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Session I: Liver Injury & Dysfunction in Patients
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Session IA: What should we be looking for?

DR. SENIOR: Thank you, Bob. What Bob Temple says is very encouraging to all of us who have been working in this field. The implication is that what we're doing over the last decade has been having an effect, an impact, decreasing the problem. That's remarkable. I think you'll hear later in the meeting that hepatotoxicity of drugs has now fallen into second place behind cardiovascular toxicity, and I think that has resulted from a combination of all that's happening: these conferences, the guidance that we all wrote together, the NIH/DILIN conference, that the whole thing together is beginning to have an effect. We announced this meeting with a kind of mysterious title; Lana and I are going to try now to explain what is it we're looking for, and why. So, Lana, give us your view.

LANA PAULS: I'd like to first introduce my co-moderator for this session, Dr. Bob Fontana. If you will to come up to the stage, please, then I'll get started.

Lana Pauls  What is meant by looking?

DR. SENIOR: Thank you, Lana. Well, Lana has revealed the secret. It's information, that's what we're looking for. That's the theme of this year's meeting: looking for better information.

John Senior  Why is the probable cause so important?

Dr. SENIOR: I did send out these slides for their comments to the six advisors who are all session moderators, and we hope that each of them will speak for a couple of minutes. I see Mark Avigan and Paul Watkins, and here is Bob Fontana. So, come forward and be ready to speak for a couple of minutes on this proposal. Bob?
DR. FONTANA: Well, thank you, John. These are unreviewed slides, so just some comments, and in light of having seen these slides a few days ago, and thinking a little bit about this. I think we all know that the difficulty here is that drug-induced liver injury is a clinical diagnosis, and a diagnosis of exclusion, and in general, it's uncommon. And so, we're all looking for more objective and reliable ways of saying, "Yes, it is due to the drug versus these other things." As John and Lana alluded to, you first have to start with the universe of possible causes, and then by process of elimination and differential diagnosis, come to a diagnosis of possibly due to the drug.

One of my first comments on what John is proposing with the logistic regression process is that some of those other things on the list, like alcoholic hepatitis, gallstone disease and congestive heart failure are also clinical diagnoses, where you basically have to do the same thing and find some positive features and negative features. There is no rigorous scoring system for any of those. So, to get to robust coefficients in a logistic regression, you'd have to have very good data on those alternative etiologies and then be able to apply them at the patient level, and I think that's a pretty tall order for us to do, to be able to get there. What we're doing in the DILIN group, and I think you'll hear about this in the next couple of presentations, is saying, "Well, let's start with the bias sample, where patients are being referred to the network and so on," and then we come with a gradation amongst the patients referred to us, and that's the DILIN causality score. And then from the data we have on these well characterized patients, can we come up with sort of a logistic regression to differentiate the definite, very likely's from the possible unlikely's, and as we've started down this road, we already have, I think, 900 cases. We have heterogeneity of drugs, time to onset, severity and so on and so forth. So I think the general proposed process of using multiple clinical factors together into, hopefully, some mathematical algorithm is where we all want to go, but I think we're at the beginning of this and it's going to take a lot of data that's prospectively collected, in order for us to get there. So, that's sort of my comments.

DR. SENIOR: Thank you, Bob. I'm going to ask the moderators of the various other sessions to speak. I see Paul Watkins, who is one of the moderators for the next session, and I
hope Leonard Seeff is around. Paul, do you want to comment, and Leonard, are you here?

LANA PAULS: You can do it from the back, if you want, too.

DR. WATKINS: Yes, well, I want to just congratulate John for coming up with a potentially transformative way to look at the problems that we're all dealing with. Of course, first, you know, John did the graphing of the liver chemistries as log, upper limits of normal. As you can see, all the values on one stage of the eDISH plot, which I think really, is transformative and should be the way that liver safety database is routinely managed and analyzed in the future. Now, this idea of really quantifying what an expert does anyway, when you look at a case, which is, look at your experience and look -- try to get an estimate on the frequency of the various possibilities and actually, turn it into mathematical models is clearly, you know, a great way to go.

I think the most important thing for an expert, in evaluating cases in the real world is, you know, what is the frequency of the events for that drug, which is like looking at the relative frequencies of the causes of acute liver failure, and then the signature presentation of the drug, which most drugs actually have, whether it's cholestatic hepatocellular mix, time of onset, rate of resolution, when you stop the drug, et cetera, and those sorts of things, you could imagine, building into such an algorithm, and the exciting thing we're now getting into are genetic associations. For instance, with flucloxacillin DILI, the single most important question you can ask, in coming with a causality assessment is, does that patient show HLA-B*5701? That beats out age, dose, duration of dosing, et cetera, and building in those kind of genetic associations, potentially other things, like newer biomarkers would be important.


DR. SEEFF: Well, as John has decided that the theme of this particular meeting is to look, and as a clinical hepatologist I had always thought that's what had to be done, and you see somebody with abnormal enzymes, or abnormal liver chemistries, you need to look to see what the cause is. The difficulty, as we're hearing, is how can we distinguish drug-induced liver injury, which turns out to cause actually a very small fraction of all the cases that have abnormal enzymes? How do we really make that diagnosis? I think in the last five years, there's been a dramatic improvement with the DILIN group, working to try to look at this issue in more detail, and develop better ways, perhaps of making the diagnosis and the Bayesian process is something that we've been talking about for some time; perhaps, this is the time to move to it. I'm also
struck by one other thing, and that is, that there is obviously a difference between liver injury in the pre-marketing clinical trials versus what happens in real life. What I learned, since I've been now at the FDA for a short time, is that there is sort of a rote decision that you stop a drug, when the enzymes become abnormal and they reach four times or five times or six times the upper limit of normal, stop the drug. Now, obviously, one is concerned about what this may, in fact, imply, but it does not necessarily mean that this is, in fact, drug-induced liver injury. By stopping the drug without trying to find out what the cause is, it may in fact remove a drug from a person who needs one, that is very effective. So, I think that this whole theme now about thinking about abnormal liver chemistries as a large world, and a small portion of that is a result of drug-induced liver injury, and outgoing now, as we've learned more and more is how to, in fact, improve the ability to assess whether this is really drug-induced liver injury. The issue is going to come up, and I think Paul mentioned it, just briefly, about adaptation. I had to give a talk on adaptation and that, itself, is a big problem. So, I'll talk more about that later. But I think that the message that John is trying to put across here, that is, to look for the cause, rather than to assume that an abnormal enzyme or bilirubin in the person who is on a drug is a result of that drug, is something we really have to move toward.


DR. AVIGAN: Well, I think the idea of using Bayesian thinking to clarify differential diagnosis is really right on the spot, and I really do congratulate you for putting this in a kind of mathematical framework. I think, though, that there are important challenges that we have to face, in terms of feeding what that equation would be, that would be computed. First of all, we don’t have very good measures of incidence of drug-induced liver injury for specific drugs. We have various data streams, each which has limitations. I talked about this a little bit at the NIH meeting, but we tend to interpolate different data to come with a kind of quasi-quantitative measure of incidence. Incidence of DILI in users of the drug is one limitation that we need to improve on. We need to get better information, with regards to risk quantitation at the population level.

The second point is on the idea of excluding other alternate diagnoses, a little bit like what Bob was talking about. This is very problematic, particularly for some diagnoses, which are also somewhat fuzzy. One that comes to mind to exclude is auto-immune hepatitis, where there
can be unmasking of auto-immunity, in conjunction with drug exposure, and we don’t actually understand where the boundary of idiopathic auto-immune hepatitis is, with relation to drug effects, and there may be, in fact, some overlap, and the criteria for auto-immune hepatitis have been debated.

Finally, the third thought is the problem on confluence of injury. If DILI occurs, it may have a different implication for certain kinds of patients. What comes to mind as an example are the TB drugs or the AIDS drugs, used in patients who have chronic viral hepatitis, where there is some evidence that has been published over the years, that the two together actually have worse outcomes at the rate -- in terms of frequency effect. So, in conjunction with the idea of alternate diagnoses, you know, pick and choose on your menu, you have to also consider the idea that in some cases, two processes together can have confluent effects.


DR. REGEV: Well, first, John, I want to congratulate you on bringing this topic up for discussion. I think it's a big issue, and we struggle with this every day. I think one of the biggest issues, when it comes to information about patients that have idiosyncratic liver injury, is that fact that it's almost invariably post-marketing. It's not during clinical trials, and drug companies rely on the treating physician to get this information. I joined in the industry four years ago. I was not aware of the enormous problem of physicians being just not willing to give this information to drug companies, and I think there will be no ability to analyze this information, until we actually have this data, and right now, we have very little data, as you know. The actual case descriptions lack almost 90 percent of the information, and I think the way to do it eventually, will be by using electronic medical records that, once you press the button of each drug-induced hepatotoxicity, you will be asked several questions, that you will need to answer as a physician about whether you have looked at hepatitis B serology, hepatitis C serology, hepatitis A, in certain conditions? Have you researched Wilson's disease, and eventually, when you press the final button, it will be automatically forwarded to FDA and to the drug maker. I don't think there is any solution, before something like that will be available. The other problem is, not only the lack of will to actually voluntarily give this information, but there is an inherent bias, I think by all of us, but physicians out there look at drug-induced liver injury as the default diagnosis. This is a very interesting phenomenon, and I think there is a lot of psychology behind this. We could guess if
this is something -- we like to guess the obvious. Sometimes, I'm consulted on cases where a case was reported to the company and it is a significant liver injury, and I'm amazed at how the tendency is to blame the drug, and completely ignore hepatitis, viral hepatitis or immune hepatitis, any other cause, and I'm sure there are reasons behind that. I think one last thing: there is also bias by investigators collecting patients and publishing them. It's very interesting, that even when we publish cases, we tend to look at the drug-induced option more than at others. I just recently read a case report in the literature about a patient that had all the features of auto-immune hepatitis, but was on this particular drug and the diagnosis was drug-induced liver injury, and then the drug was discontinued. The patient was on prednisone and Imuran, which usually treats auto-immune hepatitis. The result, six months later off the drug, was that the patient had another episode, and the reporter still thought this was drug-induced liver injury. I think we have this tendency, and it's something that will affect the data analysis in the future. That's it.

DR. SENIOR: Thank you, Arie. Our final commenter is Chris Hunt, after which, we'll open the floor for general discussion. Chris, are you around?

DR. HUNT: Yes, sorry, over here. Just wanted to say again, as per everybody, I think these are great questions and I think following on with what Arie was saying, I think with electronic medical records, which are robust, and I think you'll hear more tomorrow about this, you can actually really interrogate using millions of patients receiving millions, you know, millions of drug exposures. The potential risk and repair factors that could be actually identified with very large population data, that we haven't really explored to any great extent in this forum. We're at a new place, and I think that's one area that will be really quite rich in giving us more information about risk factors, repair factors and the effect of concomitant medicine. I think this is an area to which everybody will want to stay tuned. Additionally, I think we actually have not fully utilized the information from our clinical trials. Many folks across PhRMA are actually interested in partnering to see whether or not we can better predict liver signals earlier and risk factors for early liver injury. So, I think those two areas are really ripe for the picking, and hopefully, we'll be sharing information in those two areas, both at this meeting and future meetings. Thanks.
Open discussion (IA)

DR. SENIOR: Many good comments. I'd like not to make this a debate between me and the commentators. I certainly want to listen to what people think. Does anybody have any thoughts? Jack Bloom?

DR. BLOOM: It's a particularly brilliant proposal, John. To Bob's reservations, which I think are the most substantive, as far as the challenge to this, there is a way forward, learning something from the clinical pathologists who calculate the predictive value by sensitivity, specificity and prevalence. Theoretically, it would be possible, to take each of the differential diagnoses and based on prevalence and the empirical markers, calculate the probability, and it would be a complicated algorithm, but it could be done by filling in the blanks, letting the computer do it, where you would have the probability of the differential diagnosis factored into the whole algorithm, so that you were compensating, or you were addressing some of the subjectivity that Bob's concern addressed.

DR. SENIOR: All right, Bob Temple had a thought.

DR. TEMPLE: My main thought is, I think it's very important to distinguish between, as I think Leonard was saying, the pre-marketing and the post-marketing setting. There is a lot of uncertainty, post-marketing. You don't have the viral assessments and all of that. Pre-marketing, I would allege, it's not as hard as all of that, and I'm not sure whether the formula helps. We've generally felt that what we're looking for is bonafide, secure, unreserved cases where there was no other explanation. So, you always have to, obviously, rule out hepatitis. We're getting better. We can rule out more different hepatidities. If the person is alcoholic, you generally don't count as a case, because you're not sure. If there is any sign of major obstruction, you don't count that, because that's probably not one either, and my experience, historically, maybe it needs to be updated, is that it's not that hard. I remember going over the early lumiracoxib cases. It was clear, there were six perfect cases with no other explanation and the control group had none. There was nothing to it. So I'm not totally sure how much the formula helps, in the pre-marketing setting. Now, post-marketing, I think it probably does. But you know, if someone has overt heart failure and the transaminase goes up, and the bilirubin, you don't count that as a DILI case. I think you had a similar experience, when you and Merck went over, I don't know, whatever statin it was. It was fairly clear, that the cases of elevated bilirubin associated with transaminitis, were not
credible. They recurred after the drug was stopped. They were associated with obstruction. It wasn't all that hard. In the post-marketing setting, I agree that you probably are missing enough information. So, I think it's worth talking about, how much that really helps, to see whether the drug is causing idiosyncratic liver injury. I think you mostly know, from looking at the data.

DR. SENIOR: Thank you, Bob. Bob is quite right, there is a world of difference between controlled clinical trials and selected subjects and so forth. Where the company and the FDA are working together, to try to predict from preapproval studies what will happen in the real world of clinical use of the drug, where things are sort of messy, where there aren't all these inclusion and exclusion criteria, where things aren't always done right, where we don't get much information. We have much better information from clinical trials, no question about that, and I think Arie was saying, we need a better system, but how are we going to get it? A plaintiff's attorney can subpoena all the physician records and hospital records. The FDA, I don't believe, has that authority, to subpoena the records. Most of our reports are coming in -- 93 percent are submitted by sponsoring companies -- and those reports are often of very poor information content. They're often gathered by a sales rep or something, or reported by a family member. They're very poor reports. We can't make any head or tail of them, and we don't have the authority to subpoena all the records, like a plaintiff's attorney does. Now, getting Congress to give the FDA that authority is not going to be easy. May not be -- Bob, is that right?

DR. TEMPLE: No, I wouldn't count on it.

DR. SENIOR: Anyway, these are very important points and we want to hear from as many people as possible, to weigh in on this matter. Here is Jay Hoofnagle.

DR. HOOFNAGLE: Jay Hoofnagle from the NIH. I'd first like to say that actually, RUCAM is a pretty good system. The difficulty with RUCAM is that nobody knows how to fill it out. It wasn't very well described, in the original paper, written by people who were French. But if you look in the literature and how RUCAM is used, it's always mis-calculated, so one thing we need is a nice manual operation for RUCAM. In developing them for DILIN, we found that it is a morass, because all the elements are just not well described. All the elements in RUCAM, though, are the important elements. They're there. It's just poorly described. So, what the DILIN group is doing is trying to develop a computerized RUCAM. So, you can go to your internet and just fill in the data and it will give you a RUCAM score. But in doing that, we find, we have to define them.
They're not in the literature, and from that, we hope then to go to a better improved RUCAM, 2011 RUCAM, that will capture some of these things. Let me also say something about the literature was criticized, and the literature in DILIN is very interesting. You see, this is a rare disease. You know, actually, it's a common disease. Drug-induced liver injury is not that uncommon. What is rare are the causes. So, even the most common cause, isoniazid-induced liver injury, is rare. Drug-induced liver injury is a bunch of rare diseases, and that's how you have to think about it. It's not going to be captured in your clinical trials, when you enroll 1,000 or 2,000 patients, unless you have a real stinker, and even, you know, the FDA can block it before it comes in, thank goodness. But for the others, let's take celecoxib, it's a wonderful drug, it's used by millions of people. It can cause clinically significant liver injury, but it's one in 100,000 or one in 1,000,000. So, how can we get these cases to people who can see them? What I would suggest is we also use the literature. There is the bias of the literature, and the reason why they insisted it was a drug, because if it was just auto-immune hepatitis, they wouldn't get a publication, right? So, they had to say, "Oh, it's this drug," and this was indomethacin, or something? That was a crazy report. So, what I would suggest is that we develop a online drug-induced liver injury report, journal, and you can submit whatever case you want, and I think that would help a lot.

Let's take, for instance, erythromycin, which supposedly, causes a lot of drug-induced liver injury. If you look at the literature, there hasn't been a case of erythromycin induced liver disease reported in the literature for about 50 years. Does it not occur? The problem is you've got a case and they say, "Oh, well, it's well known, I'm not going to publish it." What I would encourage as another thing would be to create a welcoming journal to drug-induced liver disease and that way, you can kind of control what the people report, that they check off that they've been tested for hepatitis B and C and so forth. That's another approach to this.

DR. SENIOR: Thank you, Jay. We find the literature often problematical because the standards for publication and review and critique by reviewing consultants have not been set. So, some cases are published that really aren't all that informative, and they talk about drug-associated --- well, the drug was given and the reaction occurred, but they didn't establish causal linkage. So, the literature, while useful, I don't think is the final answer, until the way cases are reported and evaluated before publication become more consistent. What Jay is suggesting may lead to that improvement in the editorial standards. Now, I see a couple of hundred people out
there, who haven't said anything, and I'm sure you all care. Please give your name if I don't recognize you right away, please.

DR. MICHALOPOULOS: George Michalopoulos, University of Pittsburgh. I would just like to take a slightly different look at this, and point out that we're at the dawn of genomic medicine, and there are huge amounts of information coming to make us understand what determines what we call idiosyncrasies, that they're genomic or epigenomic or other underlying situations, which could explain, if we fully understood and tabulate them, what is really going on. There is a huge repertoire of liver biopsies sitting in paraffin blocks, in most of the departments of pathology in this country, everywhere, and the value of those, I think, has not been fully appreciated or used. One can do personalized medicine predictions from looking into polymorphism, but that can be done from the blood. One does not need liver tissue for that. But in most of normal life circumstances, there is genomic modifications, that are epigenomic, epigenetic, based on nutrition, based on many other issues, microRNAs, the methylation patterns. And the good news is that there are now wonderful, massive throughput analysis, methodologies all over the place, that will allow us to establish databases, so that in four or five years, we can start tapping into those, and we can make them public, along with the publications, as Jay Hoofnagle said, which I fully support, we'll probably be able to get to the bottom, as to what is really going on. At this point, we're looking into the surface symptomatology, the underlying substations at the hepatocyte level, at the level of the other cell to the liver, has yet to be fully understood or investigated, with the current tools that we have. Thank you.

DR. SENIOR: Thank you, George. Forgive me for not recognizing you. You know, I have seen your picture and read your papers and invited you to speak, but I hadn't met you in person, before today. Anyway, thank you very much.

DR. INTILISOY: Hi, my name is Evren Intilisoy. Twelve years ago, I was part of the Mount Sinai team, was part of Will Lee's group for liver failure, and for 12 years, I've been in the industry. Most recently, I am at McNeil, Johnson & Johnson. So, I think, Dr. Senior, you were very clear. I think the challenge is getting the history, the history, the history. We've heard that loud and clear, and we also heard that industry is calling many of these cases, and I think the challenge for industry, being on the other side now, is that the people on our side may -- don't have the experience that this group has, in terms of getting that history. So, you're getting cases from
individuals that are not tied into liver failure experts, and on the other side, you have people that don't know how to evaluate. One suggestion would be that sponsors create an intake form, so that if a liver case is truly coming in, that they really understand the pertinent positives and negatives that they have to build in, above and beyond the normal forum. So, if you get a case from a sales rep or a pharmacist or from a hospital, that you'll -- you would be able to have the safety representative from the company walk through, you know, the differential, and potentially, add value and hopefully, at the end of the day, we'll get better and better information, because I think it's going to take time before we get electronic databases in, by the time the FDA can subpoena, you know, records.

DR. FONTANA: Evren, I would totally agree with that comment, that if you think about it, most drugs that are being tested are not being tested for patients with liver disease. So, the principal investigators you dealing with are not gastroenterologists or hepatologists. Their familiarity with this differential diagnosis, which is fairly detailed -- and we all can struggle with making a diagnosis of Wilson's disease or auto-immune hepatitis -- is very limited. You have to, if you will, strike while the iron is hot. Having it literally in the research protocol, written in as an appendix, so, you can immediately refer them to it and have a checklist, so that you can get those tests ordered quickly. I think in clinical trials, after a patient has to be discontinued, the relationship gets a bit disrupted between the investigator and the patient, and their willingness to come back and get extra blood work and so on, is lessened. If you could get that information quickly and also, have a reminder checklist, I think that would be a great improvement. And that form could be used, certainly, where it probably would add even greater value, beyond the post-marketing side, as well.

DR. SENIOR: I see Jim Freston. Jim is a past President of the AGA, consultant to everybody, including DILIN. Jim?

DR. FRESTON: Thank you, John. I haven't had that description before. As a clinical pharmacologist, hepatologist, I tend to see the world as a series of dose-response curves, and in the field of DILI, I see three different dose response curves. One is in the area of the interface between pre-clinical studies and clinical studies, trying to predict DILI, based on pre-clinical evidence. There, we're way down at the lower left quadrant of the dose response curve, in my opinion. The corollary to that is if we put more emphasis on that, we can get a big boost in output.
for not very much energy, in my opinion. The second curve, though, I think we're working on the flat part of the dose-response curve, and that's the part where we take the clinical data from clinical trials, submit it to the agency, and the agency makes a call. I think that part of it is very good, right now, and I think we're protecting a lot of people, because of the decisions that have been made by the agency, in recent years, using the data generated by industry. The third part where we're lacking, obviously, is in the clinical reporting and adjudication of cases out there, in the real world. So, I'd like to see in future meetings emphasis and more energy put on trying to do better at predicting -- let me back up. Industry is still spending a lot of time and money, mounting big trials, only to find that they have hepatotoxicity, late in clinical trials, and so, the drugs are killed. This is happening frequently. That's an enormous waste of time and money. If we put energy into that early prediction of cases, I think it will be well spent.

DR. SENIOR: Thank you, Jim. Paul?

DR. PAUL WATKINS: Just to follow up on a point Chris Hunt made, about the value of clinical trial data --- As someone who has looked at a lot of problems that have come up post-marketing, when you go back and look at the clinical trial data, you see that the severe events that can be only detected post-marketing, actually arose in the same window of susceptibility as ALT elevations in clinical trials. That's certainly been true for ximelagatran and troglitazone, et cetera. So, that even a few cases, if they all look the same and you have access to the clinical data, you can be reassured or it definitely can convince you, that this is a real association. Furthermore, in the case of lapatinib and ximelagatran and lumiracoxib, really, the genetic associations were all found after the drugs were on the market, by going back to the clinical trials, and having archived samples. Then those associations, in fact, may with lumiracoxib get the drug back on the market, but could be very useful in causality assessment, as I mentioned before. And the real challenge is that currently, clinical trial liver safety databases are not in a uniform format, and so, I think it would be great if the companies did, going forward, agree to put all their liver safety information in the eDISH format, into a common format, just like EKG's were done, with Norm Stockridge a few years ago. There should be a liver safety data warehouse, just like there is an EKG safety, you know, warehouse, EKG warehouse, and then to have the ability, in a uniform format, to go back and see pre-clinical data, and by clicking on individual patients, actually see what the signature of the ALT elevations were, in fact, whether DNA was collected on those
individuals. If additional serum samples were saved and archived, when they were actually, you
know, obtained, relative to the time course of the ALT elevations in the John Senior plots, and I
think that would really be a major step forward prospectively, in being able to really solve these
problems, come up with better causality assessment tools, through genetic links, and also, of
course, mechanistic understanding. So, thank you.

DR. SENIOR: Thank you. Now, you don't have to be a great luminary to speak. You
don't have to be a muck-a-muck of any kind. We want to hear from as many people as possible,
and we have another 15 or 20 minutes left to do it, before we take a much earned break.

DR. DOUG KELLER: Okay, since I'm not a great luminary, I'm following in exactly what
you're saying. Doug Keller, Sanofi-Aventis: I'm a toxicologist. I don't know that much about the
clinical side of things, but I want echo what was just said about the potential value of some pre-
clinical data here, and I think where we can get some value is from understanding the molecular
mechanisms of injury. That's something you don't get out of clinical trial data, and there could be
a role, I think, for linking the clinical effects and pre-clinical effects, by understanding the
mechanisms a little better. In drug development, we don't often look at the mechanisms of
toxicity, unless there's a reason to do it. So, often, if the animal studies are pretty clean, we don't
do a lot in this area and therefore, when there is a clinical signal that we haven't seen pre-
clinically, we have to go back and scramble and get the information. But if we did a little bit better
job of looking at mechanisms, once the drugs got to a certain stage of development, where
they're really getting into large clinical trials, then there could be some part of a causality score
that could look at mechanisms and whether there is a plausible explanation from the molecular
level, for the injury.

DR. SENIOR: Before Mark speaks, we have heard very little from the north side of the
room, other than from Chris Hunt. So, some of you guys on the north side have a few comments.
Now, Mark has been at the FDA, how long, Mark?

DR. AVIGAN: It's close to -- I hate to say it, it's a chunk of my life..

DR. SENIOR: Well, I'm into my 16th year. Of course, Bob Temple has been there, since it
was practically established. I have a checkered career where I had 29 years in academia, and then
16 years in the industry as an officer and as consultant, and I'm coming up on another 16 at the
FDA. That's a lot of years. Mark, go ahead.
DR. MARK AVIGAN: By the way, I also have an eclectic background. I wanted to just point out an important lesson learned about clinical trials and doing genetic testing, which is a very important point. We have learned, and this is a lesson that really needs to be permeated in the pharmaceutical community, that more samples should be collected systematically, not just in active cases, but really across the board in a clinical trial, so that there are adequate numbers of controls, in conjunction with those patients who have a phenotype of DILI, to create a statistically sound data set, from which to analyze. One of the things we've observed in some of the studies that have been done in the past, with the drugs that have been mentioned, is that the data in the clinical trial data system has been fragmentary. And it would be much stronger if the industry decided to systematically, at least in some trials, collect samples when there was a potentially hepatotoxic problem. It would give much more power to the studies. The other thing that is very important to do is to document phenotyping of cases of liver injury, because over time, we can learn more about the signature of the specific drugs that cause the rendering. So, those two pleas will go a long way to satisfy Dr. Michalopoulos' points about doing genotyping.

DR. SENIOR: Thank you, Mark. We're particularly interested to hear from industry, because the industry controls the flow of information into our MedWatch AERS system, and I hope somebody will think about how that information flow can be improved, because it isn't very good at the moment. Please, introduce yourself, name and institution.

DR. SAM JACKSON: My name is Sam Jackson and I work for Amgen, and I would just like an informal show of hands, here, about who in this room thinks that our post-marketing data are sufficient enough to build a robust model for predicting or even describing drug-induced liver injury? Hands, please. (not many) I've heard a lot of comments today about, you know, where our bang for the buck is, and I think that there has been a lot of work done in the pre-clinical setting and in the clinical trial setting, I think reference has been made to that. But I would suggest that our biggest gains could be made in the post-marketing setting, if we could improve our ability to collect those data, and you know, it is the responsibility of the sponsors. But as a practicing clinician, I can count on one hand, how many reports I've made to FDA, and I was met by hepatologists who specialized in drug abuse. So, that's about it. Thank you.

DR. SENIOR: Thank you.

DR. AVIGAN: We'll see if this microphone works any better for me. So, I talk about
eclectic backgrounds. I'm a gastroenterologist, an epidemiologist and I worked in vaccines for Merck. I'm going to tie these together to make a specific suggestion. In a world of vaccines, post-licensure, I think we do a reasonably good job, and there is a program which is called the vaccine safety data link, which is a collaboration between the FDA and the CDC, often working within industry. So, using the VAERS system, the passive surveillance system, which -- for vaccines, which is analogous to the AERS system for drugs, when a signal is detected, there is a network of managed care organizations, which have agreed to work collaboratively, to conduct typically, case control type studies with access to the relatively greater depth of data that are available within those managed care settings. There are about 10 or 12 managed care organizations that participate. This allows for follow up of signals with a greater level of precision, to determine the strength of association. So, let's think about drug-induced liver disease here, and I am very much - - I very much agree with the premise of doing a Bayesian type of analysis. But I also am very much concerned about the quality of the data that are provided to companies and to regulators, and try as we might, we are reliant upon the, you know, good will and professionalism of clinicians, to adequately report and capture the data. The proposed -- the blue sky proposal here is, I'm wondering if we can provide some incentive to a few managed care organizations, to set up something analogous to what has been done for vaccines. Managed care organizations could potentially be incented to assure that cases of potential drug-induced liver disease were followed up, where all the exclusion criteria were identified, so that we had a robust set of data that would allow us to make more sense of what is the dilemma we all face now. That is the imprecision of the quality of data that come in through the passive reporting system.

DR. SENIOR: Thank you. I couldn't agree with you more. I think that the quality and content of the information, which is largely related to post-marketing cases that we're mainly worried about, is critical. And I think that's controlled by the sponsoring company. We can't get good information very effectively. Over 90 percent of reports to AERS come from sponsors. Now, it may be reported to the sponsor by a physician, but the physicians are busy practitioners, don't have time to do all that. So, we don't get the information. Now, in my experience in the industry, I was vice president for clinical trials world-wide at Sterling Winthrop before it was abolished, and I was consultant to industry for another 11 years after that. My experience has been that during the development of a drug, until it's approved, you have a great collection of medical scientists,
and all kinds of scientists working on it. But when it's approved, that team is disbanded and put on some other project and the approved drug is turned over, principally, to marketing and sales folks, who don't have the same perspective. So, when any report comes in, they're mortally afraid that an adverse report will reduce their sales. So, they don't really want to report it. But it would help the industry, and I think it's to their advantage to find out the true cause of the liver problem, which is probably not their drug at all, if they would find the information, and get it for us. Now, it's not going to be obtained by sending a sales rep out, because they don't have the medical background. If the industry would read the reports that they send into AERS, and give it to one of their consulting physicians, they would see how bad they are. We simply can't make a judgment on what we get in AERS reports, despite data mining and all the rest of the pokery that goes on. The quality of reporting can be immensely improved by the industry itself, and it's to their advantage, because the problem is likely not to be caused by their drug.

Please, announce yourself and state your name.

DR. JUDY RACOOSIN: You're not hearing from the north side of the room, because you can't actually see the north side microphone, I think. Judy Racoosin, FDA. So, tomorrow, I'll speak on how it -- what we can learn from large databases. But having spent about nine years working on the safety of neurology drugs, I just want to speak to an issue that's come up a lot. I want to take it a step further because I think this key of getting the information from people reporting to industry, -- from numerous incidents of having cases where you knew what the transaminase was, but you didn't know the bilirubin -- that that key interchange is on the first interaction, with whoever is answering the phone at the sponsor, who is taking that first case. When liver comes up in the conversation, that automatically has to drive the person answering the phone to go to that liver checklist, that one of the earlier speakers referred to, so that when the reporter is sitting there with their chem profile and they report their ALT and their AST, that the person answering the phone says, "Oh, and while you're looking at that report, can you also tell me the total bilirubin," because even getting that far will take us further than, you know, many of the times that we find this just with transaminase. I would just encourage the people in the room who are working with the physicians answering the phones, that there be a specific template for that first interchange. I think there are probably people in the room who are on the post-marketing and OSC and what not, who are dealing with these reports now, who are.
There is difficulty in getting back to reporters. You know, I think it's been mentioned numerous times, they don't necessarily have the time or the energy or the motivation to come back and give much more information. So, that first interchange is going to be the pay off. And so I just encourage people, you know, I think it's going to be problematic to get back and forth, and so, whatever information can be obtained on that first interchange, we had, on multiple occasions, encouraged sponsors to develop those kinds of templates to capture the information. On that first exchange, is where that has to happen. Thanks.

DR. SENIOR: Thank you, Judy. Judy Racoosin is going to talk tomorrow, about the OMOP program. Let's alternate between south and north, so south gets the next shot.

DR. BARBARA WARNER: Okay, hi, I'm Barbara Warner from Novartis, and I have a couple comments apropos to what you just said, John, and what Judy just said, as well. With respect to post-marketing reports and getting the information at the first go-around, I mean, I think everybody would absolutely agree with that. I know Novartis does have a checklist, for liver problems, and if someone from safety receives the report, they have the checklist and they immediately ask these other questions. However, if the sales rep gets the information, and the sales rep never asks or tries to elicit any safety reports, of course, but if he/she gets one and doesn't have this checklist, because according to regulatory guidelines he/she is trained of what he has to get. Part of that training about liver or cardiovascular or anything else specific, is totally missing, and they would tell us, "We don't have to collect that, because it's not required by the regulators." So, I don't mean to push back against you, necessarily, but if you would require that we have certain information, that would also be helpful. So that we could put pressure on marketing and sales, to have them learn this, but you are more influential on them than we are, sometimes. But I would further say that with respect to post-marketing reports, to get things actually reported, commenting on what the other fellow said before, it would be to have inspirational speakers talk about drug safety to medical societies, which I actually don't think I hear. But some medical schools also do teach about drug reaction reporting, and that would be valuable. Lastly, I just want to say that Novartis has a CRF for liver, that we have developed, and if we had the algorithm that Dr. Senior was referring to, about different diseases, it would help us a lot. Thank you.

DR. SENIOR: Thank you. We have just four minutes left. We're going to have north
side, south side, north side, and then we’re going to take a break. So, north side is next. Briefly.

DR. DENESH CHITKARA: Denesh Chitkara from Merck: I agree with all of the comments here. I think gathering the information would be most helpful to evaluate the causes of elevations in liver enzymes that we see during clinical trials. We've interpreted the FDA finalized guidance as almost a requirement to collect this information on patients who receive these elevations within clinical trials. I'm just curious, I've heard Novartis. I wanted to hear if there are other members across industry who have also similarly interpreted that, as to absolutely get that information in their clinical trials and to report that when certain cases like -- that meet the biochemical criteria of Hy's law, occur. A show of hands: do any other industry -- within industry - - initiative, such as -- it seems like a lot of people have interpreted the same way.

DR. SENIOR: Thank you. Please.

DR. ROBERT ROTH: Bob Roth from Michigan State. I have a question, as a naive basic scientist in this sea of clinicians, and it really plays off something that Mark Avigan said, which was questioning whether two processes can come together in confluence to produce some effects, that is, a drug and some other process. I guess the question is, are clinicians missing some drug-induced liver injury effects by considering conditions as either/or, and I think this kind of came up, John, in your first example, where if I look at that, it seems to me, that patient might have been suffering from a combination or an intersection of effects of the drug and effects of hepatitis.

DR. SENIOR: Thank you, Bob. Final comment.

DR. SURKS: This is Howard Surks, also from Merck. In looking at some of these liver cases, as they come in clinical trials, it's really remarkable, sometimes, how complex the work up can be and how difficult differential diagnosis can be. Sometimes, the cases are quite subtle. One proposal, and I wonder how the committee and other audience members feel, would be to have something like an adjudication committee for clinical studies, that could be either within the company or more centralized across the industry, that would have the expertise to look through these complicated liver cases to make sure that all of the relevant information has been complete. I understand some of that could be done by centralized case report forms that guide what information should be collected. But more importantly, to help to provide expert opinion, as to what the most likely causes are, or if there is any particular information that should be
collected for that case.

DR. SENIOR: Thank you. The purpose of our scheduling a generous time for open discussion was intentional. We wanted to hear from as many of you as possible, and we hope you will continue to think about and comment on these issues, to us. There are a number of ways you can do so. But we're going to take a break now, and I want you to hurry back and be in place, in time, at 10:30 a.m. to hear from Jay Hoofnagle. Jay has been doing an absolutely spectacular job of looking at each of the drugs that have been reported to cause liver injury, and he is going to give us a preview of the program that he's going to put up on the National Library of Medicine internet, for the whole world to share. So, we're looking forward to hearing Jay and we want you back in place at 10:30 a.m. sharp. Have a nice break.

BREAK
LANA PAULS: This morning, we were talking about what we should be looking for. The second half of Session I, or Session IB, is how have we been looking? Our first speaker for the second half of this morning is Dr. Jay Hoofnagle, and John alluded to what he was going to talk about, in terms of what he is proposing for the National Library of Medicine. Dr. Hoofnagle.

**Jay Hoofnagle  LiverTox - a new resource from the NLM**

DR. SENIOR: Jay has done really an amazing tour de force. Like Hy Zimmerman, he knows the world's literature. He has read the 10,000 papers and can cite them. He knows so much, and what he has done is absolutely spectacular. He did most of it by himself, with the help of staff and a couple of interns. This is an amazing accomplishment, which you will begin to appreciate as you begin to use it. Now, in order to facilitate that, Jay, we will make available to you the email addresses of all of these people, so you can get their critique.

DR. HOOFNAGLE: Right.

DR. SENIOR: As they think about it, when you're ready. Now, Jay has done us at the FDA a compliment, in that he stole our name. We used to call our access to the website cder/livertox. Well, they liked that so they took it, and we gave it, gladly.

DR. HOOFNAGLE: You didn't patent it; too bad.

DR. SENIOR: That's okay.

DR. HOOFNAGLE: We did.

DR. SENIOR: The 700-pound gorilla gets to sit where he wants, and we can't compete with the National Library of Medicine, or the whole NIH. Okay, our access is now by going to the FDA home page (www.fda.gov, and typing into the search window: “liver toxicity.” That gives you access. It's almost the same, but a little bit different. My view is that there really are no hepatotoxic drugs. There are drugs that are more likely to cause injury to people than others, but the difference is in the response of the recipient, not the drug. The drugs don't cause injury in most people, only in some people. So, the essence is not the drug difference, it's the response difference. Now, why do some people respond adversely, more to some drugs than others? That is what we need to investigate. So, if we had something that was causing too much trouble, it's
no longer a drug. Remember carbon tetrachloride. We used to give it to people to get rid of intestinal parasites. Well, it was causing trouble, so, it's no longer a drug. It's now a certified hepatotoxin. Chloroform used to be used for anesthesia. No more. It was too toxic. So, it's no longer a drug. The emphasis is on the need to understand individual recipient’s responses. What Jay has done is absolutely a treasure house of information, which we hope you will look at and comment, before it gets announced to the world. Now, are there any general comments? Jim?

DR. FRESTON: Very nice presentation, Jay, as usual. I had mentioned to Dr. Hoofnagle earlier, that it's about time that the full program was made available, because many of us have benefitted from it already. He looked at me quizzically, and that's because we asked Jay, what he's found so far with regard to certain drugs. My question and comment has to do with the facet that Dr. Serrano is developing whereby the data are entered from MedWatch, using a prescribed format that will probably be more complete than is usually used. Let me just back up. One of the problems with using RUCAM in drugs, in development, is that you get a higher score if the drug has been reported in the literature, or is in the label, to have caused DILI. Well, drugs in development may be causing DILI, but they're certainly not in the literature yet, and so, some in the industry have said, "Well, if we have a few cases in our own database that have a high probability of being DILI, even if they haven't been reported, maybe we should use that in the RUCAM." The problem with that, of course, is that approach makes sense, but it's never been validated. So, back to your scoring system and the use of MedWatch. Have you given thought to inviting industry to use this mechanism when they get a high probability case, or one that's got quite a lot of information at least? There are going to be -- confidentiality won't be an issue, because they're going, that MedWatch is going to the agency, anyway, and then, if it's published on your site, that could count as sort of an unofficial publication.

DR. SENIOR: Jay, did you have a comment?

DR. HOOFNAGLE: Yes, we haven't quite worked out this issue of so-called publication, whether this database of submitted cases will be available to everyone or just to us. At the present time, it will be just us. We have to work this out. We have to maintain, you know, this wall of separation of personal identifiers and so forth. We haven't quite figured that out, yet, whether we'll be able to do that. The person who enters it has the option of submitting: there
will be a check box 'submit to the FDA', or 'allow putting into the NIDDK database'. But this is an issue of grading the likelihood that a drug causes liver injury. From a DILIN network, we're using the published literature; everybody points out the problems with the published literature, but it is what's there. For instance, if you look at the NSAIDs, which I'm working on now, the package inserts all say, "Can cause enzyme elevations. Can cause hepatitis," and almost all of them say, "Some of it can be fatal." So, we have a drug like ketoprofen. Well, this doesn't cause much liver injury, but it gets the same score in RUCAM as does diclofenac and sulindac, which pretty clearly kind of stand out as potential problems. So, I think that type of gradation is what we can do to improve RUCAM. Now, there is rare information, I agree, that's why I think a journal of drug-induced liver injury would be very helpful, so that these could be reported, and everybody could look at them.

DR. SENIOR: Thank you, Jay. One of the concerns is that although we have a wonderful attendance -- this is a marvelous turnout, and you people are influential -- the people who are not here may be even more influential. It's been my experience and the experience of others, that most pharmaceutical companies are schizophrenic. They have an expert group of doctors and scientists to develop the drug, and then when it gets approved it's turned over to the marketing and sales people, who are mortally afraid of any adverse findings. So, they don't get reported such that we can really use the information. So, it's very important that you who are here from industry, go back and try to get the marketing people to understand that it's in their interest to find out that the reaction was not caused by their drug, but by patient disease, which requires information. Yes?

DR. HOOFNAGLE: I think what John said is correct. These drugs do not cause -- it's not hepatotoxicity That's perhaps, the wrong word to have used. These are idiosyncratic reactions in certain patients. You have a drug that's only hepatotoxic at all to one in 1,000, one in 10,000. It's just terminology, I know, but somehow, it gives you the wrong impression, that the drug itself is inherently toxic, and it may not be at all.

DR. TERSHAKOVEC: Andy Tershakovec with Merck. That actually is a good set-up for the comment that I had. So, this goes across the two sessions that we've had today, and the comment about that you're dealing with issues that are patient-specific and not the drug, so much. I think that gets into issues about consent and labeling patients being at risk, and
insurance, and things like that. I think we need -- people mentioned legislator in the beginning, and if there is any way to make sure that you have a protection for patients, you know, if we're going to get information, to work up patients in the era of genomics, and we're going to identify people who are at risk, we have to make sure that there're not going to be obstacles to working up patients, because they're concerned about being labeled and being high-risk, and not being able to get insurance, et cetera.

DR. SENIOR: Right, thank you very much for those good points. Lana?

LANA PAULS: Thank you. We are going to continue on this theme of how we have been looking for DILI, and I'd like to introduce Dr. Bob Fontana, who was up here earlier. He is from the University of Michigan in one of the DILI programs. He's going to be talking about retrospective and prospective DILI cases.

DR. FONTANA: All right, well, thank you, Lana and John, for the opportunity to represent my co-investigators in the NIDDK and multiple other individuals who have been contributing to this for the past 8 years.

Robert Fontana  
Prospective & Retrospective DILI cases

DR. SENIOR: Thank you, Bob. Please stay up at the table because you and Lana are going to moderate the rest of this session. I think we ought to hold the questions until we hear from Dr. Lee, and then discuss both papers afterwards. Is that okay with you?

DR. FONTANA: Sure, sure

William Lee  
Characteristics of the ALF population
DR. SENIOR: Thank you, Will. I don't see where Lana has gone -- here she is, Lana. Why don't you lead -- moderate the discussion for these last two speakers, please?

LANA PAULS: Jay, if you want to join us at the table, or at least be available by a microphone, that would be great. So, we have both north sides and south sides of the room, but then, of course, there is only 10 minutes between this and lunch. So, how much discussion am I going to generate here? Jack?

DR. BLOOM: Thank you. Very nice discussions. You've outlined, very nicely, distinguishing between DILI and other causes of hepatotoxicity. Do you feel that there's any refinement in either approach over recent years, in teasing out the possibility that these are coinciding? Of course, we're particularly concerned about whether it's anti-viral as in oncolytics, where both the drugs and the underlying disease may be producing signals that confound the possibility of DILI. It would make sense that at some incidence, these are going to coincide.

DR. FONTANA: Well, I can try to answer that. Certainly, with the hepatitis E data that we generated, we went back and looked at our original causality score and then in light of this new serologic information, it did change our causality assessment, as you might expect. Now, you can only do that for viruses for which you can confidentially test. We're already testing A, B and C, and CMV and EBV, and now, HEV. There're lots of other viruses out there, but there are, assays and things and what their phenotypes may be are not well characterized. I think it's certainly possible, and in those 9 cases they had gotten into the database because someone thought the drug had caused a liver injury. Is it theoretically possible that they had coincidental hepatitis E and also had drug-induced hepatotoxicity exactly at the same time? I think that's always possible, but is it probable? I don't know. When you have good PCR positivity and seroconversion, I think for sure, those patients had acute hepatitis E. To say we're getting into multiple hits, all at the same time, I think is beyond what we can confidentially say.

DR. LEE: One way is to look at the indeterminate group, and I didn't mention that during my talk. In the ALF indeterminate group, first of all, it's possible that the investigators just didn't do the test, okay. So, along that line, there is a paper in Hepatology in February that showed that 19 or 20 percent of the indeterminate group turned out to be acetaminophen-adduct strongly positive. So, we presume that they are real acetaminophen cases. If the investigator didn't do the
test, he may have had some history of acetaminophen ingestion, but there was no parent compound found. He was uncertain that the case was a real acetaminophen case. It's easy to say retrospectively, "Oh, God, you called that an indeterminate case," but it was really an acetaminophen case. So, that's one thing. But there is also a paper in February Hepatology related to looking at the histology on a group of indeterminate patients; the primary finding was that a lot of them, more than 50 percent, have a histologic picture of auto-immune hepatitis. So, then you go back and you say, "Well, okay, were these cases fully tested for all the auto-antibodies that you should have done," and in some instances, they were not. Part of it has to do with how deeply we, even experienced people, are able to get into etiology and these unresponsive, literally, patients.

DR. SALMINEN: Willie Salminen from FDA. This question is for Dr. Lee. Are you making any attempts with the DILIN to look at relative risk of the drugs that rank at the top of the list, for acute failure? Something like the antibiotics are ranking way up there, really high, but there are millions of prescriptions, though. So, is it really a risk, relative to other drugs out there, that you're seeing?

DR. LEE: By the way, we report all of these cases to FDA and we've worked out a system where we're going to have data drops to FDA on a regular interval. I don't think we've done that, no. That's very interesting. One item would be to look, for example, at Augmentin, because Augmentin is hugely prescribed, and actually, DILIN has as many, or more, Augmentin cases, because their threshold is low, and there are fewer fulminant cases of Augmentin, very few, just one or two, perhaps. But no, we've never tried to write about. That's a paper that we should write, for our cases, but it's really out of our universe, rather than out of the real prescribing universe.

DR. SALMINEN: I know that's a huge problem, trying to get that denominator part. As my boss always says, you try to get the number of prescriptions out there, and what drugs are people exposed to; it's very difficult. All right, thanks.

DR. HOOFNAGLE: You know, if you knew the rate, let's say, of isoniazid, hepatotoxicity and fulminant hepatic failure, you could use that as an index for all the other drugs, if you knew the rates of the prescriptions. Do you see what I mean? And kind of guesstimate the rates of fulminant hepatic failure from the other drugs.
DR. CAI: Yes, I'm John Cai from AstraZeneca. I have a question to Dr. Lee, and also, maybe to Dr. John Senior, as well. So, I look at the prognosis and think that some chronic and sub-acute disease, liver disease, have much worse prognosis. I don't know how much of that comes from the combination of the underlying disease and the drug administered to those patients. Also, for Dr. John Senior, the FDA guideline recommends us to include patients with underlying liver disease, in at least one pivotal Phase III trials, I guess as underlying stable liver disease. If there is a combination of underlying disease and the drug -- how much of that would affect the industry and also, the patient's risk? Thank you.

DR. LEE: You know, there are always cases that include two different diseases, aren't there? I mean, we have something like 11 hepatitis C cases in the acute liver failure study, but none of them are fulminant hepatitis C. It's a hepatitis C patient that took 30 grams of acetaminophen, or hepatitis C patient who was on isoniazid. Now, was there synergistic effect? Yes, possibly but I'm not convinced. I think if you took 30 grams of acetaminophen, it's an acetaminophen case. And if you think about the hep C patient population, those of us that treat hep C patients know a lot of them are psychologically compromised and they have a lot of issues of drug dependence and depression and so forth. So, then you get into all kinds of muddy cases, and it's tough, but Bob stated, 26 percent have multiple drugs, and it's very hard to sort even out the multiple drugs. But I would say when you get to acute liver failure, it's a specific syndrome, and I don't think many of them are chronic. We have been tasked about whether there are some chronic cases mixed in. I don't think there are very many. We don't get biopsies, however, on everyone because they're all coagulopathic and they're hard to biopsy, and if you've got an anti-HBc IgM, you kind don't need pathology. You might show that they had cirrhosis and okay, it's acute-on-chronic, but that doesn't really help you clinically. It's not essential to management. Does that help?

DR. SALMINEN: Thank you, yes.

DR. REGEV: Arie Regev, Lilly. I'm actually asking about the patients that you just mentioned. Bob, what is the thinking about this growing percentage of two drugs causing disease? Are you thinking these are cases of two drugs causing DILI, or is this just a case of you didn't pick the one that did it, or -- and if you do think it's two, what are you thinking about the mechanism?
DR. FONTANA: These are very challenging. The reason that they're coming up is that polypharmacy is increasing in our society, appropriately, as we manage more diseases earlier on, and so on. Within the database, most of those cases come up as potentially two drugs or more, because of the temporal association, and there have been prior reports of those individual drugs causing the liver injury that we're trying to adjudicate. So, it's a combination of guilt by association, because of timing and its prior profile. Now, is it a drug/drug interaction, or is it really that you just can't tell? I don't think we have any evidence that there's a consistent combination of drugs that's doing it. So, I don't think it's just an obvious drug/drug interaction. When you look at these cases, it's not that the patients were taking escalating doses of one and then happened to add in another and then, boom, all of a sudden -- it's not like that. So, I don't think it's clearly a drug/drug interaction. What we do, since we don't know for certain, is to score each drug, and then at the end of the day those will contribute to subsequent analyses.

Mechanistically, you know, hard to know, since we don't know the mechanism for each individual drug, it's really speculating for multiple drugs.

DR. HOOFNAGLE: It was so confusing. I have cases where the patient in the preceding two weeks had received augmentin, quinolone, and telithromycin, and came in with severe hepatitis. What do you make of that? But those are in DILIN, and I think they're actually very nice, because it shows that some cases, no matter what you do, you can't say exactly what it is.

DR. LEE: Right, so, here is another one. Neither Keppra -- I could never pronounce the generic, it's levetiracetam, or something like that, only it's about twice as long. So, Keppra is an anti-seizure drug, and temozolomide, Temodar, is the oncologic agent to treat brain tumors. So, neither of these drugs was thought to have significant hepatotoxicity, and yet we've seen four cases that we think are temozolomide-induced. However, most of them were all on Keppra, so --

DR. HOOFNAGLE: And they were both stopped at the same time?

DR. LEE: And they both stopped at the same time, and they may have been started at different times, but they were always within a latency period. So, the patient had a brain tumor. They'd get put on Keppra, then they get put on temozolomide three weeks later.

LANA PAULS: We have time for two more quick questions. We're going to go to the north side of the room first, please.

DR. CHANG: Hello. Charles Chang, Bristol-Myers Squibb. This is just a detail question,
about how you score Augmentin. Do you see the same level of DILI with amoxicillin alone, or do you call Augmentin a case of polypharmacy, since it's two drugs?

DR. FONTANA: Well, I know for a fact, in our database, at least, you know, we've been prospectively collecting all comers. Augmentin is the most common agent. I think we're up to 63, in the prospective registry, and I think we have one or two of amoxicillin alone. Again, it goes back to total use. Augmentin may be more commonly used, but amoxicillin is pretty commonly used, also. So, you know there are data to suggest that it's the clavulanic acid component of that from multiple lines of evidence. So, I do think it's probably that combination, there.

LANA PAULS: Okay, one last question, please.

DR. MICHALOPOULOS: Yes, I'd just like to make the comment that from the point of view of tissue availability in liver failure, we have a bit of an abundance and deprivation. Most of them, of course, cannot be biopsied because of all the obvious coagulopathies and all of that. But the 24-25 percent that get liver transplants, the whole liver comes out, and it is kind of an under-studied story there, that sets a panoramic variety of different histological pictures that we see in those livers, anywhere from absence of hepatocytes, to progenitor cells, to a whole variety of things. So, I think that's an area worth putting some emphasis, because there is a lot of biology, well coming into understanding now liver regeneration, back on the situation with regeneration during failure, this is an area we really need to concentrate more.

DR. LEE: Yes, I think that's a great comment. The only point I would make is that by the time they get to transplant, even though it only may be a matter of three or four days, this is the thoroughly exhausted 800 or 600-gram liver that's basically all stroma and not much hepatocytes. The other thing is, and it's real world, somebody has got to be sitting there in the middle of the night, ready to catch a piece of liver and snap-freeze it. We have maybe 18 or 20 or 30, but it requires a little bit of extra effort from people, typically in the middle of the night and you have to wrest it away from the surgeon and then also from the pathologist.

DR. MICHALOPOULOS: Well, being a liver pathologist, I would like to say that this is not all that bad. In the shrunken liver, acute yellow atrophy, there is a great variation in the number of bile duct cells expressing hepatocytes markers. I think this a very important area to concentrate on, because these are cells that provide the SOS pathway, and we do not need to have it frozen. Paraffin is perfectly good for these kinds of studies. So, I think we should still
concentrate on that, not declare it an impossible mission. It can be done; it's really very easy.

DR. LEE: But you don't have to get up in the middle of the night.

DR. MICHALOPOULOS: There are people actually available 24 hours a day.

LANA PAULS: Okay, with that, I think we're going to close Session I. I want to thank my co-moderator Bob Fontana and all of the panelists this morning. Just a couple of housekeeping issues. Please return to the room promptly at one o'clock. Lunch is out on the mezzanine. And just for the future, in the afternoon, at about 5:00 p.m. there will be a reception, to test your liver, from 5:00 to 6:00 p.m. Then there will be an informal discussion, to talk about comments on the guidance from 7:00 to 9:00 p.m., and all of those things will occur in this room. Thank you.

LUNCH