how to deal with the issue of challenge among persons who have suffered apparent drug-related liver injury

So my point is that there is obvious reluctance based on ethical, medical and medico-legal considerations to undertake and report challenged data, and therefore the literature is sparse on this issue. I've been looking around, trying to find out if anyone has maybe overtly done such things. There are circumstances in which this may occur and I suspect that in the pharmaceutical companies there may be large databases that would be helpful. But data can sometimes derive from reports of so-called inadvertent challenge in which a drug was given to a person who unknowingly had had previous liver injury from the same drug, or from the pharmaceutical databases that have collected and analyzed the effect of a cautious readministration of a drug previously implicated in causing liver injury.

Precise rules are not yet available on how to deal with the issue of challenge among person who have suffered apparent drug-related injury.



Thus, I think that challenge can be classified into three forms. One is continuing challenge, which is a situation in which you continue the use of an implicated drug when raised enzymes are identified in the hope of establishing whether adaptation rather than liver injury will occur. The deliberate rechallenge is the readministration of an implicated drug with the intent of re-inducing the liver injury to prove its implication. Third, there may be inadvertent rechallenge, as I've indicated, where the patient resumes use of a drug that unknowingly had been responsible earlier for causing drug injury.

So I made a little figure, which my six-year-old granddaughter would have done a heck of a lot better job of than I did. So I would say in the continuing challenge, here we start the drug. We know that there's an abnormal ALT and we decide that we're going to continue to use the drug and the enzymes hopefully will come down. This is continuing challenge.

Here's the situation of deliberate rechallenge, where you start the drug, if the ALT goes up, stop the drug, wait until it comes back to normal and then you deliberately rechallenge and see what happens.

And finally there's the inadvertent rechallenge where somebody was unaware of the fact that the drug had been used previously and that it, in fact, had been associated with abnormal ALT and then you give the same drug and up go the enzymes and this is an inadvertent rechallenge.

So I think that standards need to be defined in regard to the timing, the dose, the length of rechallenge, what constitutes a positive rechallenge and under what circumstances rechallenge can be used for confirmation. And, in addition, there needs to be a search to identify specific biomarkers of drug-induced liver injury that would be helpful in distinguishing between what is adaptation versus what is clear cut hepatotoxicity. Thank you very much.

(Applause.)