DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

OPEN SESSION

Wednesday, June 11, 2003

8:35 a.m.

Holiday Inn Gaithersburg
The Ballrooms
2 Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Joan P. Chesney, M.D., Chair
Thomas H. Perez, R.Ph., M.P.H. Executive Secretary

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Mary Glod, M.D.

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Michael Aschner, M.D.
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Joseph Lau, M.D.
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Robert Nelson, M.D., Ph.D.
Judith O'Fallon, Ph.D.
William Oh, M.D.
Don Mattison, M.D.
Thomas Newman, M.D., M.P.H.
Rebecca Flynn O'Brien, M.D.
Kevin Smith, Ph.D.
David Stevenson, M.D.
Benjamin Wilfond, M.D.
GUEST SPEAKERS

Susan Sheridan
Connie Schomann, R.N.
Marshallyn Yeargin-Allsop, M.D.

FDA

Robert Justice, M.D.
Susan Cummins, M.D.
Dianne Murphy, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order/Introductions

DR. CHESNEY: Good morning. We are ready to begin what is going to be a very full day. I would like to welcome you all to this Pediatric Advisory Subcommittee Meeting.

I would like to start with the usual roll call, if we could maybe start down at this end with Dr. Murphy.

DR. MURPHY: Dr. Dianne Murphy. I am the Office Director for the Office of Counterterrorism and Pediatric Drug Development and also the Office Director for the Office of Pediatric Therapeutics. Thank you.

DR. CUMMINS: I am Dr. Susan Cummins. I am a team leader in the Division of Pediatric Drug Development with the FDA.

DR. JUSTICE: Robert Justice, Director of the Division of Gastrointestinal and Coagulation Drug Products at FDA.

DR. NELSON: Robert Nelson, pediatric critical care medicine at Children's Hospital, Philadelphia, and a member of the committee.

DR. GLODE: Mimi Glod. I am head of the section of Pediatric Infectious Disease at the

Department of Pediatrics, the University of Colorado, School of Medicine, Denver, Colorado, member of the committee.

DR. DANFORD: David Danford. I am Professor of Pediatrics in the section of Cardiology, University of Nebraska Medical Center, Creighton University. I am a member of the committee.

DR. FUCHS: Susan Fuchs, Associate Professor of Pediatrics, Northwestern University Medical School, and pediatric emergency physician, Children's Memorial Hospital, Chicago.

DR. O'FALLON: Judith O'Fallon, statistician at the Mayo Clinic Cancer Center, Rochester, Minnesota.

DR. HUDAK: Mark Hudak, Professor of Pediatrics and a neonatologist at University of Florida, Jacksonville.

DR. FOST: Norman Fost, University of Wisconsin, Professor of Pediatrics, Director of the Bioethics program and Chair of the IRB.

DR. CHESNEY: Joan Chesney. I am Professor of Pediatrics in the Division of Infectious Diseases at the University of Tennessee

Health Science Center.

MR. PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. EBERT: Steve Ebert, Professor of Pharmacy at University of Wisconsin, Madison, an Infectious Diseases at Meriter Hospital in Madison.

DR. GORMAN: Rich Gorman, pediatrician in private practice in Ellicott City, Maryland, and a member of the committee.

DR. MATTISON: Don Mattison, staff at NICHD.

DR. IP: Stanley Ip, Assistant Professor of Pediatrics at Tufts University Medical School.

DR. FREEMAN: John Freeman, Professor of Pediatrics and Neurology at Johns Hopkins.

DR. ASCHNER: Michael Aschner, Professor of Physiology and Pharmacology at Wake Forest University School of Medicine.

DR. O'BRIEN: Rebecca O'Brien, Assistant Professor at Tufts University School of Medicine in the Division of General Pediatrics at the Floating Hospital in New England Medical Center.

DR. WILFOND: I am Ben Wilfond, a pediatric pulmonologist at the National Human Genome Research Institute and also with the

Department of Clinical Bioethics at the NIH.

DR. SMITH: Kevin Smith, Vice Chancellor of Research and Dean at the Graduate School and Professor of Chemistry at Louisiana State University.

DR. OH: I am Bill Oh. I am a neonatologist who is Professor and Chair of Pediatrics at Brown Medical School.

DR. NEWMAN: I am Thomas Newman, Professor of Epidemiology and Biostatistics and Pediatrics at UCSF and a general pediatrician.

DR. LAU: I am Joseph Lau, Professor of Medicine at New England Medical Center, and the Director of Agency for Healthcare Research and Quality Evidence-Based Practice Center.

DR. STEVENSON: David Stevenson. I am a neonatologist and Professor of Pediatrics at Stanford University, also serving as Senior Associate Dean for Academic Affairs at that institution.

DR. CHESNEY: Thank you.

Today's session is devoted to the current epidemiology and therapeutic interventions relevant to hyperbilirubinemia in the term and near-term newborn or, in other language, the current state of

medical practice with regard to management of neonatal hyperbilirubinemia and the potential role for new drug therapies in the prevention and management of jaundice in this population.

We have a very, very full and interesting agenda, and we are particularly honored to have speakers today, both scheduled and in the open public hearing, who have contributed so much to and for some their life's work to this issue.

I also have to remind myself that Agency doesn't bring issues with straightforward answers to the Advisory Committees. The complexity of today's topic is an example of the kind of issue that they do bring to advisory committees.

Before asking Dr. Murphy to begin the meeting, I wanted to make two comments. The first is because it is a very full agenda, I would request that all the speakers adhere as closely as possible to their allotted times.

If anyone goes 10 minutes over their allotted time, Tom and I may have to intervene, which is very uncomfortable for us, so if we do intervene, please know that we are sympathetic to your wanting to share everything you have with us.

The second issue is that many, if not all

of you, in the room know that there is a closed meeting tomorrow on a subject related to today's discussions.

In order to protect the privacy of tomorrow's meetings, we ask the speakers and particularly the committee members and the invited consultants who have had material which they have read in great detail for tomorrow's meeting not to comment today on the content of tomorrow's meeting.

Finally, I wanted to thank all the members of the Pediatric Division and the Division of Gastrointestinal and Coagulation Drug Products for all the work they have put into today's meeting and to thank Tom Perez, our Executive Secretary.

Our first speaker is--my apologies--we have to do conflict of interest statements.

Tom.

Meeting Statement

MR. PEREZ: Thank you and good morning.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics to be discussed at this meeting

are issues of broad applicability. Unlike issues in which a particular firm's product is discussed, issues of broad applicability may involve many industrial companies and academic institutions.

All special government employees participating in this meeting have been screened for financial interests as they may apply to the general topics at hand. Because Dr. David Stevenson has reported interests that could be affected by today's discussions, the Food and Drug Administration has granted him a waiver under 18 U.S.C. 208(b)(3) that permits him to participate. A copy of the waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30, of the Parklawn Building.

Because general topics could involve so many firms and institutions, it is not prudent to recite all potential conflicts of interest, but because of the general nature of today's discussion, these potential conflicts are mitigated.

With respect to FDA's invited guest speakers, Susan Sheridan would like to disclose that she is president of a consumer advocacy and

educational group called PICK, Parents of Infants and Children with Kernicterus. PICK receives charitable contributions from industry, however, all members of PICK are volunteers and receive no compensation for their activities.

With respect to all other participants, we ask, in the interest of fairness, that they disclose any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. CHESNEY: Thank you, Tom.

Dr. Dianne Murphy is going to speak to us to give us a very brief overview of the topic for discussion today. As you all know, Dr. Murphy is Director of the combined Office of Counterterrorism and Pediatric Drug Development, and the Director of the Office of Pediatric Therapeutics at the FDA.

Opening Comments

DR. MURPHY: I wanted to take a moment and first thank the committee, the Pediatric Advisory Subcommittee, who now has built quite a formidable experience in pediatric drug development for being so loyal and consistent, and being here when we have these meetings. I know that we have them

fairly regularly scheduled for you all, and it is a demand on your time. We want to always express to you how sincerely we appreciate your ongoing effort because I think in the arena of pediatric drug development, we need to have a very consistent core of people who can address the myriad of issues that are going to come forward as we continue to develop products for children.

I wish to also thank--when I looked at the list of invitees and speakers, I am always impressed at the commitment of people to put time and effort in what I know are extraordinarily busy lives to come and advise us. Again, our sincere thanks to everybody who has taken that time to do that today.

Also, the people who worked so energetically to put this together - Dr. Susan Cummins, Dr. Shirley Murphy, Dr. Debbie Birenbaum, Rosemary Addy. They have put together I think a wonderful package that articulates for you what the issues are. They made one mistake. They asked me to try to provide the overview for you, so that is what my job is this morning.

I am supposed to focus you on the fact of what the Agency does and put that in perspective as

to how to think about the questions we have asked you.

[Slide.]

This table could be quite extensive with many variations upon the theme, but, in general, what the Agency does when it decides to approve a product, it must find that it is safe and efficacious for an intended population, for an intended use, but that comes in many ways.

The very top line here is a therapy that might be even OTC, a therapy which has very low risk, a few side effects, and has tremendous benefit for somebody with allergies, let's say, so you have an OTC product.

That product is going to have a different safety profile than another product which would have a high or intermediate risk, but also would bring great benefit to the patient.

In this, the number of patients who might be exposed could be anywhere depending on the number of options that are available to the patient, any other options, and actually the degree of these risks as to how many might be involved.

I think today, we really are going to be talking about drug development where the risks are

in this arena, where the benefits are, and can we define a population that would fit in this category or not, or are we not in this category.

We are asking you to think about what is the population that would warrant therapy, how do we identify it, and what are the things that we should be asking for if we are going to develop a product as to its safety profile and its benefit.

To do that, we have to first go through many of the areas that are being brought up for discussion today, which is what is the status of the therapeutic interventions that we have available and what is our status of knowledge in this area.

I have put on these other things just because, yes, there are products that have lots of known high risk, not a lot of benefit, but if there are absolutely no other options, they are actually products that may get approved in this area, too.

So, there is a complete spectrum and what we are simply asking you today is not simple, it is very difficult to consider drug development for therapy of hyperbilirubinemia, what are the kinds of risks, and for what kind of population.

[Slide.]

Right now, these few slides summarize where we think, I will try to define that table in graphic form. We have a very high risk intervention for very few patients that are involved usually, and were willing to take it because there aren't any other options when we reach this point.

[Slide.]

We have another intervention earlier on, more patients involved, less risk, and where are we, is this where we want to go with drug, or is it really here, where is it, what is the population, and what is the safety profile for that population.

Those are the sort of things we want you to be thinking about as you go through the broader issue of where are we today in this field in our knowledge of hyperbilirubinemia and how it occurs, what the prevalence is, what the incidence is, and what the interventions are and should be.

[Slide.]

That is again summarizing in a very simplified way, we need to be able to put these therapies where you decide the population would be would really define what the risks might be, because you are going to be really defining whether

you are going to expose a lot of patients or a few patients.

I hope that hasn't muddied the water, but again, summary from a drug development point of view, you are going to develop a drug, you want to know what is the population that is going to receive this intended therapy and how do we define the efficacy and the benefits and the risks of that product.

Thank you very much.

DR. CHESNEY: Thank you, Dr. Murphy.

Our next speaker is going to be Dr. Tom Newman, who will give us a historical background and selected recent research findings relative to this issue.

He is a professor in the Departments of Epidemiology and Biostatistics, Pediatrics, and Laboratory Medicine at UCSF. We thank him for coming to speak with us today.

Historical Background and Selected Recent Research Findings

DR. NEWMAN: Thank you.

I think the slides for my presentation are on the lefthand side of your little packet there. This is what I was asked to talk about. I guess

maybe I am getting old if I am talking about history. It is usually people who have been around a while.

You will see that a lot of this presentation is kind of focused on my perspective. You will see sort of an overemphasis on research that I have done and on the history that I have experienced myself. I am sure that as others speak, we will be able to even that out a bit.

[Slide.]

But I will be talking about the history leading up to the 1994 AAP guideline which I participated in writing, the content of the guideline, what has happened since then, and some research findings focusing on research we have done at Kaiser Permanente, and close with some unanswered questions if I have time.

[Slide.]

Starting in the 1950s, and, of course, I was not around much in the '50s, so this is based on reading the literature and talking to people.

Before the '50s, there was a lot of Rh disease and kernicterus that was mostly from Rh disease, and in the 1950s was the first randomized trial that showed that exchange transfusion could

prevent kernicterus in children with Rh disease, but it is interesting that in that trial, the benefit was restricted to babies who had a cord hemoglobin of less than 11, and bilirubin was not even measured in that trial, so the index of severity for the Rh disease was how anemic the baby was at birth.

But, in fact, by doing exchange transfusions and treating these very anemic and sick babies, it was found that kernicterus could be prevented because, of course, when the red cells were made compatible with the mothers, the hemolysis was reduced.

The data relating kernicterus to bilirubin were observational data sort of added parenthetically at the end of an article in the New England Journal by Shaw, et al., where they said that since they had started keeping the bilirubin level below 20, they had not seen any cases of kernicterus, and that 20 mg/dl sort of stuck for many years as the level to try and keep the bilirubin below.

The other thing that happened in the '50s was a randomized trial, the only other randomized trial I know of where kernicterus ended up being an

endpoint, but this was a randomized trial of prophylactic sulfisoxazole in premature babies, and the sulfisoxazole displace bilirubin from albumen and caused kernicterus in the intervention group, in the group that got it, and that contributed to our understanding of kernicterus and how it is causally related to bilirubin, but especially unbound bilirubin.

[Slide.]

Moving quickly now into the '60s, that was when Rhogam was developed and used, which really has just about wiped out Rh disease. There was a lot less kernicterus. Looking in the literature, then, there were debates, you know, when the only intervention for hyperbilirubinemia was exchange transfusion and Rh disease was going away, there were all these other groups who had high bilirubin levels and it was unclear how they should be treated - should you do exchange transfusions in babies with ABO disease and nonhemolytic jaundice and in preemies, and that was debated. Phototherapy was first used in the 1960s.

[Slide.]

Moving into the 1970s, the Collaborative Perinatal Project, which enrolled babies between

1959 and 1966, a big cohort study looking at neurodevelopmental outcome in babies that were followed from actually before birth, their mothers were followed.

There was some kind of worrisome data from the Collaborative Perinatal Project that suggested that kernicterus might be the tip of the iceberg, that is, there was some statistical difference in neurodevelopmental outcome in Bailey scores at less than a year in babies who had higher bilirubin levels.

This was mostly seen in low birth weight babies, but it raised this concern that there is kernicterus, which is one extreme, but there might be subtle neurodevelopmental problems, and the same sort of concern about lower level bilirubin toxicity was raised by the finding of yellow staining of the brain at autopsy in premature babies, which was also called kernicterus, so it was a little bit unclear how much of that yellow staining was actually primarily due to kernicterus or later event.

But certainly in the 1970s is when phototherapy really took off partly fueled by these concerns and the fact that the only other treatment

was exchange transfusion, we could measure bilirubin, we could treat it with phototherapy, reduce the levels, so phototherapy became very popular.

In the 1960s, most babies in the U.S. were bottle fed. In the 1970s, we really saw an increase in breast feeding.

[Slide.]

That brings us up to the 1980s where my own personal experience starts. I was a resident in pediatrics from 1980 to 1983 at UCSF, and I was taught that bilirubin is a neurotoxin, it's a brain poison was what I was told, and that we did phototherapy when the bilirubin level hit above 14 to 15 mg/dl, and exchange transfusions, if it got above 20. This was not a good time to be doing exchange transfusions.

This was San Francisco 1980 to 1983. There was a lot of HIV in the blood supply. So, part of my formative experience was doing exchange transfusions and then later finding out that probably they weren't necessary and wondering if I had given any babies AIDS and knowing that there were going to be babies who got AIDS from exchange transfusions.

Also, when I was a resident, this article called "Vigintiphobia," fear of 20, came out sort of a light-hearted questioning of why we were so worried about 20 and suggesting that maybe in babies who did not have Rh disease, that was too low a level of bilirubin to worry about.

Then, just sort of incidentally, but a very striking result was that in a study, an autopsy series, there was just this abrupt disappearance of kernicterus when the benzyl alcohol preservative was removed from the bacteriostatic saline in neonatal intensive care unit. Again, that might have been displacing the bilirubin from albumin.

[Slide.]

Moving into the 90s, this is when I started doing research on jaundice in babies. Jeffrey Maisels and I published a couple of articles that were sort of a more systematic examination of the literature than what Watchko and Oski had done, but I definitely give them credit for, at least for me, making me think this was something worth reviewing.

Articles suggesting that it really, that the epidemiologic term here is effective

modification or interaction, it really was not reasonable to generalize from Rh disease babies in the '50s to well, breast-fed babies in the '90s in terms of estimating what is the risk of neurologic damage from a high bilirubin level, and this evidence that if 20 was the level that we need to worry about in Rh babies in the '50s, then it surely wasn't 20 for well babies in the '90s.

This led to the 1992 paper which had recommendations for less aggressive treatment of jaundice in babies, also fewer laboratory tests because the laboratory tests that were then recommended were mostly not useful.

With Mark Klebanoff, I re-analyzed data from the Collaborative Perinatal Project, those data were available to Mark, looking specifically at this issue of was there really good evidence that at lower levels of bilirubin, there was neurologic damage, and got I think very reassuring results for intelligence for the IQ measures and for hearing, and reassuring for definite neurologic abnormalities, but the sort of small but statistically significant increase as bilirubin levels went up in abnormal or suspicious findings.

The trouble is that bilirubin levels in

that study were fairly low and that the biggest burden of sort of extra abnormal or suspicious findings came in babies who had bilirubin levels between 10 and 15.

In that paper, we calculated that if everybody in the whole Collaborative Perinatal Project's bilirubin level had been kept below 10, the population frequency of these abnormal or suspicious neurologic abnormalities would have gone from 15.1 percent to 14.85 percent, so we didn't think it was a very important effect.

Then, the AAP practice parameter, which was one of the first practice guidelines that the AAP did, was in 1994. Around the same time, beginning in the '80s and into the 1990s, hospital stays for newborns got shorter and jaundice really moved from the inpatient problem that it was when I was a resident to an outpatient problem and the problems of babies with jaundice needing to come back and get a bilirubin test, and then come back again and get another bilirubin test, and when they needed phototherapy, to be readmitted, and that really was a change from the 1980s.

[Slide.]

The AAP Guidelines addressed more than

treatment, but I think probably the most important difference with the guidelines was raising the thresholds for treatment somewhat, varying them by age, and then the next version of the Guidelines, that will even be a little bit smoother rather than changing abruptly at 24, 48, 72 hours.

You can see that most of the jaundice, most of the babies getting phototherapy are, because bilirubin peaks after about three days, more than 72 hours old. Of course, if it is rising fast, you need phototherapy sooner, but this sort of said it is reasonable to do phototherapy at 17, but you can individualize and not all babies are the same, but you really probably should do it if it gets above 20.

If phototherapy fails, you should do an exchange, and if you are starting out above 30, you really probably should just do an exchange although some of these babies, the bilirubin drops fast and then they end up not getting one.

[Slide.]

So, what has happened since then? Well, I will show you some data on some of these things. One is that there are a lot fewer exchange transfusions being done unless phototherapy, there

is a concern about kernicterus coming back, about an increase in kernicterus.

In 1996, the Newborns' and Mothers' Health Protection Act was passed, which mandated coverage for at least a 48-hour length of stay. That became effective on January 1st of 1998.

PICK, which has already been mentioned, Parents of Infants and Children with Kernicterus, was formed, and I think had a major influence on bringing attention to kernicterus as a problem.

I guess there has been more of a focus, not so much on when we should be treating jaundice and whether we should be doing phototherapy at 15 or 20 or when, but I am trying to figure out who is going to need it and trying to determine that before babies leave the hospital. We are sort of acknowledging this problem of jaundice having shifted from an inpatient to an outpatient problem.

Those are some of the things also, it shows some data on.

[Slide.]

These are some data from Israel that I think most directly address this question of the influence that the AAP practice parameter may have had. Anyone who is the practice guideline

business, this is a totally remarkable change. The Guideline was published in '94, the amount of phototherapy done, a 63 percent drop in these two hospitals, and an 85 percent drop in the number of exchange transfusions just in this relatively short time period.

I think for those who are trying to change doctor behavior with guidelines, the key is to issue a guideline that tells the doctors to do what they want to do anyway, and that they don't have to do something that they didn't want to do anyway, and then you get very good adherence to the guideline, because most of us never I mean really liked to do an exchange transfusion, and to sort of be given permission not to have to do that, that is the way you get good adherence to your guideline.

My guess is that this has happened elsewhere, as well, that nobody really liked doing exchange transfusions, and phototherapy, readmitting a baby to the hospital and putting them under the lights is not much fun either, so people were happy to be kind of I think be given permission not to do as much.

[Slide.]

These are data from Kaiser Permanente,

even more remarkable. These show adherence or lack thereof to the AAP Guideline, just published in May of this year in Pediatrics.

Just to orient you here, these are 11 different hospitals in the Northern California Kaiser Permanente system. You can ignore the green bars for you and just look at the red bars.

The red bars are the proportion of babies who received phototherapy for whom the Academy of Pediatrics said it was recommended. Remember that slide showed you before of the Guidelines, the AAP said that for over 72 hours, consider it at 17, and do it at 20. Well, the green bars are the percent for consider, the red bars were the bilirubin, most of these babies had bilirubin levels over 20, what percent of them got phototherapy.

You can see that it ranged from about 27 percent in hospital 9, up to about 75 percent in hospital 10, so a huge inter-hospital variation, but overall, almost half of babies at Kaiser with bilirubin levels between 20 and 25 didn't get treated with phototherapy in 1995-96.

We don't have data from before that. My guess is this is somewhat of a drop, but also talking to many of the doctors at Kaiser

Permanente, they were never as worried about bilirubin as we were at UCSF, I think. So, big differences by hospital and many babies not getting phototherapy.

We did look at the lab tests and the vast majority of babies who didn't get phototherapy with bilirubin in the 20's did have their bilirubin repeated, and it was documented that it went down, so maybe it was 21 and then the next day it was 19, and it just went down by itself.

[Slide.]

The next point I was mentioning was the increase in concern about kernicterus, and this is kind of a raggedy slide because I scanned it from a photocopy of cases in the pilot kernicterus registry.

I show this because this sort of slide has been used to raise concern about kernicterus, and I think kernicterus is a problem, but the methodology of the registry isn't sufficient to answer the question about whether there has been an increase because kernicterus wasn't being looked for, for the registry early on, so the method of ascertaining cases which involved asking people to report them would lead to an increase or to a

picture like this, probably whether or not there had been an increase, so I think we think we just have to be careful.

The issue I don't think really is has kernicterus increased as the issue is, is it there and can we reduce it.

[Slide.]

In terms of again the Kernicterus Registry, these are the definitions from the recent paper in Journal of Pediatrics, the criteria for case eligibility. I think one of the things we are going to come back to, a central question really in deciding whether to treat hyperbilirubinemia with drugs is how bad is hyperbilirubinemia, how dangerous is it, how many cases of kernicterus are there.

The problem that we are going to come to is that kernicterus is not always a yes or no definite thing, and there is going to be a tradeoff between sensitivity and specificity.

The criteria to be in this registry included either acute symptoms of kernicterus, which are listed there, or chronic sequelae abnormality in at least two of the following including extrapyramidal movement disorder, gaze

abnormalities, auditory disturbances, intellectual deficits, enamel dysplasia of deciduous teeth.

Although many or most or maybe all of the kids in this kernicterus registry may have kernicterus, I don't think we can say that. We don't know that, certainly not from these inclusion criteria, because these are nonspecific. There are many, many children who have intellectual deficits and auditory disturbances who clearly do not have kernicterus.

Many, many kids with cerebral palsy have enamel dysplasia of their teeth. Many kids with hearing loss have teeth problem, so these may be sensitive criteria for kernicterus, but they are certainly not specific, and it makes it hard to interpret data from the kernicterus registry.

[Slide.]

So, what do we know about how common kernicterus is, because I think that is a key question. In the recent publication, 90 cases in 15 years in the U.S., if they had complete ascertainment, which I think is not possible, not even close, that would be an incidence of 1 in 700,000, so there is both way underestimation from underreporting and possibly overestimation from

non-specificity of the case definition.

We have been looking for many years now for cases of kernicterus of Northern California Kaiser, where there are about 28,000 births per year in term and near-term babies, and in 111,000 cases, we have looked very closely because we have all the bilirubin levels, and looked at all those with very high bilirubin levels.

In this month's Pediatrics, we have a paper describing the 11 children who had bilirubin levels over 30 out of those 111,000, so 1 in 10,000, and none of them got kernicterus.

We have also started looking in earlier years. We don't have the lab data, so this is relying on discharge diagnoses, but I am working with a neurologist, Dr. Yvonne Wu, who is studying cerebral palsy, and she has reviewed the charts of all the kids with cerebral palsy diagnoses in this cohort, and we still haven't found any cases of kernicterus in this now about 230,000 babies.

In the California cerebral palsy project, this is a personal communication from Susan Cummins who was involved with that study. They had 1 case in 155,000 out of a total of 192 cases of cerebral palsy, so a small proportion of cerebral palsy.

One other population-based report comes from Denmark where there is a report of increasing kernicterus between 1994 and 1998, 5 cases, but with a denominator there, that would be about 1 in 65,000.

That is kind of hard to interpret because it is hard to know whether this is the right denominator, 94 to 98, or it should include a few years before or a few years after, but that would be an increase.

The trouble is that we don't have that sort of data in the U.S. because it's a much bigger country and we don't have an easy way of knowing how many cases there are.

[Slide.]

So, the problems in trying to figure out how common kernicterus is--and I am sure you will hear more about these later--there is no uniform surveillance, there is a trade-off between sensitivity and specificity in case definition. If you don't want to miss anything that might be kernicterus, you will include a lot that probably aren't, and the diagnosis of kernicterus is often delayed and uncertain and contentious.

This is especially true if the baby didn't

show symptoms in the newborn period, and it is very hard to tell someone who has some of the symptoms of cerebral palsy or kernicterus from someone who just happened to have a high bilirubin and had those anyway.

My best estimate is that it is probably somewhere between 1- and 200,000, or 1- in 500,000, which would be between about 8 and 20 cases per year in the U.S., and just to mention that people should be very careful about extrapolating from the U.S. to other countries because kernicterus appears to be much more common in some other countries, especially in Africa.

I was just struck at the Pediatric Academic Society's meeting just last month, the report from Southern Nigeria, where they described kernicterus in 9 of 20 infants admitted with bilirubin levels over 15, or 40 percent, and this is because they were putting camphor on the umbilical cord stump, probably in some kids who had G-6 PD deficiency. So, kernicterus is definitely a problem some places in the world, a much bigger problem than in the U.S.

[Slide.]

So, moving on now to the selected research

findings, and I think the things that I talk about are jaundice in the first 24 hours, how much does that tell you that this is a baby who is at very high risk and needs bilirubin measurement and close, careful follow-up, using bilirubin measurements before discharge to predict who is going to develop hyperbilirubinemia, end-tidal carbon monoxide, and a risk index sort of as a placeholder for just the idea that the history and physical gives you a lot of information about the risk of developing hyperbilirubinemia.

Just most recently last month we presented the idea that combining clinical information with bilirubin measurements is probably the way to go.

[Slide.]

This first slide, there is a tendency I think in the medical-legal cases especially, and this actually I think comes up not infrequently to sort of paint a picture.

Here is a baby who was jaundiced at less than 24 hours and no one checked the bilirubin level, and now the child has kernicterus and there is this very clear causal relationship and the doctors messed up, but if you actually look at studies to say, you know, is jaundice at less than

24 hours really pathologic, you first have to say, well, there has only been, as far as we know, one study that looked at babies at less than 24 hours to see whether they were jaundiced or not systematically, and that was by Davidson in the '40s, and they compared that to bilirubin levels, and I think it is generally accepted that when the bilirubin level gets above 6, most observers can observe jaundice, but there is quite a few data about how many babies have bilirubin levels more than 6 at less than 24 hours, 41 percent at a mean of 72 hours in Alpay's study, 25 percent at a mean of 21 hours, 47 percent at 24 hours, so to say that anyone with any jaundice at all in the first 24 hours automatically has pathologic hyperbilirubinemia probably wouldn't fit most people's definition of pathology.

[Slide.]

We looked at this at Kaiser because we reviewed charts for a nested case control study trying to predict which babies would develop bilirubin levels of 25 or more, so we had charts on just a random sample at birth.

These are not the cases, these are mostly controls, babies who never developed high bilirubin

levels, and we just looked at when jaundice was first noted in the chart.

Of course, having something noted in the chart and having it be there are two very, very different things. Presumably, the ones that are noted in the chart are a subset although sometimes people noticed jaundice at nighttime and then in the daytime, it seems to be gone when the light is better and babies are in the sunlight, but this shows the percentage of babies in whom jaundice was noted in the chart at Kaiser almost always by the nurses up to about 6 percent at 24 hours.

So, that is few enough that you would think that it would be pretty abnormal and taken seriously.

[Slide.]

But then what we looked is, okay, so how soon after this supposedly pathologic jaundice was noted in the babies at less than 24 hours, how soon did bilirubin levels get done, and these are cumulative, so within six hours in 19 percent, within 12 hours in 38 percent, less than half actually had a bilirubin level measured within 24 hours of when they were noted to be jaundiced, if they were noted to be jaundiced at less than 24

hours, and two-thirds eventually got a bilirubin level.

So, one of the themes here is that, number one, we have had very little or no kernicterus at Kaiser Permanente in many years and with a couple hundred thousand babies; and, number two, it is hard to say it is because jaundice is managed very aggressively or according to guidelines there.

The phototherapy slide and this slide suggest that this is true, that the low frequency of kernicterus at Kaiser I think is due mostly to the fact that at Kaiser, we have a denominator, it is not due to extraordinary efforts to treat jaundice.

I think in the interests of time I will skip that one.

[Slide.]

So, continuing with free discharge risk assessment, and everyone will be familiar I think with this graph from Bhutani, et al., looking at bilirubin levels over time, showing how important it is to know the baby's age in hours when interpreting a bilirubin level, but again for pre-discharge risk assessment, I want to emphasize that babies are going home between 24 and 48 hours.

These points, the points between the 40th percentile and the 95th percentile are not all that far apart, and this I think is very relevant for predicting jaundice using transcutaneous measurement, so just keep these numbers in mind - 5 mg/dl is the 40th percentile and 8 is the 95th percentile at about 24 hours.

[Slide.]

This is one of the instruments that is used. It is wonderful not to have to poke babies and do heel sticks for bilirubin levels. It costs $4,000 and $7.00 each time you use it.

[Slide.]

These are data looking at how accurate that machine is compared to HPLC. What I just want to call your attention to is that, you know, it is pretty good especially when the bilirubin levels are between or less than about 10, but that the error range is really plus or minus about 2, 2 or 3. It says it is up to plus 3 or minus 2 would be the 95 percent range. What is being plotted here is the difference between the HPLC and the transcutaneous measurement.

So, if, for example, you measure the value and it's 7, then, it means, well, probably it's

between about 5 and 10, but if you remember that 5 was the 40th percentile and 8 was the 95th percentile, the ability of a transcutaneous measurement at about 24 hours to predict who is going to develop subsequent jaundice is probably going to be pretty imperfect.

[Slide.]

This is another technology which it had been hoped would help determine who was hemolyzing and therefore how much bilirubin was being produced and who would be at risk of subsequent severe hyperbilirubinemia.

It turns out that for each molecule of bilirubin that is made, a molecule of carbon monoxide is made, so as long as you have a non-smoking mother and not a bad air pollution day, you can measure the carbon monoxide in the baby's breath and get a direct index of bilirubin production.

[Slide.]

The good news is that it is better than a direct antiglobulin test, better than Coombs' test of predicting who is going to get jaundice, but a Coombs' test is really not very good, and it is not as good as a total serum bilirubin measure, which

is not too surprising because the bilirubin measurement sort of reflects both production and excretion, and the carbon monoxide only reflects production, and it is kind of pricey - Herschel pointed out it is cheaper than a Coombs' test, but the machine costs about $20,000 and about $14.00 each time you use it.

[Slide.]

A low tech approach, which just involves a history and physical, we suggested, and again at the Pediatric Academic Society's meetings a year ago and last year, validated this for another two-year birth core.

This was developed for babies born in '95 and '96 to predict who would develop a bilirubin level over 25, which actually should be easier. It should be easier to predict who is going to get over 25 than over 17 or 20, because it should be a higher percentage of kids who have risk factors.

Without going through it in detail, these are the risk factors - exclusive breast feeding, having had a family history of jaundice, bruising, Asian race, cephalhematoma, and so on, and those give you a lot of information about who is subsequently likely to run into problems.

[Slide.]

I know the AHRQ folks will be talking about this later, so I will be very brief here, but if you use the area under the ROC curve to estimate how well can we predict who is going to develop hyperbilirubinemia subsequently, there is a range. Most of these values are in the 0.8-something range.

This is the original study that used that graph that I showed you, that used the bilirubin percentile group, came up with a high area under the ROC curve, but probably the babies with lower bilirubin levels were less likely to get a subsequent one, so that it is probably biased a bit towards being high, and this is probably the better estimate of the accuracy of the bilirubin level measured at 24 to 36 hours because Stevenson, et al., used the same Bhutani groups, but this was in a multicenter study, it wasn't just in Philadelphia, and this was calculated by me from their data.

The area under the ROC curve, by the way, 1.0 would be perfect and 0.5 would be worthless. This was the estimate for the end-tidal carbon monoxide. It was quite a bit worse. The risk

index, this is actually the 0.83 is when we validated on a separate group of babies, but again it is trying to predict much higher bilirubin.

What we did most recently is we just showed that by combining the bilirubin and information from the risk index, this was done all with computerized data, so we didn't have breast feeding, but we had a substantial increment in the ability to predict bilirubin level by saying now only what was your bilirubin when you were 36 hours old, but what was your gestational age, which turns out to be key. Babies who are 36 weeks, 37 weeks, much higher risk, how old was your mother, what was your race, and so on, that enhanced prediction.

[Slide.]

Moving on to the long-term effects of hyperbilirubinemia, what are the bad things that it can cause, and certainly at the top of the list is kernicterus, it turns out the next most bad thing that hyperbilirubinemia can cause is probably exchange transfusion. We really would like to avoid doing that. It is a risky procedure and especially people have less practice with it than they used to.

Phototherapy, phototherapy is something we

would rather not do. It is not totally benign. It probably doesn't have long-term effects, but it involves separating the mother from the baby, and it's costly and disruptive.

Then, I want to address this issue of more subtle neurodevelopmental effects. I know other people will be talking about this, as well. There are definitely transient effects on brain stem responses and on behavior, and one of the questions is are there any long-term effects on hearing or motor or cognitive outcomes or behavior.

[Slide.]

I just want to tell you a little bit about a study that we are just finishing year 4 or 5 of this study, looking at babies with very high bilirubin levels, bilirubin levels of 25 mg/dl and up.

There is another case group, which is babies who were readmitted with significant dehydration and randomly selected controls, all born within a defined cohort 1995-98 Northern California Kaiser Permanente Medical Care program hospitals.

What we are doing is bringing these children back when they are 5 years, 1 month, and

having full neurodevelopmental evaluations by psychologists and child neurologists who are blinded to whether the child is a dehydration case, a bilirubin case, a control, or both. We have a few who were both dehydrated and had hyperbilirubinemia.

I am going to go ahead and show you some data for this, but they have to be regarded as preliminary. The data collection, if everything is on schedule, will end in February 2004, when the last of the babies born in 1998 turn 5 years, 1 month.

[Slide.]

The outcome variables for this study are a standard neurologic exam by a child neurologist. These are IQ tests, the Wechsler Preschool and Primary Scale of Intelligence for children and Visual Motor Integration test all done by a psychologist.

A Motor Performance Checklist, which was developed by an Australian occupational therapist for five-year-olds, turns out to be just the sort of thing that we were interested in because it is very practical items with a lot of face validity like jumping, throwing, hopping, catching, you

know, using scissors to cut out a square, and we measure how well they follow the lines, putting beans, how many beans can they put into a bottle in 20 seconds, and so on.

These are all blinded, and then the Child Behavior Checklist and Parent Evaluation of Developmental Status by the parents.

[Slide.]

Here is where we are as of a few months ago. Of the 140 babies who had bilirubin levels over 25 in a four-year period, we were able to get 86 of them to agree to this study. We would have liked to do more, but this is pretty good considering this involves the family taking basically a half a day off to come to a site to get all these tests done, and we have done about 70 percent of the exams completed, so I am going to be showing you data on done and entered 60 babies who had bilirubin levels over 25, about twice that many controls, a lower consent rate from the controls. You know, we tried very hard, but there just isn't too much way that we can get the controls to be as interested in the study as the parents who have experienced a dehydrated or very jaundiced baby.

[Slide.]

This slide shows, I will try to show now just a description of the patients in the study. These are the bilirubin levels. Of course, the cases all had bilirubin levels over 25, but I have to say this is mostly a study of babies with bilirubin levels between 25 and 28. We already have reported on these babies who had bilirubin levels over 30.

Remember, there were 11 babies with bilirubin levels over 30, but a number of them weren't in the study or hadn't been examined yet.

Some of the controls had bilirubin levels in the teens, even a couple over 20, the vast majority never had a bilirubin measured.

[Slide.]

As expected, there were differences in the maternal race and ethnicity with an excess of Asian moms among the cases and a fewer than expected Blacks and Whites and Hispanics about the same.

[Slide.]

Not much difference in education. The trend toward the bilirubin cases being a little bit better educated.

[Slide.]

No difference in family income. This is

28 or 27 percent had family income more than $100,000, so this was not an impoverished group. This is what you have to make to live in the Bay area.

[Slide.]

As expected, the gestational age was quite a bit younger among the cases. See this big excess of 38, 37, 36 weeks. We added the 35-weekers later, so we actually recruited additional controls at 35 weeks.

[Slide.]

This one sort of surprised us, the duration of breast-feeding because we thought this would be a big confounder we would have to worry about, that the cases would much more likely to have been breast-fed for longer. This wasn't the case.

The big risk factor was exclusive breast-feeding, exclusive breast-feeding during the birth hospitalization, which is what was associated with being the case, but not any breast-feeding, not just whether you had any breast milk or not, and not duration of breast-feeding.

[Slide.]

So, now some results, first unadjusted and

then I will show you adjusted. The short answer is that there is only one statistically significant finding so far, I will show you on it. It goes in the direction of favoring the bilirubin cases.

The verbal IQ, the trends were towards higher IQ's and the unadjusted verbal performance, and this is the test of visual motor integration, nothing statistically significant, all higher for the cases.

[Slide.]

Adjusting for race, ethnicity, parental education, income, and so on, nothing is statistically significant, and generally, the two numbers move a little bit closer together and usually the bilirubin is still a point or two higher although for performance IQ, they did switch directions, but not statistically significant.

[Slide.]

Remember, this is that test, the Motor Performance Checklist which when it was developed, it was considered that scores above 4 were abnormal, and this is also not statistically significant. These are, you know, you get a point, that is, higher scores are worse, you get a point you fail if you can't throw or catch a ball, or

stay within the lines when you are cutting out a square, and so on. So, no difference there.

[Slide.]

This is kind of unexpected. The blinded neurologic exam, which we had the neurologists rate from normal, normal questionable, which is a child that they still thought was probably normal, but there was just something a little bit iffy, you know, maybe a little bit hypertonic or brisk reflexes or not too great at the tandem walk or something that they didn't think was abnormal, but that in order to maintain a high sensitivity, they were just going to say questionable.

Abnormal was where they felt that this was a child who definitely was abnormal, but minimal means there was minimal or no functional disability, so that it didn't really affect the child, but they could see that there was a pattern of maybe a very slight hemiparesis or something, and then there were very few who had anything more severe. This came out statistically significant in favor of the bilirubin group. They had fewer questionable to minimally abnormal neurologic exams.

[Slide.]

I will close with some unanswered questions. I think we still don't know what the incidence of kernicterus is. We know that it's not common, but given that we have very few large series with denominators, it is quite possible that something other than treatment of bilirubin is what makes Kaiser Permanente better that average, and it could be higher than I think.

What we really need to know is not just what is the risk of kernicterus, but at what level of bilirubin, what the risk is at different levels of bilirubin, is there any risk at all between, say, 25 and 30, or 20 and 25, and, if so, what is it because what we are going to have to do is balance risks and benefits in treating. As you get above 30, 35, it is very hard to make guidelines about things like exchange transfusion if you don't know these numbers.

What factors modify these risks? I think this is key because two different babies who have a bilirubin level of 30 may be at enormously different risks of kernicterus depending on other factors, such as other illnesses the child may have, you know, hemolysis being best demonstrated, but I think there is at least good anecdotal

evidence that babies who are septic have a much higher risk of kernicterus, and so on.

We need to know what are the risks and costs and efficacy of treatments. We don't really have a good feel for that, large series of exchange transfusions, careful looking at long-term effects, if any, of phototherapy, and certainly any new treatment, this would be key.

Ultimately, I am afraid we are going to have to come up with some sort of decision about how many tests and treatments it is worth doing to prevent one case of kernicterus because there is always going to be uncertainty. Kernicterus is very rare, you can't always predict it. It is always going to involve treating many, many patients who aren't going to get it anyway in order to prevent one who does, but how many that should be, I think that is an unanswered question.

[Slide.]

To close, the problem I think is that it is going to very hard to show that a new drug or any other treatment will improve neurologic outcome in children with jaundice because the bad outcomes are just too rare.

So, we are faced with effects on bilirubin

levels, which is really a surrogate outcome, and not knowing for sure whether if we lower bilirubin levels, we do anything except avoid the treatment.

So, we end up treating with a drug to avoid phototherapy and exchange transfusion, which are both things that we choose to do at certain levels. So, it is going to be a difficult decision, I think, how much data on safety we need to approve a drug intended to prevent treatments like phototherapy and exchange transfusion for a risk factor, which is a high bilirubin given our current uncertainty about when those treatments are indicated.

I think I am out of time, so thank you.

DR. CHESNEY: Thank you very much.

We will have time for discussion of the presentations after the next group of presentations, and the next group of presentations have been allotted one hour.

Just by way of introduction, in February of 2003, the Agency for Healthcare Research and Quality published an evidence report on several question with relevance to the issues being addressed today.

We are going to be hearing from three

authors of this report, and the first presentation is by Dr. Lau, who is Professor of Medicine at the Division of Clinical Care Research at Tufts-New England Medical Center, Director of one of the AHRQ evidence-based practice centers, and Director of the Boston Office of the New England Cochrane Center.

He is going to first discuss the methods that were used to develop the report.

Agency for Healthcare Research and Quality Report

DR. LAU: Thank you.

[Slide.]

My colleagues and I will be talking about the evidence report that was produced under the Agency for Healthcare Research and Quality's evidence-based practice center program.

I would like to acknowledge other investigators on this report.

[Slide.]

The evidence report process involved a rigorous, comprehensive synthesis and analyses of relevant scientific literature. It uses explicit and detailed documentation of the methods, rationale, and assumptions.

The scientific syntheses may include

meta-analyses and cost analyses, and a broad range of experts is included in the development process in formulating the research questions and the peer review process.

What is important is that the reports do not make clinical recommendations, we primarily summarize evidence.

[Slide.]

A systematic review process involved initially formulating well-focused research questions because this is a very broad topic, and we cannot do all the questions.

They involve forming a technical expert panel and through several rounds of iterations of teleconferences, and we finalized a set of research questions.

We established the evidence-based practice center protocol for this review, establishing inclusion and exclusion criteria, and then we perform a comprehensive literature search, screen the abstracts and the full articles, and finally abstract data and perform critical appraisal of the literature, and then perform the analyses, summarize, and interpret the results.

[Slide.]

The key questions that were formulated along with the technical experts are listed here. What is the relationship between the peak bilirubin levels and/or duration of hyperbilirubinemia and developmental outcome?

What is the evidence for effect modification of the results in Question 1, the previous one, by gestational age, hemolysis, serum albumin, and other factors? My colleagues will not be talking about this due to time, but you can refer to the evidence report that has been published and available on the web site.

[Slide.]

The third question. What are the quantitative estimates of efficacy of treatment for: reducing peak bilirubin levels, for example, the number needed to treat--I will define that later--at 20 mg/dl to keep total serum bilirubin from rising; reducing the duration of hyperbilirubinemia, that is, the average number of hours by which time total serum bilirubin greater than 20 mg/dl may be shortened by the treatment; and improving the neurodevelopmental outcomes.

[Slide.]

The fourth question is what is the

efficacy of various strategies for predicting hyperbilirubinemia, including hour-specific bilirubin percentiles? This will be address later by Dr. Stanley Ip.

The last question is what is the accuracy of transcutaneous bilirubin measurements? This will be addressed by Dr. Rebecca O'Brien.

[Slide.]

The medical literature search involved searching the Medline and Premedline databases in September 2001. This yielded over 4,000 citations.

We also consulted other experts and reviewed the bibliography of relevant review articles for potential additional studies.

Also, in 2002, we also performed a supplemental search for case reports of kernicterus.

[Slide.]

The general inclusion criteria for the studies were all human English language literature, newborns between birth and one month, healthy, full-term infants equal to 34 weeks of EGA or about 2,500 grams, and also each study must have at least 20 subjects per arm except for Question 1 and 2, which we lower the number to 5.

Additional criteria were also applied to specific questions.

[Slide.]

The total number of full articles retrieved based on screening of over 4,000 abstracts were about 663. The number of studies included in the report, 138, although there was some overlapping in number.

The specific number addressing each of the questions is listed here. For Question 1 and 2, there were 37, and then also there were 28 kernicterus case reports; Question 3, 21 studies; Question 4, 10 studies; and Question 5, 46 studies.

[Slide.]

In summarizing the evidence, there are several parameters that are generally recognized that are important to sum up - the methodological quality of the study, that refer to the internal validity, the study design, conduct, and reporting of the study.

Then, also the applicability, how well the study can be generalized, sometimes also called external validity about the patients, population and setting.

The study size is also important to

capture to represent the weight or the precision of the evidence. Then, finally, the effect or the results, associations, or the test performance.

[Slide.]

In evidence reports, it is typical to also provide some measure of the methodological quality, but the quality is something that is difficult to measure, so this is some caveat that needs to be interpreted.

It generally refers to the design, conducts, and reporting of the study. Because studies may be from a variety of types of design, we generally follow three-level classification, and then apply to each type of study designs.

There is Grade A, B, and C, least potential bias to C, which is significant bias that may invalidate a result, and B is somewhere in between.

[Slide.]

We also generally use the applicability scale although not directly applied in this report, which also is Category 1, 2, and 3. Category 1 will be a study that is representative of the target population.

So, instead of using this scale, we just

report the report in the tables, the country of origin of the study, as well as the racial composition of the population.

[Slide.]

Now, I am just going to describe some of the quantitative methods used in the evidence report before I turn it over to my other colleague to describe the exact results.

[Slide.]

For Question 3, there was a question about the NNT or the number needed to treat, and that is what are the quantitative estimates of the efficacy of the treatment for reducing peak bilirubin levels.

[Slide.]

The definition of the NNT is that if you have a clinical trial, this is a typical 2 by 2 table, the treatment and no treatment arm, and the event and no event. In this hypothetical example of this trial of treating bilirubin level at 15 mg to prevent it from rising, so rising is the outcome.

In each of the arms, there will be 100 patients, and in no treatment arm, let's say 20 patients out of 100 will rise beyond the 15 mg, and if you treat at this level, only 10 patients will

rise, so therefore, one way of estimating the benefit of this treatment will be the risk difference or the absolute difference, so it will 10 over 100 in the treatment group minus 20 out of 100 in the control group or minus 10 percent or 10 percent reduction of absolute event rate.

NNT is defined as an inverse of the risk difference or 1 over 10, or 1 over 0.1 is an error, or equal to 10. What that means is that you need to treat 10 patients in order to prevent one baby, bilirubin from rising.

So, some believe this is a useful metric for understanding the benefit of the treatment for clinicians.

[Slide.]

For Question 5, collection of the study reported several measures of diagnostic performance. The most common one is the correlation of two tests or the r value, and one can also then combine study that address similar question, however, combining the correlation value is not the ideal approach in examining the agreement between two test methods, and the Bland and Altman method, already Tom Newman has shown earlier, is the preferred approach. I will

describe that in a little bit.

[Slide.]

This is the Bhutani paper, that I am sure you will see repeatedly over and again, showing the result of the HPLC versus the BiliChek, and has reported an r value of 0.91, so sound like a fairly decent r value.

[Slide.]

But a problem with the correlation that is shown n this slide is that its black diagonal line's identity, that is, this is an exact matching, the 25 mg measure on the device being investigated is equal to the same value by the reference standard, but any other highly correlated line or this shown to have correlation of 1, will be maybe misinterpreted as being a perfect test where a substantial bias may be so, that is, some study may consistently overestimate the actual level.

So, correlation is one of the conditions of being a measure of a test, but not sufficient.

[Slide.]

The limitations of the correlation in assessing the methods are summarized here. It provides a measure of the strength and

directionality of the association, but not agreement.

The correlation measures ignore bias, and the coefficient does not provide information as to the clinical utility of diagnostic test, and also the correlation is dependent on distribution of the serum bilirubin, as Tom also mentioned earlier.

I already mentioned the last point.

[Slide.]

Now, the Bland and Altman method assumes that the true value is unknown. It takes the average of the paired measurements as the best result, the pair of the reference standard and the device being investigated.

It plots for each pair of the measurement, the difference in result between the device against the average results, and this also removed statistical artifact of plotting the difference against either of the measurement as long as the built-in correlation problem.

This magnitude of the bias can also be estimated as well as the standard deviation of the difference. So, this is again, Tom has shown you this slide showing the mean of the reference standard and the device being investigated on the x

axis, and on the y axis, plotted difference between the two devices, and midline is the average of all the scatter plot, which is slightly above zero, suggesting there is a small bias in the device being investigated, and then also you can establish the distribution of what is known as the limit of agreement. Tom already mentioned some of the other issues.

But then also out here in the high bilirubin end, you can also see that there are more underestimation by the device being investigated, so you could then also better appreciate the how the new device being compared performs.

[Slide.]

Other methods we used in our report is for diagnostic performance combining test performance or sensitivity and specificity. There is a number of ways that this can be done, not always used, such as combining sensitivity and specifically independently, but there is some problem with that, but sometime may be useful.

The most common method is the summary ROC curve, and I will just describe this very briefly.

[Slide.]

This is a meta-analysis method to combine

multiple study diagnostic performance when study address similar issue. An assumption is that studies differ because of different thresholds being reported. The solution is to fit a receiver operating characteristic curve that best describe the data, and I am just going to show you very briefly what this means.

[Slide.]

This is a standard diagram showing the population, the certain value on a horizontal axis, for example, the bilirubin value from the very low to high, and in health population, there is certain distribution of the bilirubin level and in the--well, I guess this is the high bilirubin level, the label is disease, and different thresholds may then be applied to define what is important or high or low.

The different threshold would then produce different sensitivity and specificity, and as shown here, using a low threshold will result in high sensitivity and a high threshold will result in the lower sensitivity, but higher specificity, so there is an inherent trade-off.

Similarly, in the summary, SROC method, this is some examples of it with the ellipsis

representing the individual studies performance, sensitivity and specificity, and when we fit this curve around, we can then describe this collection of studies. The X there is the independently combined sensitivity and specificity to give you an idea where this average overall what this performance may be.

I think I will stop right here.

DR. CHESNEY: Thank you. Dr. Lau, for those of us who are uninitiated, could you just say once again what does ROC stand for and what does SROC stand for?

DR. LAU: The ROC stands for receiver operating characteristic curve, and SROC just adds Summary on top of that. ROC describes the trade-off of the threshold effect in the individual study. The Summary ROC is a meta-analysis method to combine multiple studies.

DR. O'FALLON: Would you explain the different shapes of those studies? Some of them are oval, some of them are--

DR. LAU: The oval shape represent the weight of the study, and they are not in x and y dimension, it is not the same, because in the disease arm and the non-disease group, it is

different number of patients in the different groups, so they are proportional. It is just to give you a visual impression of the disproportion.

DR. CHESNEY: Thank you. I am sure we will have more questions for you in the session after this.

Dr. Ip is our next speaker. He is an Assistant Professor of Pediatrics at Tufts University Medical School, and he will be presenting findings of Question 4 from the AHRQ Report on bilirubinemia, and I assume you will tell us again what Question 4 is.

DR. IP: Question 4 is asking what is the efficacies of the different strategies for predicting hyperbilirubinemia. Tom Newman actually did most of my talk for me, so I will just go over some of the details.

[Slide.]

When we reviewed the studies, there are a total of 12 different studies and 10 publications. Some of the publications combined two different methods into one paper.

In terms of the methods, as listed here, there are cord bilirubin, serum bilirubin, the first 24 hours, the ETCOc, the carbon monoxide

predischarge risk index, and the predischarge risk zone by Bhutani.

[Slide.]

As you can see, these studies, they are very, very variable. They are from like seven different countries. The subjects ranged from 50 to almost 3,000. Some study subjects consist of term babies, some consist of term and preterm babies. The proportion of breast feeding varies from like 4 percent to 90 percent. Some of them include ABO incompatibility, some of them don't. Some received phototherapy, and some don't.

[Slide.]

The other issues with these group of studies, out of the 12 studies, there are 8 different definitions of hyperbilirubinemia, so it almost makes it impossible to compare is one strategy better than another strategy.

As you can see, there is even one study that use clinical jaundice as an endpoint. In other words, the way they define hyperbilirubinemia is just by looking at the baby. If the baby is yellow, they say, yes, that kid is hyperbilirubinemic.

On the other hand, after they have

identified it, when they measure the bilirubin, the range went from 6.4 to 19.3.

[Slide.]

I am just going to go over several different papers in terms of each method and just highlight certain points. The first method in terms of the cord bilirubin, Carbonell in the 2001 paper and the 585 nonhemolytic babies assessed--that little sign should be greater than or equal to--2.2 mg/dl in the first, in the cord bilirubin, it will predict total serum bilirubin greater than or equal to 17 on day 3 to day 4. The sensitivity of this test is only 22 percent.

In Knudsen's paper, when he changed the definition from 17 to 11.7, you notice the sensitivity went up to 71 percent.

In the very last paper, in Risemberg, his subjects only consisted of ABO incompatible babies, so it is a highly selected population. He also raised the threshold of definition. You can see the sensitivity and the specificity went up quite a bit, 92 and 100 percent.

[Slide.]

This is just to show you more of the ROC curve we discussed earlier by Dr. Lau, showing that

this is from the Knudsen studies, and so you can pick any point you would like to set up as your test threshold, so if you use 2.05 as the threshold, then, you get certain amount of sensitivity, like about 70 percent, and a false positive rate of about 20 percent.

[Slide.]

The other methods is basically measuring the early serum bilirubin level. Some of these papers actually included transcutaneous bilirubin as part of their study. The first one was done in India out of 274 subjects, and basically, they find that if you use 3.99 as a cutoff point, this was drawing sometimes between 18 to 24 hours of life, it will predict to a TSB of greater than 15. The sensitivity is 69 percent, the specificity is 66 percent.

The author noted that these are acceptable figures for the India population, but they said it needs to be validated, and they said they are happy with that result and using that population.

In the Carbonell study, out of 1,500 and some babies, he says the TSB at 24 hours greater than 6 predicts to a TSB greater than 17. The sensitivity is like 100 percent, and if you

combined with a 48 hours TSB, greater than 9 predicts like 17.

Carbonell also did transcutaneous measures using the same threshold. The numbers are comparable. They don't look as high both in terms of the sensitivity and the specificity.

Seidman, in Israel, 1999, out of 1,100 babies, he calculated odds ratio using multiple logistic regression analysis, predicted that if you have a TSB greater than 5 at 24 hours of age, it is high significant to predict a day 2 TSB greater than 10, day 3 greater than 14, and greater than 17 later on.

The other factors that he looked at, you see at the bottom, the odds ratio for day 1 TSB is 36.5, which is high predictive of high bilirubin later on.

[Slide.]

Anyway, the other significant factors are the day 1 TSB measurement and apparently you can calculate, depends how high it goes, and it gives you a certain odds ratio, maternal blood type, maternal age, and so forth. To, this is one method of predicting high bilirubin is looking at risk factors analysis.

[Slide.]

Tom Newman did the same. He mentioned earlier the Kaiser studies, and these are the original data from his paper. He showed that if you have early jaundice the first 24 hours, your odds ratio of having high bilirubin is like 7.3, which is like the highest.

So, what he did in his paper was he wanted to know if you can predict high bilirubin after discharge, so he used the other factors, not the early discharge because they are already in that group, and then he basically combined them into an index score and see if you can predict extreme bilirubin of greater than or equal to 25.

[Slide.]

This is the ROC curve from Tom Newman's study. You will notice that you can see the risk index of 10, which is at the upper lefthand corner, the most upper lefthand corner, which is the preferred point if you use that as a cutoff point.

Just to talk about that risk index of 10, Tom did a calculation. If you use risk index of 10, because it's the low prevalence of the disease, your positive predictive value at that setting is like 0.027 percent, which is very, very low. So,

what he concluded is you are going to have to treat like 370 kids with a risk index of 10 to prevent one kid from reaching greater than 25, so that is a huge number of patients to treat to get at one kid.

[Slide.]

The other method is basically to use ETCOc as a predictor of high bilirubin, which has been done by Stevenson back in 1997 on kids with hemolytic jaundice. Also, Okuyama, in Japan, decided to use the same technology to see if it will work for kids who don't have hemolytic jaundice, and he finds that if you have a ETCOc greater than 1.8 ppm at 48 hours, it's a good predictor that that group will have TSB greater than 15.

Notice the very high positive predictive value of 40 percent in that particular population.

[Slide.]

Now, we talking about the Bhutani paper from '99, where he had started out with 13,000 infants who fulfilled a criteria, and out of the 13,000, only roughly 2,800 who had two TSBs done at the same institutions, so those 2,800 were the subjects for his study.

[Slide.]

What he did was he basically did a bunch of different bilirubin at different time, and you can calculate 95th percentile from each group.

[Slide.]

This is an early curve that Tom showed, that you can have different curves and giving different percentiles.

[Slide.]

So what Bhutani did was depending on where you were at the predischarge area, you can predict to whether or not you are going to stay at the greater than 95 percentile, which is how he defined hyperbilirubinemia.

So, for instance, if you look at the upper lefthand corner in A, you will see that if you start off at greater than 95th percentile, roughly 40 percent of that population stays in that zone, so he considered that would be a high risk.

On the other hand, if you look at the lower righthand corner, in D, if you start off with less than 40th percentile, none of those kids went on to be in the high risk zone in the greater than 95th percentile.

[Slide.]

This is the Bhutani curve where Tom showed

the calculated area under the curve of 0.93.

[Slide.]

So, if you use the 75th percentile as a cutoff point, as shown by this ROC curve, you get a sensitivity of like 90 percent, a specificity of 85 percent, and a positive predictor value of about 21 percent. So, what that means is you are going to have to treat roughly 5 kids who have greater than 75th percentile to prevent 1 kid from reaching greater than 95th percentile in his population.

[Slide.]

It is of note that Bhutani's study population is very different from a typical U.S. population. As you can see in his study, he had 41 percent African-American while the national population is 15 percent. He had 4 percent Hispanics, and the national population is 21 percent.

[Slide.]

Stevenson decided to look at both ETCOc and TSBc to see if it will improve the prediction. As Tom mentioned earlier, it really didn't improve the prediction of the accuracy of hyperbilirubinemia.

[Slide.]

The interesting thing about the Stevenson study, because it was done over in like nine different multinational centers, he actually used the raw data from the Bhutani population and see where the 95th percentile is for his study population.

As you can see, the 95th percentile varies anywhere from 38 percent to 6 percent, so it's very, very highly variable.

On the other hand, if you just look at the ones with the study size greater than 100, the variability is not too bad, and then it's from like about 5 percent to about 10 percent, but nevertheless, it is not really comparable to the Bhutani population.

[Slide.]

In summary, it is not possible to directly compare the accuracy of various strategies for the many reasons we have stated before. It is also very apparent that the higher you have the TSB at an early age is associated with hyperbilirubinemia three to four days later. In fact, that is probably a better prediction than if you try to say that if you have a low TSB, you won't get a high hyperbilirubinemia later.

The hour-specific nomogram looks promising. It has a high AUC, but further validation in different populations should be done.

DR. CHESNEY: Thank you.

Our next speaker, and then we will have a question and answer session, is Dr. Rebecca O'Brien, who is an Assistant Professor of Pediatrics at the Floating Hospital for Children at Tufts-New England Medical Center, and she is going to review for us the accuracy of the transcutaneous measurement of bilirubin.

DR. O'BRIEN: I have 10 minutes, is that right? I will try to do my best to get through this.

DR. CHESNEY: Actually, you have plenty of time. I don't mean two hours, but you do have 20 minutes.

DR. O'BRIEN: I will go through some of it quickly, though.

[Slide.]

I am addressing Question 5, which was looking at the accuracy of transcutaneous bilirubin measurements in our evidence report. I think these terms are familiar to all of you, but I will use TcB to reflect transcutaneous bilirubin, TSB to

reflect total serum bilirubin, and HPLC, which was used in some of the newer studies of the BiliChek device as either high performance or high pressure liquid chromatography.

[Slide.]

We had 47 qualifying studies in 50 publications that actually looked at the test performance of the transcutaneous bilirubin instruments to predict total serum bilirubin.

The four devices that were included in these studies included the Minolta AirShields bilirubinometer, and clearly this has been the most studied device. At the time of our review, there were three studies on the BiliChek device with 809 subjects, the Icterometer was in 4 studies, and 1 study reflected the Colormate III.

[Slide.]

We will start with the AirShields bilirubinometer, which is in 2002 called an AirShields jaundice meter. This is a handheld device, I think similar to the picture you saw with the BiliChek. It uses fiberoptic techniques that illuminates the skin and subcutaneous tissue, and then you analyze the intensity of the yellow color spectrophotometrically.

This particular instrument requires development of an index, and it appears to be institution dependent, and their correlation curves have different intercepts on the y axis, and we will talk a little bit about that, and it does require daily calibration of the instrument.

[Slide.]

It has been studied for over 20 years. It has been studied in diverse patient populations. In about half of the studies we looked at, they actually looked at test performance generally reported as a sensitivity and specificity of the transcutaneous instrument to predict a threshold of interest of total serum bilirubin.

Measurement sites were generally performed in most of the studies at the forehead and mid-sternum, and several of the studies reported on other sites.

[Slide.]

Again, challenges of combining these studies for meta-analysis include that authors use different total serum bilirubin thresholds of interest. Some used 10 and some used 12, some used 15, and it does limit a little bit of our ability to perform meta-analysis.

The studies that we were able to combine, we combined three studies that used total serum bilirubin of about 11, 11 studies we are trying to predict total serum bilirubin over 13, and in 3 studies over 15.

[Slide.]

The studies predicting TSB greater than 11 were 500 paired samples. They were done at the forehead. Using a random effect model, the pooled estimates of sensitivity and specificity, as you can see, were in each study individually here, and then the pooled sensitivity of about 76 percent with a specificity of about 80 percent.

You can really see the variability, though, of this index that is developed at each institution and where Maisels used an index of 20, Knudsen used an index of 9.

[Slide.]

Then, to predict total serum bilirubin of 13, there were 11 studies, so I didn't show you a table, but I will show you this summary ROC curve for this particular predicting total serum bilirubin over 13.

There were 1,560 paired measurements. Again, the cutoff index ranges in the various

studies anywhere from 13 to 24, and we will show you the summary ROC curve that while it isn't quite a clean threshold effect as we will show you, so there does appear to be some heterogeneity in the way this performs.

Using a pooled estimate, however, of all of these 11 studies, we have a sensitivity of about 85 percent, a specificity of about 77 percent.

[Slide.]

So, this is the summary ROC curve. Again, I guess the perfect test, all of these gray points would all be kind of right along this line, and this would be the lowest levels of the transcutaneous measurement, and then you would lose sensitivity as you went to higher levels of the index.

It sort of fits. This is 15 index, this is a 22, this is a 21, but there is a lot of scatter over here, this is 20. So, it is not a totally neat fit as a test.

[Slide.]

Then, for predicting total serum bilirubin over 15, again, there were only three studies that could be combined here. Overall, they actually looked pretty good with a sensitivity of 95 percent

and a specificity of 67 percent for the Minolta AirShields.

[Slide.]

Now, looking at just how well does the transcutaneous measurement from the Minolta AirShields correlate with the total serum bilirubin, and again with all the limitations that Dr. Lau spoke of, this was really what most of the studies actually do talk about and do present as data. It does help us when we look at some of the factors that may affect how well this device works though.

[Slide.]

So, in these studies, the r values ranged from 0.52 to 0.96. When they were pooled, the correlation is about 0.84. There is details in the evidence table on page 241 for those who are interested later.

[Slide.]

Again, he spoke about the limitations, I will skip this slide.

[Slide.]

But when we were looking at the factors that affect the test accuracy of the Minolta Airshields bilirubinometer, again the study designs

varied. Some of these studies were screening all infants, some were screening only jaundiced infants. They varies as to racial background, measurement sites, age at measurement, and then what was their reference or gold standard, which particular lab method did they use.

There was, however, some subgroup analysis done, and we attempted to look at some of these factors in the slides coming up.

[Slide.]

Just as a summary, there was higher correlation of the transcutaneous measurements by the bilirubinometer when the sternum or forehead sites were used in term versus near- term. It seems to correlate better with White versus Black infants, and those who had not received phototherapy versus those who had received phototherapy.

[Slide.]

Again, just sort of showing, you can see the correlation sort of drop as you move to some of the sole, the palm areas, and seem to be most highly correlated at the forehead and sternum sites.

[Slide.]

Looking at gestational age, there were five studies that actually gave separate correlation coefficients. While in the individual studies, there were not significant differences, there did appear to be a trend lower in near-term infants, and you can see this in the results here.

[Slide.]

Looking at race or skin color, there were six studies that compared correlation coefficients across race or skin color. Half of those were at the sternum site.

There were two U.S. studies that did find significant differences in White versus Black infants. The other racial groups that were studied were Malay, Chinese, Indian, and there were no Hispanic subgroups analyzed for the Minolta device.

[Slide.]

Looking at, as you can see, the correlation coefficient in black, there were three studies with this sample size of 258 and pooled correlation coefficient is 0.59 compared to the White, which was 0.75. Overall, this is how they performed.

[Slide.]

Looking at phototherapy, there were six

studies that reported on the effect of phototherapy. All of these studies had lower correlation coefficients if the children had received phototherapy. That was significant in two of the studies. With meta-analysis of the correlation coefficients, again, you can see there is a small difference in the results.

[Slide.]

The next device was the Ingram Icterometer, which has been around for a long time. It's transparent plexiglas that has five painted transverse strips or precise and graded hue of yellow color. You press this device against the infant's nose and the skin blanches.

The yellow stripes are then compared and a number is applied. Most of the studies used a number, 1 to 5 used 3 as their cutoff point. It is I think only about 7 or $8.00, so it is a low cost device.

[Slide.]

The studies reported the correlation coefficient here. There were four studies of the Ingram Icterometer. The reason why there is two in India, these were near-term, preterm infants, and these were term infants. You can see there is

really sort of a variability in how it performed, but overall, pooling the results, it appeared to be fairly highly correlated.

[Slide.]

Looking at test performance of the Ingram Icterometer, there were three studies that actually reported on the test performance, generally, a sensitivity and specificity. Two of these studies were looking at a TSB of 12.9. The threshold of the Icterometer TcB measurement was 3, and Bilgen's study in Turkey found 100 percent sensitivity, Schumacher found an 82 percent sensitivity although, with experience with the device, apparently this goes up to 95 percent, and then in the Indian studies, again performing a little bit less well in preterm versus term in terms of sensitivity.

[Slide.]

The next device is the BiliChek device. At the time we did this review, there were three studies. This is a device that used multiwavelength reflectance and therefore, theoretically, can improve on the transcutaneous measurement by accounting for bilirubin, hemoglobin, melanin, and thus things like skin

color, skin thickness, pigmentation.

There is a fiberoptic probe that is placed on the forehead and multiple measurements are made and averaged together after contact.

[Slide.]

These three studies, again, we have heard certainly the Bhutani study, it is very similar to what he did with the hour-specific nomogram although he was trying to use a transcutaneous measurement with the BiliChek to look at the same.

The difference in these studies is this is the first time we sort of saw people using a gold standard or reference standards of the high performance liquid chromatography, and this was used in the Bhutani study and in the Rubaltelli study.

Rubaltelli also used lab serum bilirubin and actually compares the transcutaneous instrument to the lab, and we will go through these in the next several minutes.

[Slide.]

I am sorry this is such a busy slide, but again here are the three studies, Bhutani, Lodha in India, and Rubaltelli. Again, very high correlation was found in the Bhutani study, and he

again using the threshold of the transcutaneous bilirubin instrument as measured by the BiliChek, and the transcutaneous measurement at the 75th percentile to predict serum bilirubin of the 95th percentile.

By using this, again lower threshold of the transcutaneous instrument has 100 percent sensitivity. I think it was 23 out of the 419 actually fell into that range, so it is a small number of infants who are falling into that 95th percentile.

The study in India did not perform quite as well, and certainly appeared to perform less well when you were looking at higher total serum bilirubin levels with a sensitivity of only 20 percent.

Rubaltelli is probably best seen on an ROC curve again because he uses multiple thresholds, but again it sort of summarizes that as you lower your threshold, your sensitivity is higher, and he did this at several levels, which we will show in the next couple slides.

[Slide.]

In the Bhutani study, again, this was a sample size of nearly 1,800 samples with 490 term

or near-term infants. He had a very low Hispanic population, I think as Stanley had alluded, he had Whites and Blacks were represented.

There were 11 different devices used in the study, BiliChek devices, and as noted, his correlation was high.

[Slide.]

Again, this sort of shows graphically, and I think that the one point, though, most of these points are at bilirubin levels, HPLC bilirubin plotted here, and transcutaneous, and you can see that there may be--and again it's hard to say--a little bit more variability at the higher levels.

[Slide.]

Again looking at this as a Bland/Altman or error distribution plot, I think Dr. Lau sort of pointed out that maybe there is a little bit more variability at high levels, but you are dealing with sort of a plus or minus 3.23 and 2 negative here, the BiliChek does appear to slightly underestimate, so that the mean is a little bit higher, the HPLC value.

[Slide.]

Rubaltelli again was a multicenter study. It was in six different European hospitals and it

used infants who were going to have a TSB done as part of their care. There were multiple users. He was trying to look at how this might actually perform in real life, multiple users of the BiliChek. There were multiple lab measurements of serum bilirubin, and then all of these were compared to a gold standard of the HPLC serum bilirubin.

There was one single lab that did the HPLC measurements, and he found that the correlation of the transcutaneous measurements with HPLC were high, although not quite as high as the laboratory, they were fairly close.

[Slide.]

This is sort of graphically looking at correlation, this being the BiliChek versus--I am sorry you can't see this--but BiliChek versus HPLC here, the lab versus HPLC here. They again both had very high correlation, perhaps a little bit more variability with the BiliChek.

[Slide.]

Then, again, looking at an error plot, again, this is the BiliChek device. I know you can't really read this. This is plus or minus probably about--this 2 standard deviations here--I

think this is about plus or minus, probably 3 positive, 3 negative here, and again looking at the HPLC serum bilirubin versus the lab serum bilirubin, perhaps a little bit narrow, but again these are sort of comparing these two. He also compared the BiliChek to the lab, but sort of, of interest, how those two compare.

[Slide.]

Then, looking at how they perform as a screening test. Again, we see these ROC curves and looking at how this is an ROC curve here to predict a bilirubin over 13, again by the HPLC method, predicting bilirubin over 15, and again predicting bilirubin over 17.

In this, the solid line represents the treatment measure, and the dotted line, the serum bilirubin as measured by the lab. While they seem to operate closely, it is probably maybe here we can see that the lab and the dotted line probably performs a little bit better than the transcutaneous. Again, anything, the perfect curves are going to be as high up into the lefthand corner as you can be, and that is why people use sort of the area under the curve, although at this higher level, they seem to perform very comparably,

if not a little bit better with the transcutaneous instrument.

[Slide.]

Then, in this final study by Lodha, there was 109 jaundiced Indian infants with serum bilirubins of 8, showed fairly high correlation, but the subgroup with higher bilirubins appear to perform less well with a correlation only of 0.64.

[Slide.]

There was one study that compared the Minolta to the BiliChek, and it does appear to perform better, at least by looking at correlation coefficients with the BiliChek correlation coefficient of 0.94 and the jaundice meter or the Minolta AirShields jaundice meter of about 0.7, and skin color was significant for the jaundice meter, but not for the BiliChek.

[Slide.]

Again, this just shows you sort of graphically, again with this Bland/Altman error plot, there is a lot more variability using the jaundice meter as opposed to a lot tighter fit here using the BiliChek.

[Slide.]

Finally, just one other device, there is

only one study, and it only reports on correlation coefficients. It is the Colormate III, and I guess for the sake of time, I will kind of just go quickly with this, that it requires a baseline measurement prior to the development of jaundice, so it requires sort of all infants to have some measurements done and then it is done by computer analysis to correct for some of the color luminosity, redness and yellowness.

It does appear to have a very high correlation, they are reporting 0.956. Again, it has only been studied up through about serum bilirubins. It tends to underestimate again, and only up to serum bilirubins here probably of about 15.

[Slide.]

This is the only other interesting thing in the study. They sort of actually compared how does visual inspection do compared to this transcutaneous device, and you can see that the transcutaneous device does appear to improve with a better correlation than our visual inspection for detecting jaundice.

[Slide.]

I think this is looking at phototherapy.

[Slide.]

Just to kind of finish up here, just to say that it appears that the transcutaneous bilirubin measurements by all three devices definitely appear to have a linear correlation to total serum bilirubin, but as noted by Dr. Lau, the correlation coefficient alone doesn't really provide us information on how well this particular diagnostic test works, however, many of these studies did not really report performance data. At least half of the Minolta studies only reported correlation.

It is going to be highly dependent on where you are measuring your distribution of serum bilirubin. It appeared that the devices may perform less well as screening tests at higher levels of bilirubin, but I think we need more information and more study there.

Again, the Minolta AirShields tends to perform best at the sternum or the forehead, less well in Black infants versus White infants, did not appear to perform quite as consistently across the studies when we look at the summary ROC curve.

I think the limitations with the Ingram icterometer, there really were a small number of

studies that evaluated that, and it does have some observer visualization, some issues around objectivity. It does seem that it performs better after people have used it for some time.

There is a new BiliChek device that theoretically corrects for the effect of melanin and hemoglobin that may be an improvement over the older devices, and I think we recommend future research to confirm these findings in larger sample sizes with more diverse populations and really look at the effects of phototherapy.

Thank you.

DR. CHESNEY: Thank you very much.

We now have some time for questions and discussion of the presentations by Drs. Murphy, Newman, Lau, Ip, and O'Brien.

Dr. Fost.

Discussion of Presentations

DR. FOST: Two questions. One I think is for Dr. Ip, and the second for Dr. Newman and Dr. Murphy.

It seems to me negative predictive value would be more helpful than positive predictive value. That is, if we had a number at discharge that could confidently tell us that this child will

almost certainly not develop a worrisome bilirubin level, that that would be very helpful.

I just want to make sure I understand your slide on page 9 of your handout, called "Predischarge Risk Zone."

Do I understand that to say that if a bilirubin around discharge is less than the 75 percentile, that has a 99.5 percent negative predictive value of a worrisome bilirubin?

DR. IP: That's correct. Basically, the symbol is wrong. It is greater than equal in 75th percentile. What that says is if you have a child who is less than equal to 75th percentile, then, that kid is not going to get in trouble according to the Bhutani population.

DR. FOST: Thank you. Then, a question for Dr. Newman and Dr. Murphy.

There has been a lot of discussion of risks and benefits, but not much about cost. You just alluded to it in your last slide. I am wondering if you or any of your colleagues are doing any studies or estimates of cost-benefit or cost effective analysis of various interventions.

That is, suppose there were a drug that was completely safe and could completely reduce the

risk of serious hyperbilirubinemia, are there any estimates of what the cost per case of kernicterus averted would be?

My question for Dr. Murphy is what do you see as the FDA's role in those sorts of policy question, that is, suppose there were a drug that were 100 percent effective and completely safe, but it cost a million dollars to prevent a case, does that have any role to play in the approval process?

DR. MURPHY: I think I can answer that pretty quickly, which is our job is to assess whether a product is safe and efficacious. We don't determine the price, and that other agencies would determine the utilization of that product. It clearly is a concern to us, but really our mandate is to make sure it works and how to describe it, so it would be safely used, and then work with other agencies in trying to integrate that information with any decisions that they make.

DR. NEWMAN: You ask I think an excellent question, one in which we don't have enough data. It is actually the next grant I am planning, which would be if you add up sort of all the bilirubin levels, all the extra days in the hospital, all the extra outpatient visits, the home phototherapy, the

hospital phototherapy, the exchange transfusions, all of the money we spend to try to prevent kernicterus, and even then we are not successful, so there is still cases of kernicterus.

So, if there were a magical, totally safe drug that would just basically eliminate all that or a whole lot of it, it would be worth a lot. I can't give you a cost per patient of what it would be worth. I am sure the company making it would figure out a way to price it, so that it would make them money, but it could conceivably save a lot of money.

What happens is that there are some cases of kernicterus, there are some kids who are destined to develop jaundice, who are easy to find and obvious in preventing kernicterus and the ones who present early with jaundice or who have all the risk factors, who are easy to follow.

It costs a lot less money than trying to prevent those last few, sort of unpredictable cases that show up without risk factors, so that it will be unless you are going to give the drug to everybody, there will some sort of incremental cost-benefit thing where the cost per case prevented and the cost efficacy is much better in

the higher risk kids and eventually it tails off to where it might just not be worth it.

But if the drug were completely safe, you would give it like vitamin K to everybody.

DR. CHESNEY: Other questions? Yes.

DR. MATTISON: In the evidence report, you commented on the relative lack of information in a single bilirubin value, and spoke about the need to think about other strategies for measuring bilirubin, so it brings to mind sort of a common theme in developmental toxicology, which is to try to understand mechanism and then relative value of peak concentration versus area under the concentration curve.

I imagine that as we talk more today, we will get at some of this, but I wonder if you would like to comment a little bit on strategies or ways of thinking about improving strategies of measuring bilirubin, single versus multiple values, frequency of sampling, and so on.

DR. IP: Dr. Mattison is referring to our conclusion on a separate part of the evidence report, which we did not discuss. Basically, it is what happens to the majority of the kids who gets high bilirubin, but they don't have kernicterus.

When we reviewed the studies, there were a very limited number of studies that actually address that question. In fact, most of the other studies, they all had kids who are preterm, term, they are sick, they have comorbid factors. It is very difficult to sort out if those factors are not responsible, if they have any kind of detrimental incomes, so our conclusion was using one single bilirubin is really insufficient to predict what is going to happen to these kids seven, eight, 10, 12 years down the line.

The problem that I see is, first of all, way that the peak bilirubin is measured, the way it is even reported in the literature, it seems to me a lot of times it is not necessary, the peak bilirubin level. That is one problem. I glanced at some of the kernicterus case reports. They have peak bilirubin done like 24 hours before something happened, you don't know what happened 24 hours later, it could be higher, it could be lower.

The other thing is everybody talks about there is a huge variability of bilirubin measurements between laboratories, so when you are comparing studies across different nations, across time, that it is not really a good predictor model.

So, as you said, maybe we can use the time of exposure, how long have these kids been exposed to under certain bilirubin and see what happens in the long run, or maybe have to look at other factors.

The other issues, we can discuss this at length, is how we define kernicterus in the first place. The problem that I see is the terminology is that we always say if you have neurological impairment with a history of hyperbilirubinemia, that is how you have kernicterus, so what that means you can't really say that it is the bilirubin causing it because you define it that way, so it gets involved.

DR. CHESNEY: Yes, Dr. Oh.

DR. OH: I have a comment and a question for Tom Newman. I would agree wholeheartedly that a key outcome for any intervention in hyperbilirubinemia is neurodevelopmental outcome, and yet as you pointed out, the kernicterus incidence is so low, and we don't quite know the new developmental outcome of hyperbilirubinemia, so it brings up he issue of the follow-up that you have.

Ideally, compliance rate of 80 percent or

greater is desirable in any follow-up study, with 60 percent, I was just wondering if you had a chance to compare the variables of the 40 percent that you didn't follow with those that you followed, particularly with reference to the bilirubin level and the socioeconomic status.

Can you comment on that?

DR. NEWMAN: It's an excellent question. The biggest concern we have, I mean, of course, we would like to have 100 percent in both groups, but the potential for bias is that we have a higher percent participating in the bilirubin group than in the control group, and the concern is what if the controls who choose to participate are those who are a little bit more worried about their child, and therefore, they want this free neurodevelopmental assessment.

We haven't looked at these data yet, but the ways that we are addressing that is that all the data I showed you are in what we call the full participants, but when people say no, then, we still ask them, well, will they at least fill out the questionnaires for us.

One of the questionnaires I didn't show data on is called the PEDS or the Parent Evaluation

of Developmental Status, where we specifically ask the parent, do you have any concerns about your child, and there is 10 questions, you know, how your child understands speech, how your child speaks, how he uses his hands and fingers or arms and legs, and so on.

What we at least will be able to do is besides the socioeconomic variables and race and other variables, see whether we do see evidence of increased participation in the control group according to whether the family was worried, and then, of course, we can stratify in those variables and just compare among both the cases and the controls.

We do know that most of these parents of these five-year-olds think their kids are fine, and most of the kids are fine, so if we stratify just on whether the parents said they had any concerns, and we started the study before, so we have whether they had any concerns at age three, age four and five, and so on, we can address that, but we haven't looked at data comparing participants to non-participants yet.

DR. CHESNEY: Dr. Ebert.

DR. EBERT: A lot of your information was

directed towards specifically looking at identifying individuals with high bilirubins, but yet you also mentioned earlier that because the risk of kernicterus is so low, perhaps we should look at more the risk or the need for therapy.

Is there a way that we can overlay the AAP guidelines for treatment with some of these risks to look at what would be the predictor for the need for phototherapy or the need for exchange transfusion?

DR. NEWMAN: I am not positive I understand your question. I mean I think we can look at predictors of bilirubin at a certain level, and that I think has the advantage that since phototherapy is, as you saw in the slide of the different hospitals, varies a whole lot from doctor to doctor or hospital to hospital.

I think we are better off trying to predict bilirubin level above 15, 20, 25 than trying to predict something like exchange transfusion or phototherapy, but even then, these are retrospective observational studies and we are restricted by whether the doctor chose to do a bilirubin or not, and if you have doctors who don't believe jaundice is a problem and don't choose to

measure bilirubin, all of our data from Kaiser on sort of incidence of bilirubin at different levels are all minimal estimates because when we get up above 20, 25, we just assume that if it wasn't measured, they didn't have it, so there may be slightly higher estimates.

I am not positive if that answered your question.

DR. EBERT: That really was what I was getting at, but looking at the ultimate outcomes and the issues on impact on health care and the things that we need to do to treat patients effectively, I guess the end result, the true treatment is a lower incidence than it is of finding that elevated value.

DR. NEWMAN: Yes, and again, I think if you allow as an outcome, doing less phototherapy, then, of course, another way to achieve that outcome is to change your guideline. One of the problems with the surrogate outcome of bilirubin is that given that the bad outcomes are so rare, you know, we could less phototherapy. We could say, well, we are going to do 22 instead of 20.

That would have a big impact on cost on phototherapy. Actually, in one study looking at

comparing hospital and home phototherapy, and looking at the cost, the biggest determinant of cost wasn't whether you did it in the hospital or whether you did it at home, it was whether you decided to do it at all, because there was so much variability, and the variability results from the rarity of the outcome and the lack of data.

DR. CHESNEY: Dr. Gorman has a question, but if I could ask one first. Dr. Newman, do we know anything about autopsies of premature and normal infants today in terms of how much bilirubin staining there is?

DR. NEWMAN: David may know this better than I do. There was sort of a flurry of activity in the '80s about autopsies in preterm babies, and then I haven't seen much more of that, that it went away when they took away the benzyl alcohol, but I do bigger, "weller"--more well babies, so if any of the neonatologists here knows that--I haven't followed closely autopsies in preterm babies.

DR. CHESNEY: Dr. Gorman, do you have a question about "weller" babies?

DR. GORMAN: I was going to let the neonatologists with expertise try to answer that question first.

DR. STEVENSON: I am not aware of any large, systematic review of autopsy data that would address that directly, at least recently, and I am not sure what your experience is, but anybody else who knows anything about it could comment, as well.

DR. HUDAK: I think that is correct. I think the literature shows that basically, premature babies who die because they were very sick had bilirubin staining of the basal ganglia at relatively low levels, and I think that is sort of uninterpretable information, and it certainly doesn't address the broader issue, and it doesn't say anything about whether premature babies are more at risk for kernicterus at lower levels although it was certainly interpreted by neonatologists for many years that way, but there is nothing recent.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: This question is to both Dr. Newman and to whoever reviewed the 38 case reports of kernicterus. I also had several formative experiences. One was measuring theophylline levels in the thought that it might help people with asthma for many years.

I have that same deja vu all over again while I look at all this chasing of bilirubin levels. I am going back to the question of causality of bilirubin and kernicterus.

I will ask the question in a reverse way. We have talked about the confounders and the potentiators for bilirubin or in bilirubin and kernicterus. In that series, has there ever been a well child who has developed--a well infant--I ask this question at the risk of offending my neonatology colleagues--a well infant, term, at any bilirubin level, who has developed kernicterus?

DR. NEWMAN: I would say yes. Some people say, but if developed kernicterus, you must not have been well, so there is a little bit of circularity there. There are children who, at the time they were discharged from their birth hospitalization, looked perfectly fine, who are readmitted with very high bilirubin levels, who have what looks like the kernicterus that babies in the 1950s with Rh disease used to get.

To me, the causality is more convincing if they started out well and come in symptomatic. I mean they come in with a high-pitch cry, arching, and opisthotonos, maybe seizures, and there are

some of those kids who then, you know, they get an exchange transfusion, and some of those acute symptoms seem to get better, and if they are left then with the classic sequelae like used to be seen with Rh disease, to me, that is pretty convincing.

It is much harder when they don't have that acute picture or when they end up with something which is sort of a partial syndrome. They have cerebral palsy, but it is spastic, and not athetoid, and they don't have the hearing loss, so they have just the hearing loss, but otherwise they are fine.

The courts often end up settling these or they lead to lawsuits, and it's people arguing about is it kernicterus or not, because the child has something which is abnormal, which in the parent's mind may be very much associated with the jaundice and the treatment for it, because treatment for jaundice, especially when it involves exchange transfusion, is a very salient and frightening event, but what the child has, it becomes unknowable.

The MRI findings of the increased T-2 signal and the globus pallidus would be very suggestive, but I haven't seen enough studies that

looked at kids who have athetoid CP, who never had a high bilirubin, to see how often they have similar basal ganglia findings on MRI.

DR. GORMAN: So, in your review of the case reports, you think the answer is yes, well babies with high bilirubins and no other disease, trying not to be circular, develop kernicterus?

DR. NEWMAN: Yes, apparently well babies, babies who have nothing else wrong with them that we can identify, but it's rare.

DR. GORMAN: Well, always placing the most emphasis on the most recent data, Pediatrics arrived on my doorstep yesterday and because of this meeting today, I actually scanned the titles and saw your article on bilirubin without kernicterus in several babies.

I know everybody in California is above average, your IQ scores are all above average despite whether they were high bilirubin'd or not, but I will leave that as it is.

I had a second question which I am now blocking on completely, but it will come back to me.

DR. NEWMAN: Just commenting on the babies over 30, it was only 11, so the quick rule of 3, if

you observe zero out of 11 or zero out of 10, because one of them did die of apparent SIDS, you know, the upper limit of that could be a kernicterus rate of 30, 40 percent in babies with bilirubin levels over 30.

There is no question in my mind that it occurs, but probably somewhere in the range of 1 and 2 in 500,000.

DR. GORMAN: If you had to predict, and this is the other question, which of the potentiators or confounders are going to be most difficult to sort out, which would you point to? I will use that to any of the group that presented. Is it the hemolysis, is it the sepsis, is it the gestational age, is it medical intervention?

DR. NEWMAN: Oh, that's a tough one. I would say medical intervention is going to be very hard to sort out, because babies who have symptoms, you know, that is one of the indications, that is one reason they would be more likely to get an exchange.

In reviewing some of these case reports, I mean that come from medical-legal consultation, I have seen ones where the child came in with a high bilirubin and seemed to be okay, and the exchange

transfusion seemed to make them worse, you know, they either had a seizure during the exchange or something happened, because it's kind of, you know, it's a big thing to do, so I think that would be--I was looking through the cases on the plane that I have reviewed, you know, there is several of them that have this sort of iffy infection.

They have a little bit of a fever, but people say you can get fever from kernicterus. They have staph epi or something in their blood culture, maybe a little low platelet count, it is just not stuff where you can tell, maybe there was an infection. A lot of them have some white cells in their urine, but negative urine cultures, but they got antibiotics, so I would say sorting out infections, some have like a little CSF pleocytosis, you know, sorting out those things has also I think been hard to say, was this just a well baby or was this a baby who maybe had an infection.

DR. CHESNEY: I think, as always, infections are the most important thing, but I would like to take a break for 10 minutes if we could, and we are going to have more discussion after the break. It's about 10 of 11:00, if we could come back at 11 o'clock and then we will

address Question 1, which really is general enough that we can continue some of this question and answer.

Thank you.

[Break.]

DR. CHESNEY: For the next 10 to 15 minutes, although there was an initial and very general question, what we would like to do is two things. One is to allow people to continue to ask questions of the speakers, but also please raise any issues which you feel have not yet been discussed about this area, that have not been raised by this morning's speakers.

Any questions, any issues that haven't yet been raised? Dr. Danford.

DR. DANFORD: I have a question primarily addressed to Dr. Newman. It has to do with that multiple logistic model for predicting people who end up with total serum bilirubins greater than 25.

I was wondering about the methodology of that because the performance of a risk index like that is generally better when you assess that performance in the cohort in which it was derived than it would be if you took an independent sample afterwards and tried to apply it.

I don't know, is the kind of encouraging looking ROC curve for that index on the derivation cohort, or is that an independent sample?

DR. NEWMAN: That's an excellent question. In fact, it hasn't been published yet, but the derivation sample is babies born in '95 and '96, and we validate it for '97 and '98, and it performed just about as well. The area under the ROC curve went from 0.84 to 0.83, and 0.83 was the one that I showed in my table there.

That is higher than what Stanley showed because that is using all of the data, and anytime you categorize it, as he did, the ROC curve that he showed from our study only I think had four points, you know, more than 15, you know, cutoffs at 10, 15, 20, and so on, but when you look at the whole data, you, of course, get additional credit for information that is contained between values that are in between there.

In fact, this would be true of the total serum bilirubin measurements, as well, which is that the area under the ROC curve for those, which when Bhutani said was replicated, was about 0.84, in the study by Stevenson, 0.4, 0.85. If instead of categorizing it, they actually looked at the

actual value, that would probably go up a little bit, as well.

DR. DANFORD: Thanks.

DR. CHESNEY: Dr. Stevenson.

DR. STEVENSON: This is a question for Dr. Ip or maybe Dr. Newman. I think Dr. Law and I think Dr. Ip mentioned that they were not going to be commenting about hemolysis although it has been mentioned several times, also infection is associated with up-regulation of the hemoxygenase gene with increased production of the pigment, and oftentimes hemolysis occurs in that context. Empirically, jaundice is associated with infection.

But I wondered what the quality of the data are with respect to the issue of risk for not so much bilirubin level, but injury in association with hyperbilirubinemia between hemolysis, anything on that at all, what is the state of the evidence.

DR. IP: We didn't really review specifically to address the hemolysis, but from what I gather, at least our task was to review healthy term/preterm, near-term babies without any kind of diseases, and all the kids with Rh, we excluded that from our analysis.

On the other hand, there are quite a large

number of kids with ABO. There is no way you can exclude them because they are part of a lot of the studies. As Dr. Stevenson knows well, the Coombs' test is not the best predictor of hemolysis, and a lot of times we just have to look at the raw data and say, well, some authors assume that if mom is O, baby is A, they must have an ABO problem regardless of what the Coombs shows, and some authors say no, you have to have the Coombs, so it is difficult to say what the end result should be.

DR. NEWMAN: I agree. I think the data here are in the form mostly of case reports. There are some studies where here is a series of babies who had high bilirubin levels and what percent got damaged, and clearly, those series of Rh babies in the '50s and the series of G-6 PD deficient babies, another group that seemed to have a higher risk of kernicterus in series at a lower bilirubin level.

The other things are case reports and sort of informally looking at case reports when you say here is a baby that looks like he or she might have kernicterus, and the bilirubin level is only 28, and then you say, yes, but the baby had a urinary tract infection or some other infection or something else that if you look at the kernicterus

cases where it occurred, say, at bilirubin levels less than about 30 or 35, children with other problems are overrepresented. I think that is about the best I can do.

DR. CHESNEY: Dr. Luban.

DR. LUBAN: I think we can't underestimate the number of children that have G-6 PD deficiency or have G-6 PD deficiency combined with sickle cell disease who are FS on screen, but eventually become children with sickle cell disease at a rate of 1 out of 400 African-Americans, and that is a group that I know we are not concentrating on with this data, but we shouldn't underestimate.

DR. CHESNEY: I have a question. Dr. Newman, I will address it to you, but maybe other people know of. We keep talking about hemolysis as being a high risk factor. Is there anything about the hemolytic process per se as in liberation of lipid red cell envelopes that enhances blood-brain barrier access for the bilirubin, do we know anything about that, are there any animal models where lipids have been given along with the bilirubin?

I realize this is a far-out thing, but we just sort of accept that hemolysis is more likely

to give it, and we assume it is because there is more bilirubin, but I wonder if there isn't some other issue.

DR. NEWMAN: I don't know the answer to that because those are sorts of studies I don't have the expertise to evaluate very well, the ones, you know, with animals, so I defer to any of the other people here who know those studies better.

I don't think it is clear why babies with hemolysis are at higher risk, but part of it is, you know, they were born in the 1950s. Mostly now, I mean our data is coming from the 1950s. Many of them, labor was induced, they were electively delivered prematurely.

You know, there are so many things different between Rh babies in the 1950s and babies now. We don't know what the risk of kernicterus is with babies with severe arch disease or hemolysis now when they get a very high bilirubin because we don't let them get a very high bilirubin.

It has become very, very hard to study. Other people may know the animal data, I don't.

DR. CHESNEY: Yes, Dr. Freeman.

DR. FREEMAN: I am just revealing my ignorance, but there is a recent paper out on

bilirubin as a cytoprotective agent, picking up as a scavenger molecule. Is there any level of bilirubin in the newborn which is good?

DR. CHESNEY: We were discussing that during the break. It is sort of like fever. I mean fever is actually a very good thing. Maybe bilirubin is a desirable thing in those infants who have lower levels.

Dr. Stevenson, you were going to answer that.

DR. STEVENSON: There is considerable data that demonstrates conclusively that bilirubin is a naturally occurring antioxidant. At levels that occur in circulation after birth within what would be considered the physiologic range, although we are still debating what that range might be, it will confer that kind of protection.

You can even thing about the teleology behind having a naked ape exposed to sunlight and oxygen, having a naturally occurring antioxidant in circulation temporarily while your other antioxidant systems up-regulate after birth.

One of the comments that I will make later is that everything is dose dependent, and if there is a level at which bilirubin is safe and may be

essential, there is also a level which bilirubin is toxic, there is no question about that from the animal work. Clearly, from our experience clinically, there are conditions in which bilirubin is associated with injury, there is no doubt about that.

DR. CHESNEY: Dr. Oh.

DR. OH: I clearly agree with Dr. Stevenson on that. My own gut feeling is that a little bit of bilirubin may be okay as an antioxidant, but too much is bad I think. That is my own feeling.

DR. FREEMAN: What is that range, Bill?

DR. OH: We don't know that. That is the question that we need to know.

DR. CHESNEY: That is comparable to fever - a little bit is good, too much is not so good.

Other questions? Dr. Glod.

DR. GLODE: I had a question for Dr. Newman. I realize that he was kind enough to just share with us his preliminary information, but it was really a comment and a question.

The comment would go to potential bias in the study. You already brought up the issue that perhaps the control families would be more likely

to enroll although I think you could also argue that the families of the children with the high bilirubin might bias the study in favor of enrollment because they were concerned about neurologic development.

But my question refers to the one area, neurologic exam area, where it was statistically significantly different in preliminary analysis, favoring the children with the high bilirubin.

I was just interested if you knew of those 86 children who had been enrolled at least, could just give us some sense of the interventions that were done. Do you know what percent had phototherapy or exchange or anything else?

DR. NEWMAN: I know that for not the 60 who have had exams, I showed data on, but for the whole group of about 140 who had bilirubin levels over 25. I think four of them got exchange transfusions, and all but one got phototherapy. The one that didn't get phototherapy, you know, was like at 25.2, and they repeated it the next day and it was lower.

So, not very many exchange transfusions, a lot of phototherapy. In terms of the bias, you are right that families of jaundiced babies who are

worried about what effects it might have had might be more likely to participate in the study.

I am focusing on the other bias because that would bias us in the direction of finding that jaundiced babies did worse, and since our trend is that they did a little bit better, the concern I have is that the controls selectively enroll who are more worried.

DR. CHESNEY: Thank you.

We have two presentations over the next hour. The first is by Dr. Oh, who is a neonatologist and Chair of the Department of Pediatrics at Brown Medical School. He is also the pediatrician and Chief at Rhode Island Hospital, and the Sylvia K. Hassenfeld Professor of Pediatrics at Brown.

He will be discussing the safety and efficacy of phototherapy for treatment of hyperbilirubinemia in the term and near-term infant.

Dr. Oh.

Phototherapy

DR. OH: Thank you very much, Dr. Chesney.

My job is to review the intervention for hyperbilirubinemia, which is actually the standard

of care today, in the next 35, 40 minutes or so.

[Slide.]

What I will do is just briefly discuss the historical event that led to the introduction of the phototherapy for the treatment, spend some time on the mechanism, in other words, how it works, and some data on the efficacy and acute side effects, as well as some long-term outcome.

[Slide.]

The first paper actually was published in 1958, in Lancet, by Cremer and others, showing that when they exposed infant with jaundice to sunlight, it has a reduction in serum bilirubin, and actually that was based in laboratory, in vitro observation that when they exposed the serum to light, the bilirubin level actually goes down.

So, they used this in vitro experience to perform a clinical trial that shows that in vivo, by sunlight, it also reduced the bilirubin, as well.

[Slide.]

Subsequent to that report, there were several clinical studies including some that were done here and some in South America in the '60s, which confirmed the efficacy of phototherapy in

lowering the serum bilirubin level, which then made phototherapy a standard of care up to today.

There is also some trials showing that the efficacy is somewhat more than the full term in terms of the low birth weight infants, and the reason for that is actually unclear.

[Slide.]

In terms of mechanism, we know that it works on the basis that bilirubin absorbs photon from the light at certain spectrum, light spectrum, which is at 400 nanometer in vitro. Following the absorption of this photon, it results in a series of photochemical reaction with the formation of three major products, and these are the isomeres that are different physical properties that allow for elimination of the bilirubin without going through the conjugation system in the liver.

[Slide.]

This is the spectrum of the absorption spectrum for the bilirubin, which is somewhere between 400 and 500, the peak being around 450.

[Slide.]

But the in vivo absorption of spectrum light for bilirubin is actually a little different from the in vitro, because the in vivo setting, the

bilirubin is bound to the albumin, and the albumin has some fatty acid that might change the spectrum of maximum absorption from 450 to somewhere around 475, 480 nm.

That explains some of the reason that the different kinds of light has variable results when the infants are exposed to this light.

[Slide.]

This is the series of photochemical reactions that are known to occur when the bilirubin is exposed to light. When the photon is absorbed by the bilirubin, it makes the bilirubin sort of excited. It excites the bilirubin, that then produce photo-oxidation. That is one of the byproducts.

It also has a change in the structure in another reaction that will form lumirubin, a substance called lumirubin, and then there is also a process called configurational isomerization, in other words, the structure is not changed, but the isomere was formed because the configure was changed, the bilirubin structure was changed, forming three different photoisomeres - 4E, 15Z, 4Z, 15E and 4E, 15E, and I will get back to that in a minute in terms of what those numerical numbers

mean.

[Slide.]

One of the interesting observations is that for 20 years or so, since Cremer's report of the efficacy of light, of phototherapy introducing bilirubin, the assumption was that the major mechanism was through photo-oxidation, and not until the early '80s, when the other mechanism was discovered or described, that people began to realize that it is not the photo-oxidation product that accounts for the major route in the elimination of the bilirubin, but it is rather the other two formation of the isomeres.

[Slide.]

One of them is the change in configuration that I talked about earlier. This is a molecular structure of bilirubin. On your left is the native bilirubin. You will note that the carbon 4, the two double band bridging the two pyrroles on the left and on the right.

Just look at the carbon 4 on your left, which is a Z, and the carbon 15, also Z, on the right. What happens is that the change in this particular model occurs in the carbon 15, so that the Z, the double band, is rotated 180 degrees,

allowing for the hydrogen ion to be essentially "exteriorized," quote, unquote, that change the polarity to make this molecule more water soluble than the native bilirubin.

The water solubility or the less lipophilic characteristic of this molecule will then allow for the particular product to be excreted through the bile and also through the urine.

[Slide.]

Now, this is a situation where the change is occurring in the structure itself, it is not the configurational change. There is an actual change in the structure. Again, on the left is the native bilirubin. You notice the 4Z and 15Z bilirubin. In this particular case, the left pyrrole ring, the structure is changed, so that again, the hydrogen ion is exteriorized and allows for the bilirubin to become water soluble and be able to be eliminated through the bile or through the kidney.

[Slide.]

The major issue here is that the native bilirubin, the 4Z, 15Z is hydrophobic and lipophilic, in other words, they are not water soluble, they cannot be eliminated through the bile

or through the kidney in the urine because of the physical property of the molecule.

The only way that the native bilirubin can be excreted or eliminated is by conjugation in the liver with the glucuronyl-transferase, the enzyme responsible for glucuronide of this particular bilirubin.

But when the bilirubin is exposed to light, the isomeres are formed, and they are less lipophilic and less hydrophobic, in other words, they are more water soluble, and therefore, it enhances elimination through the bile and the urine.

[Slide.]

The studies have shown that in terms of formation of this various product, the formation of the 4Z, 15E isomere, meaning the one that occurred through configurational isomerization, is greater than the structure change, the lumirubin, and those, in turn, are much greater in amount than the photo-oxidation products.

But the important thing is that in terms of elimination, the rate of excretion is far greater for the lumirubin than the photo isomere 4Z, 15E, and over the photo-oxidation product, so

that the rate-limiting process in terms of elimination is actually the lumirubin and therefore it is very important to remember that lumirubin is the key isomere in terms of the elimination of the bilirubin when they are exposed to light.

One other important phenomenon that one needs to keep in mind is that once the baby is exposed to the light, the formation of the various isomeres is almost instantaneous and they maintain a level that maintain a fairly good steady-state in the bloodstream. The rate-limiting state, as I said, is the elimination process, and that is what takes time.

That might explain some of the reason why the so-called continuous versus intermittent phototherapy has no difference in terms of the ability to reduce bilirubin, because the rate-limiting step is not the amount of lumirubin being formed, but the way it is being eliminated through the kidney and through the bile.

[Slide.]

This cartoon summarizes what happened to the various products of the bilirubin. The ZZ that you see here is the native bilirubin in the center. As you can see, they are transported to the liver

by binding to the albumin, and because of the nature of this molecule being lipophilic and hydrophobic, they cannot be eliminated unless it is conjugated by glucuronyl-transferase.

On the other hand, when they are exposed to light, it forms the either ZE by configurational change or lumirubin by a structural change that again are bound to the albumin, and for the ZE, it gets excreted through bile into the intestine, where then it's a reversible process, as well.

Once it's in the dark, once it gets into the intestine, it reverts back to the native bilirubin, ZZ, and recycle it to the blood.

On the other hand, lumirubin, or LR, again is bound to the albumin, gets to the liver, excreted through the bile into the intestine, and part of it is also excreted through the kidney through urine, so there are two ways that lumirubin can be excreted from the body, either through the bile into the intestine or through the kidney through the urine. The photo-oxidation product is primarily excreted through the kidney.

So, I think we have a fairly good knowledge to date in terms of the mechanism of how light works. It involves the formation of the

isomeres and the photo-oxidation product, but the major route of excretion is through the formation of the lumirubin, the structural change, and excreted through the bile and through the kidney.

[Slide.]

Now, what are some of the factors that might affect the efficacy of phototherapy? It all boils down to four major factors. One is the type of light used, either blue or green or white. Those are the three major light sources that are used clinically today. The light intensity itself, the surface area of the skin exposed to the light, and then the distance of the light to the baby.

So, all of this boils down to the irradiance that the baby receives, and that irradiance is dependent on the light intensity, the type of light used, the surface area being exposed to, and the distance from the light to the baby. Today, in clinical practice, although we don't use equipment to measure irradiance in most cases, the ideal setting will be to try and achieve an irradiance of approximately 15 to 20 microwatt per square centimeter per nanometer.

That is the setting where the maximum degree of reduction of the bilirubin takes place.

[Slide.]

Let me just walk through a few types of phototherapy devices available clinically today. One is generic fluorescent tubes, which can come in three different kinds of light - daylight or white light, which is the usual fluorescent light that you see in the household, a blue light, and then the green light.

Then, there is halogen lamps also used, fiberoptic system, and I will go through this in detail, and then more recently, a gallium nitride light-emitting diodes has also been developed and used clinically. Again, as I said, I will go through each one of these in detail.

[Slide.]

Now, in terms of the fluorescent light, this is a comparison study done by KL Tan in Singapore, published in 1989, comparing the percent reduction in serum bilirubin when the infant was exposed to either special blue or green light or daylight.

What he found is that the special blue is more effective in reducing the serum bilirubin by about 33 percent compared to green and daylight, which is about 20 percent reduction over a period

of time, or the duration of exposure are all constant.

Now, what he concluded was that it is preferable to use either daylight, because it provides enhancement of clinical observation and adequate efficacy, or blue light because it has a better efficacy, but the green light is not recommended by him because it provides neither.

[Slide.]

I have to make a note here in terms of what the blue and the green light ends up with when you do a clinical care in this baby. The blue light makes the baby cyanotic and the green light makes the baby sort of, you know, somewhere between cyanotic and being under-perfused, so it is very difficult for the nursing staff and the physician to evaluate these babies when they are under blue or green light.

So, today, in most settings, the white light is the most commonly used because it produces efficacy very similar to the green light although less effective than the blue light, but it has the advantage of a better clinical assessment compared with the other two lights.

[Slide.]

The halogen light, also called a spotlight, is advantageous in the sense that it is more compact, but the problem is that you cannot bring it too close to the baby. It has some significant amount of heat emitted that could sometimes burn the infant if you get it too close.

[Slide.]

The fiberoptic system, also called Wallaby light, is essentially a blanket wrapping around the baby, also called a Biliblanket. It has some advantages in that you don't have to use eye patches since the eyes are not exposed to the light. It is more portable, it is more convenient for mother and baby in case the mom wants to breast-feed the infant, it becomes more advantageous in the sense that you could simply have the blanket wrapped around the baby, and the mom can continue to breast-feed the infant while under phototherapy.

It is also used quite often in the home phototherapy setting. The disadvantage is that it has much lower spectral power.

[Slide.]

In fact, the study by Dr. Gale and Holtrop comparing the fiberoptic versus conventional, in

this case they used halogen lamp as a conventional therapy, showing that there is less decline in bilirubin. The yellows are fiberoptic and the black bar are the conventional. You will see the decline in serum bilirubin is much greater particularly in the Holtrop study, which has a p-value of 0.05, in the conventional therapy versus fiberoptic system.

So, one of the disadvantages of the Wallaby is that because of the lower spectral power, it has less efficacy in terms of reducing the serum bilirubin level.

[Slide.]

The most recently developed system is called light emitting diodes, which employs a narrow band of light spectrum, and the commercial company in this particular setting used the blue-green combination. It is power efficient is one of the advantages, and also has a low heat emission, but the one disadvantage is the fact that it is a very eye-irritating system. In fact, we just brought two of them into the nursery recently, and I have already got nurses at my office door saying take those away because it is very irritating for them to watch the baby under this

LED phototherapy light.

[Slide.]

This is the light spectrum of LED, and as I said, the company that developed this particular device used the blue-green spectral system.

[Slide.]

Again, in terms of efficacy, this is the study by Seidman, published in Journal of Pediatrics a couple of years ago, comparing the efficacy of LED versus halogen lamp, and you will see that the yellow bars are the bilirubin level of entry, the black bar is bilirubin level during the therapy, and you will see that there is no difference in the decline of bilirubin between the two methods of treating the baby.

[Slide.]

Now, let me just say a few words about the different modes of phototherapy.

[Slide.]

One is the continuous versus intermittent phototherapy. The reason why this was studied is the attempt to demonstrate that there is no difference in the ability to reduce the bilirubin level and allowing for the caretaker or the mothers to breast-feed the infant on an off-phototherapy

setting.

So, this is a study by Caldera where they compared the percent reduction in serum bilirubin of those that were treated with continuous phototherapy versus those that were intermittently treated, two hours on, two hours off strategy, and showed no difference in the ability of these two modes of therapy to reduce the serum bilirubin level.

As I said earlier, knowing the kinetics of how the bilirubin is excreted or eliminated, the fact that the level of the various isomere goes up instantaneously and maintains a steady state, and that the rate-limiting step is the elimination phase, it is not a surprising finding that there is no difference between continuous versus intermittent therapy.

[Slide.]

This is another study by Rubaltelli and Lau showing that although the numbers were small, there is no difference again in terms of the continuous versus intermittent therapy. This is the basis for our clinical practice of allowing mothers to feed infants on phototherapy because the infant can be taken out of the crib or the isolette

and be fed a certain period of time, then go back to phototherapy setting.

[Slide.]

The other mode of therapy that I would like to just touch on briefly is the difference between single versus double phototherapy. This is three studies that are put together in one graph, showing that the yellow bars are single phototherapy, and the double phototherapy in black bars. You will see that in all three studies, there is a significant difference in the decline in serum bilirubin between single versus double phototherapy.

Again, it is not surprising to see this in terms of a more effectiveness in terms of double phototherapy because you increase the light exposure of this baby. This is actually the basis for the AAP guideline calling for so-called intensive phototherapy. Essentially, it is recommending that if you have a level in the high range, that the intensive phototherapy using either double or some unit even used triple phototherapy, because of the greater efficacy in the double bank or triple bank phototherapy setting.

[Slide.]

I just have one slide on the home phototherapy. I noticed someone is going to speak about this issue. For several years, the committee of the AAP was very vague about whether home phototherapy is desirable or should be recommended or not until the most recent guideline, which was just published a few months ago.

This is the statement set in that guideline that I essentially put together here. It says that home phototherapy is an acceptable alternative, but the institution for the home phototherapy company should set up criteria for eligible infant that will be treated with this mode of phototherapy, and that there should be an appropriate follow-up of bilirubin levels.

This is one issue that I think is important, and that is to make sure the serum bilirubin level is done in the same institution, in the same laboratory to maintain a good consistency, and that if the bilirubin level does not decline appropriately, then, it should be admitted for more intensive therapy.

So, the AAP has decided to endorse this particular mode of therapy, but has some suggestion in terms of the guideline of how this particular

mode of therapy be, not regulated, but supervised by a person within the region.

[Slide.]

Now, there are a number of side effects known of phototherapy. Many years ago I actually did a study using fairly crude methodology to document that the insensible water loss is about 50 percent higher in the infants who receive phototherapy. It is probably related to the heat emitted by the phototherapy and the increased respiratory rate, which is also a finding that we documented in order to maintain heat balance. In fact, if heat balance is not maintained appropriately, the infant may develop fever or elevation of body temperature.

There is also some documentation that these infants may have loose or watery stool, and that the mechanism is not clear, but this has been confirmed by a couple other anecdotal studies showing that there is a change in the gastrointestinal tract in terms of a more frequent and loose, watery stool when the infant is under phototherapy.

I should point out that although insensible water loss is an issue, and it has been

confirmed by two subsequent studies, Paul Wu and Ed Bell have confirmed this observation, that it is probably more relevant in the low birth weight infant because the insensible water loss is so high, the insensible water loss is indirectly proportional to gestational age, so that an infant who is in the 26-, 28-week range, the insensible water loss can be three times higher than the full-term infant, so the change in the 50 percent would need to be accommodated in the fluid balance, otherwise, the infant may get dehydration.

But in the term infant, the subject that we are talking about today, the insensible water loss is much lower, it's in the range of 20 ml/kg/day, so if 50 percent increase is 10 cc, all you need to do is make sure that the infant has enough fluid intake to maintain water balance, so it is not a huge issue in the term infant from this particular standpoint.

[Slide.]

Now, there is also some concern about toxic effect on the optic nerve. This was demonstrated in animal study, but human study actually has not confirmed this. There was one control trial showing very elaborate visual

assessment, infants who had received phototherapy versus those who did not, and showing no difference in terms of the visual performance, but since eye patch is such a benign, non-invasive procedure, our current practice is still to use eye patch for babies under phototherapy.

[Slide.]

Just a few words about low birth weight infants. Although this is not the subject of our discussion for this particular committee, I just wanted to point out the effect of phototherapy on low birth weigh infants is probably more, to me, is more worrisome than the full term and near-term infant.

The NICHD study done in the early '80s suggest that there is a higher mortality among the infants who are enrolled in the phototherapy group, and there is also some suggestion that phototherapy may have some influence on the patent ductus arteriosus, a common problem in the low birth weight infant, not in the full term infant, and that there is some concern about association with increased incidence of blindness due to retinopathy of prematurity.

Again, these are all related to low birth

weight infants, but let me show you a couple of slides on the second and third bullets here.

[Slide.]

This is a study by Warren Rosenfeld showing that the infants--these are low birth weight infants who were subjected to phototherapy--the incident patent ductus arteriosus is lower when they shielded the chest with aluminum foil, essentially, that is what they did, compared to those that were not shielded.

They didn't quite explain why, the increased incidence of patent ductus arteriosus was not as clear as it should be. Also, the other problem of this particular study is that this is not a blinded study, obviously, because they had to put the aluminum foil on the baby's chest. Also, the assessment of the PDA was not done by echo in those days, it was done primarily by clinical assessment, and that may have some bias involved in terms of documenting the incidence of PDA.

This had never been confirmed one way or the other, so this remains a question. To me, it is not as serious as it seems to be. Also, we now have a very good way of treating these infants using the indomethacin in terms of PDAs. It is not

a concern in terms of morbidity.

[Slide.]

There is also some concern about the effect of phototherapy on blindness due to ROP, retinopathy of prematurity, and this is the data from Yeo, published in Pediatrics about three years ago, showing that the OR, the odd ratio for greater incidence of blindness due to ROP is 4.48 with a p-value of 0.03 when the peak serum bilirubin level is less than 160 micromole/liter, and that the same thing is true for the duration of phototherapy.

So, what they are saying here is that if you are aggressively treating these infants, these are very low birth weight infants, with a longer duration of phototherapy and bring the bilirubin down to a lower level, you have a higher incidence of blindness due to ROP.

[Slide.]

The problem with this data is that it is a retrospective analysis, this is a small sample size, relatively small sample size, and that the eye exam was not done uniformly. Again, the results have not been confirmed. So, this is some lingering concern that people have in the low birth weight infants from the standpoint of phototherapy

itself.

[Slide.]

Briefly, it is very difficult to assess the effect of phototherapy per se on neurodevelopmental outcome because you always have the co-morbidity of bilirubin. You use phototherapy only for bilirubin, so there is no way you could compare the phototherapy in itself in terms of outcome because by virtue of the use of this intervention, you use it when the bilirubin is high, so you need to be able to separate out the effect of bilirubin versus the effect of phototherapy itself.

Let me just show you a study that Dr. Scheidt did in 1990 using the cohort from the 1980s NICHD trial where they enrolled a group of infants into the group that received phototherapy when a certain level of bilirubin is reached and those that were not treated with phototherapy.

[Slide.]

What they found is that at one year, the MDI and PDI scores were similar between the two groups. These are all full term infants.

[Slide.]

Then, when they assessed the six-year-old

outcome, they combined both pre- and full-term infants, again, it shows no difference in terms of the verbal performance between the two groups at six years of age.

[Slide.]

Again, in the low birth weight infants under 2 kilograms, they did a separate analysis, and again showing no difference between phototherapy and the control group in both one- and six-years of age in terms of neurological finding--they were using cerebral palsy as the endpoint--and in developmental performance.

Now, as I said, it is not clear whether this is truly a negative outcome from the standpoint of phototherapy itself because you have so many confounding variables particularly with respect to the low birth weight infants. Many of these infants are sick, they have a certain bilirubin label, and we don't know what the bilirubin level dictates, I mean dictate the neurodevelopment outcome, in a much larger study, it is very difficult to assess the phototherapy itself with reference to the population that receive this treatment because of hyperbilirubinemia.

[Slide.]

So, my summary is as follows. Phototherapy, there is no question it is an effective treatment for jaundice. There is so many data over the last 40, 45 years, showing that it is an effective intervention and that the mechanism is well defined. There is no question about how it works.

There are some acute effects that are known, and if you are talking about full term infants, it is a manageable problem, in other words, the increased insensible water loss, the watery stool, and the increased respiratory rate, those are minor, to me, a minor effect that could be managed without significant concern.

At least in term infants, at least in that one study, there is no real significant adverse outcome in term infants. I went through the Medline and I couldn't find any long-term follow-up. It is amazing, in a therapy that has been on-board now for almost 45 years or 50 years, and yet I didn't see any clear-cut outcome study comparing directly phototherapy versus no phototherapy.

But I need to point out, in the last

bullet, that there are some lingering concerns about low birth weight infants because I think, not only that there are some concerns about a PDA, the blindness, and the one set of data which I did not present today because it really pertained more to the low birth weight infant is the data I just put together, will be published in Pediatrics sometime in the next few months, documenting the association between relatively low levels of bilirubin in extremely low birth weight infants--I am talking about infants below 1,000 grams--between serum bilirubin, much lower level than we are talking about with a two-year-old neurodevelopmental outcome.

There is significant association. The higher the bilirubin is, there is almost a linear relationship between serum bilirubin and the number of infants with neurodevelopmental impairment including hearing loss. So, there is some concern about low birth weight infants, but probably not in the full term infant. That is my conclusion.

Thank you very much.

DR. CHESNEY: Thank you, Dr. Oh.

We do have a few minutes if anybody has questions for Dr. Oh before we have our last

presentation.

Dr. Freeman.

DR. FREEMAN: Bill, when you measure bilirubin, do you also include the measurement of biliverdin? I mean are they separable by the standard techniques that we talked about earlier?

DR. OH: No, I think it is bilirubin that we are measuring although, yes, biliverdin is not measured, it is bilirubin primarily.

DR. FREEMAN: Okay, but biliverdin doesn't show up in those--

DR. STEVENSON: No, it doesn't.

DR. FREEMAN: The second question is do we know anything about the neurotoxicity of biliverdin?

DR. OH: I don't think we know. Do you?

DR. FREEMAN: No.

DR. OH: I don't think we know. If you don't measure it, we wouldn't know what the effect that molecule would be.

DR. CHESNEY: Dr. Newman, you had a question?

DR. NEWMAN: You didn't present any data on this, but from my own experience, I am probably one of the few general pediatricians here. To kind

of paint a picture of what phototherapy is like, some of the problems with it that you didn't mention are that a lot of the babies just don't like it because they are unwrapped, they have to be unwrapped and many babies are much more calm if they are wrapped up, often this involves, you know, the baby is in an isolette or away from the mom, and unwrapped, which they don't like, so they start crying, but you can't pick them up and comfort them because they are under phototherapy.

Then, the mothers start crying, and, you know, the mothers, they are three or four or five days post partum, it doesn't take very much to make them cry, and it is a very--I think hospital phototherapy, that aspect of it, which is that it is upsetting, I would just add that to what you mentioned about physiologic effects.

DR. OH: California may be different, but I don't see that often in my nursery.

DR. CHESNEY: It is clearly a California phenomenon.

Dr. Stevenson.

DR. STEVENSON: Well, being from California where it is always sunny, we don't have to worry about jaundice that much. One of the

comments I wanted to make in response to what Bill said is that light, it is a drug in the way that it is being used for this purpose, and yet it has not been really handled in the way that we handle evaluations for particular drug applications.

In other words, there are dose ranges recommended, but no one is really monitoring, as Bill mentioned, the doses that are being applied, so given all the different light sources and all the different ways in which they can be applied in the nurseries, the range of doses is considerable, and it is hard to know what, in fact, is happening in those environments related to this particular medicine, and much more can be done in that regard.

I know that is not the topic of this group's concern right now either, but the other thing I would like to mention from work that we have done, we have published it in the abstract form, but not published the paper yet, is that clearly, with the cool white lights, in applications in the range that we would expose human neonates to, you can see photo-oxidation in translucent small animals.

The expectation is that in translucent human beings like these small infants that Bill was

talking about, they also would probably be accessible to that light, and there could be, in fact, photo-oxidation going on in those infants independent of the predominant pathways that have been described biochemically, that is, the generation of lumirubin in that mechanism.

So, I think there is considerable concern about the use of light as a medicine particularly in the smaller infants, and it probably has some impact on the larger infants which is just not measurable with current technology.

To give you a hint about the patent ductus, again, this would be a hypothesis, but we know from the work that we have done that one of the potential alternative sources of CO, carbon monoxide, is, in fact, photo-oxidation. That has been confirmed in the absence of heme.

So, if you apply light to small translucent animals, you can generate carbon monoxide, not only at the surface level of skin, but probably in tissues, in sufficient amounts that you could actually influence the vascular behavior of a vascular tissue. CO works through the same pathways.

So, that is a hypothesis, but it shows you

that light, in fact, does have an impact and probably needs to be considered is not entirely understood with respect to all of its effects in certain categories of infants.

DR. CHESNEY: Very interesting. Any other questions?

All right. We will move on to our last speaker before lunch. Connie Schomann is a nurse supervisor with the Medstar Visiting Nurses Association, and she is going to demonstrate for us how phototherapy is administered in the home, and she will review how home visiting nurses instruct parents in the proper use of this therapy.

Outpatient Phototherapy

MS. SCHOMANN: Good morning. My name is Connie. I am a registered nurse with Medstar and I have been doing pediatric home care for seven years now. A large part of our pediatric population consists of babies that are being followed for hyperbili.

Occasionally, we get babies that are discharged from the hospital with phototherapy. Maybe they have had phototherapy for a couple days and they are sent home with a blanket to continue their therapy at home, but the greatest portion of

them are babies that were discharged from the hospital between 24 and 48 hours of age without any evidence of significant jaundice and the jaundice is picked up after they were home.

It might have been an initial pediatric visit, maybe if they had risk factors and the doctor wanted to see them in a day or two, and then they would pick up the jaundice, or maybe when the visiting nurse would go for an early maternity discharge visit, I know in Maryland, a lot of insurers provide for a home health visit from a nurse their first day or two at home, and we pretty often pick up jaundice at that time.

The important thing here I think is that most parents do not recognize jaundice in their infant unless they have experienced it before. I had had parents tell me, oh, gee, I just thought he had a little suntan going, thought he had good color.

I have walked into some homes and could tell from across the room that the baby was jaundiced and started thinking about where is the closest STAT lab, and the parents didn't have a clue. So, you can't always depend on their assessment of the baby's skin color because they

just don't have the experience with that.

So, typically, what happens once the baby gets a blood level drawn for serum bilirubin, it might have been at the doctor's office or in a morning visit, hopefully, in the morning. It takes several hours before the report comes back from the lab, and a decision might be made that the baby needs phototherapy at home.

Then, you have to contact the DME company, sometimes several of them, to find an available blanket, and you also have to talk to the insurance company and get authorization for the home phototherapy, so it can be day long process just getting this started.

It usually ends up with a phototherapy blanket being delivered to the home 9:00, 10 o'clock at night, so the parents are generally exhausted anyway.

Most companies--this blanket here came from Medstar Medical Services--most companies manage their Wallaby equipment or phototherapy equipment along with their oxygen supplies and equipment, so that the delivery to the home is actually made by a respiratory therapist, who will give the parents some instruction on how to set up

the blanket and then leave them on their own for overnight until the visiting nurse arrives in the morning.

I have Baby Billy here. I had a little girl who very willingly let me borrow her baby for demonstration purposes. He is kind of small, he is not very jaundiced, but he is a very willing participant, and he doesn't complain too much, so I will show you how it gets set up and what some of the limitations are.

There are some limitations and problems with phototherapy in the home, but generally, parents are very happy to learn that they can have this treatment at home and not have to go back into the hospital. That is not what they want to do and especially when they realize that readmission to the hospital means the pediatric unit, and not that nice, big family centered care room with the TV and the VCR and the separate sleeping accommodations, but it might be a room for two with a lounger for mom to sleep in or something like that. So, they are very willing to do whatever it takes to be able to stay at home with their baby.

When they get the blanket delivered, this is what it looks like. This is called a blanket.

It is not very soft, it is a little pliable, but this is your fiberoptic pad and it's a light, a light source if it works, the light comes right from this pad.

It needs to be applied with the correct side to the baby. It needs to be applied to the baby's skin, not on top of their clothing. It is wrapped around the baby's middle, so that as much of the baby's abdomen is in contact with the light.

They send these pieces of tape that are absolutely worthless to tape it together, so I usually tell parents to use masking tape, electrical type, or duct tape. Everybody has duct tape these days, right? It works very well to help hold these in place. They tape it around the baby with just enough space that the fingers can go in, so that it is not too tight and constricting.

The baby needs to be dressed over top of that. Normally, you wouldn't turn the light on until they were dressed, which means that a T-shirt can over top or they can be wrapped in their blanket.

The fiberoptic pad itself does not produce heat, it is cool, so that parents need to be instructed that they still need to dress their

babies or they are going to get cold if they don't dress them appropriately.

Once they are wrapped, then, you have your baby receiving phototherapy. It looks pretty easy, right? But this baby is tethered to this machine, it is not very portable. The directions will tell you it needs to stay on a firm, flat surface, so you have got this much room to move.

It can be awkward, if the mom is learning how to breast-feed, she is not very good at it, and then all of a sudden she has got all this to deal with, too. It makes it a little bit more difficult.

Basically, they are just tethered to one spot for a few days. I usually instruct parents to expect three to five days of phototherapy in the home. It does take a little bit longer than when they are in a hospital under lights. That way, if it's less than five days, they are happy.

Basically, that's it. Then, when the nurse arrives the next morning, her visits consists of head to toe assessment, she weighs the baby, and the biggest part about assessment has to do with feeding issues. As Dr. Oh talked about, a lot of these babies are breast-fed, and when the nurse

gets in there and assesses the baby, may find out that the baby has lost a lot of weight, maybe 10 percent or more.

If the baby's urine output is not very good, maybe the baby hasn't had any stools since they have been home or last stool was still meconium, then, feeding issues have to be addressed. So, a lot of times the pediatrician will order supplementation with formula or even withholding breast-feeding for 24 hours and using formula instead.

It sounds really easy, but when you have a mom who has been prepping herself for breast-feeding her baby for the last six months, and you tell her to stop, that can be pretty upsetting. It also can be difficult for them to manage because they are usually not prepared for formula.

Lactation consultants, they do a great job in the hospital preparing their patients, but one of the implementations that they have made in recent years is they have stopped giving formula samples to breast-feeding mothers because they feel that it encourages them or sets them up for failure, "Here, you are going to need this when you

can't breast-feed."

So, they no longer send this home with them, so that means that somebody has got to go out and get formula for the baby, they have got to get bottles for the baby. They have got to figure out how to make the formula.

Then, on top of all that, the mother has got to get a breast pump and hook herself up to another machine for 24 hours, every two to three hours, to maintain her milk supply So, the visiting nurse plays a very large role in helping the parents with that process, to get through that, so they can maintain good lactation and meet their goals with the baby, and continue to care for their baby at home.

Generally, they are very successful. Occasionally, a baby will turn around and have to be admitted because the bilirubin is just not responding. Usually, it's because of ABO or some other factor, but for the most part, we have very successful outcomes with this, but a major part of that success, it's not just the machine.

I think, if I can put in a plug for visiting nurses, the support and teaching and education that the nurses provide are really a

major factor in the success of this treatment.

Thank you very much for having me.

DR. CHESNEY: Thank you.

MS. SCHOMANN: Any questions?

DR. CHESNEY: Dr. Fost.

DR. FOST: I am trying to get a ballpark idea of the total annual cost of home and hospital phototherapy. Can anyone tell me what a typical charge for hospital/home phototherapy is, and the approximate number of babies a year that get phototherapy.

MS. SCHOMANN: I can tell you that this machine, the rental costs about $100 a day. The visiting nurse, the initial visit for my company is $150 for the initial visit and then $115 for revisits. They usually do visit on a daily basis. And then the lab costs. The nurses usually draw a lab each time and transport it. There is usually STAT fees at the outpatient lab, usually run around 35 to $40 for a total bilirubin.

DR. FOST: Does anyone have an estimate of the total number of babies a year?

DR. NEWMAN: For hospital phototherapy, it is a few percent, it varies a lot from place to place, but I don't know for home phototherapy.

DR. FOST: So, like 3 percent of 4 million, so 120,000 a year roughly.

DR. NEWMAN: Yes. It might be higher than that. It is 2 percent at Kaiser, but they do I think quite a bit less phototherapy maybe than some other places.

DR. FOST: And the charge for a hospital's phototherapy?

DR. NEWMAN: Figure a few thousand dollars a day, a couple of thousand dollars a day probably. But at least when we do a hospital phototherapy, it is short, it is about a day. We use three lights, we figure just get it over with quick, so it is typically about a day. It is much shorter in the hospital, it is not three to five days. It is usually a day or two in the hospital.

DR. FOST: Thank you.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I guess this is for Dr. Oh.

Have there been any studies on the intermittent versus continuous issue using the home blanket phototherapy?

DR. OH: I was going to comment that I am not aware of--the studies that have been done were all using the fluorescent lamp, the white lamp--I

am not aware of any comparative study between the Biliblanket with intermittent versus continuous exposure.

It is probably not an issue because as she demonstrated, the mom can breast-feed the baby, so there is no need to discontinue the phototherapy.

DR. NELSON: Well, there may not be a need, but from the inconvenience I suspect that intermittent therapy is probably the norm.

DR. OH: I suspect if somebody does a comparative study, it will probably show the same result as the others, I mean the principle is the same. The mechanism of excretion and the elimination is very similar.

DR. CHESNEY: Dr. Stevenson and then Dr. Ebert.

DR. STEVENSON: The mechanism is the same, but I think one of the points that Bill made would make you suspect that the differences would hardly be noticeable, the reason being is the dose that you are receiving is quite limited, so it is not a very potent way to treat hyperbilirubinemia.

So, most of us who believe that phototherapy is required as an intervention would be more inclined to use it intensively in the

rating flux range where you are going to have demonstrated efficacy.

The difficulty here is not so much that fiberoptic blankets can't generate an intense light, it's the surface area of application, which you could see is quite limited, and if you think about the total surface area, you are only dealing with part of it, so you are going to have a very limited impact on the person.

Also, you say, well, why not get a longer and more convenient tether, but then you are farther from your light source and once again you are going to lose your power, so there is a limit to how long that tether can be, and there is also a limit with respect to surface area as to how you can actually apply it.

So, there is going to be not much advantage or difference between either having it on or having it off, and that leads some people to say if you need phototherapy, use phototherapy and not home phototherapy.

I am not being critical of these options. These are only the only technical options right now available in a uniform way.

DR. CHESNEY: Dr. Oh, could you clarify

for the uninitiated, when you talk about double and triple therapy, is that two and three banks of lights or two or three colors?

DR. OH: Double is typically what you do is you have an overhead and then you put two side, you know, sort of exposing the baby to three. Is that what you do in California?

DR. NEWMAN: We just use the halogen spotlight. It makes a circle of light on the baby, and the more of them you have, the more of the baby's surface area you can get covered by one of those circles from the spotlight.

DR. OH: There are many ways you could do it, but we use overhead and two sides, and sometimes one over one side and one spotlight, so any combination would work fine.

DR. CHESNEY: I read somewhere about having the baby lie on this kind of bed and the do it over. Would that be called double?

DR. NEWMAN: We typically will have a blanket underneath the baby and two spotlights up above.

DR. CHESNEY: Triple?

DR. NEWMAN: We call that triple, yes.

DR. OH: The problem with the blanket and

then the light is that you already covered the surface, so the light on the top is not going to work. You know what I mean?

DR. NEWMAN: We have the blanket. The baby is lying flat on top of the blanket.

DR. CHESNEY: Dr. Stevenson.

DR. STEVENSON: One quick comment. You can begin to see the complexity of the application of this medicine. You can imagine the shadowing with numbers of halogen lamps and also these different devices.

So, if you look critically at the light exposure and the shadowing on a particular infant when people are doing their intensive phototherapy, tremendous variation across the surface of the individual and differences between institutions in terms of where the lights are relative to the individual.

So, dose is very hard to control unless you are measuring precisely, and then it is only good for where you measure it.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: Just a follow-up question. Have there been no head-to-head comparisons controlled for starting bilirubin level in the

absence of any other condition that would increase production of looking at in-hospital intensive phototherapy short of duration against home less intense, longer duration, had there been any head-to-head comparison at all?

DR. OH: I don't think so. That would be a good study to look at, I mean a good issue to address, home versus hospital setting. I had the same kind of strategy in our place, and I don't use home phototherapy a lot. Once the kid needs the phototherapy, they get admitted for phototherapy, very intense, and they stay one to two days and go home.

DR. CHESNEY: Dr. Oh, would you comment on the rebound? I think I read in our materials that there has been a question of rebound in bilirubin. If you do just a one day intense, do you get any rebound or more than you might with a prolonged?

DR. OH: Typically, what we do with the rebound issue is once we stop the phototherapy, we generally keep the baby in the hospital for another 6 hours and do a rebound bilirubin, and if that doesn't go up, then, we send the kid home, or if there is a good follow-up system, we would do a rebound 12 hours, 24 hours later.

DR. CHESNEY: How significant is the rebound?

DR. OH: Actually, not very much. Most of the kids will be down to between 12 to 15, 10 to 15, and then once you get the rebound, to maybe 15's. Usually, the age also is much older and we have less concern on the kid who is two days old versus 6 days old.

So, even if the kid rebound to the 15's, we are not as concerned as if it were to be two days old.

DR. CHESNEY: Is doing a rebound level standard of care?

DR. OH: I don't think so. David?

DR. CHESNEY: Dr. Stevenson.

DR. STEVENSON: Just Maisels has actually done recent work on this and made the case that for the otherwise well term infant who has this application, it is not required because it's such an infrequent event.

The one caveat that I would suggest is that if you have a hemolytic condition where you need to reduce the pigment at a very high rate, it's in those contexts where you might see a rebound if your conjugating capacity is not

improved. That is typically what you see.

If you make the mistake of doing an exchange transfusion on a child who has been breast-feeding, that is really the cause of their jaundice, you will not see any rebound whatsoever. If you do an exchange transfusion on a baby that has been producing bilirubin at a high rate with this large amount, not only in circulation, but also in the body, you will see a rebound that can be quite dramatic in that context.

So, I would say in the context of increased production, you are more likely to have a rebound, but for the general population that is not hemolyzing, which is most everybody, then, it should not be a problem.

DR. CHESNEY: Thank you.

It's 12:15 and I am collecting a list here if any of you would like to add to it of interesting phrases, so this morning we have "weller" babies and we have "excited" bilirubin, and we have another use for duct tape.

I think we could break for lunch now and if everybody could please be back at 1 o'clock, we are going to hear from the mother of a child who has kernicterus on behalf of her organization.

Thank you.

[Whereupon, at 12:20 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

A F T E R N O O N P RO C E E D I N G S

[1:00 p.m.]

DR. CHESNEY: Our first speaker this afternoon is Sue Sheridan, who is president of PICK, the Parents of Infants and Children with Kernicterus. Susan is the current president and the co-founder of PICK. She is going to present the perspectives of her organization and of a parent of a child with kernicterus. I understand she is going to have a short video, as well as a PowerPoint presentation.

A Parent's Perspective

MS. SHERIDAN: Thank you. I am David Stevenson. I am glad to see you made it back because I notice you have 45 minutes, and I have 20, so I would like to ask if I could borrow 5 minutes of yours. Thank you.

Also, Tom Perez, when I was coming up here, asked me if I was nervous about today, and typically, I really don't get nervous when I speak about this because I am so passionate about preventing kernicterus, but if I am nervous today, it is because I want to make a difference, I want every word that I say today to influence you on helping prevent kernicterus.

I am very grateful and honored to be included in this and to be quite honest, I am relieved that this dialogue is taking place today. I have been following this debate for almost a decade.

I look at kernicterus and, well, the prevention of kernicterus as actually a patient safety initiative rather than how to manage jaundice. I am passionate about patient safety, not only because my little boy suffered brain damage from kernicterus, but I also lost a husband last year because of a medical error.

He had a cancer that was diagnosed properly as a sarcoma, but it was communicated to us as a benign tumor, so while the pathology was lost for six months in the mail, the tumor grew into my husband's spine and it eventually killed him.

So, I hope that my words today can reorient you to a patient safety focus because there are a lot of things that we can do to prevent harm to babies and daddies.

As you know, my name is Susan Sheridan. I am from Eagle, Idaho. I have two children. My little girl McKenzie, is 5. She had severe

hyperbilirubinemia from AO incompatibility. She got a TSB, she was tested, she was diagnosed, she was treated, and she is fine today.

I have a little boy Cal, Cal Patrick, who is 8. He was born a well baby--somebody asked a question about well baby--almost 38 weeks gestation. He was visually assessed at 16 hours to be jaundiced, at 23 hours to be jaundiced, at 33 hours to be jaundiced with no TSB taken. He was discharged head-to-toe jaundice, no TSB with the words that jaundice is normal, don't worry, put him in the sunlight if you are worried about it.

I took Cal back two days later to the pediatrician. He was becoming lethargic and his suck became weak with breast-feeding. I took him to the pediatrician. He was board certified, he's an AAP fellow, was familiar with the AAP guidelines. He sent us home to wait 24 hours.

Again, no worry, no indication that anything abnormal was going on. Well, we chose not to wait those 24 hours because our son was deteriorating, and we took him to the hospital. When Cal was admitted, his bilirubin was 34.6.

Again, there was no concern. We were told that kernicterus did not happen anymore in the

United States, and they chose not to do a blood exchange transfusion because he was close enough to 30, they recalled, which was the new benchmark that the AAP had indicated for an exchange transfusion. This was their interpretation of the AAP guidelines.

So, we watched Cal. Twenty-four hours after readmitting Cal--and this was a hospital that delivers 5,500 babies a year, this is a JCAHO-accredited, Level 3 NICU hospital, so this was not a country hospital--we sat there for 24 hours. At 24 hours, Cal began arching his neck backwards, and he developed a high-pitch cry that sounded kind of like a cat, it was very disturbing.

I indicated to the doctor something was happening to my son, and the nurses of 20 years experience on the pediatric floor, neurologists, ENT, and pediatrician, we all watched Cal suffer brain damage before our eyes, and we didn't know it. Nobody knew that these were the classic indications, these are the classic symptoms of the onset of bilirubin encephalopathy.

They used phototherapy, a double phototherapy for Cal's treatment, and it failed him. Like 25 other babies in the pilot registry

that I think Tom was talking about earlier today, Cal has kernicterus.

Actually, Cal likes to be a part of my presentation sometimes and he was helping me prepare a presentation a couple weeks ago, and he knew his sister when she was born, when she had severe hyperbilirubinemia and was treated, and he asked me, "Mom, why doesn't McKenzie have kernicterus?"

I thought that was an excellent question, and that is precisely why I am here today. I am also here today, as they mentioned, as co-founder and president of PICK. PICK stands for Parents of Infants and Children with Kernicterus.

We formed about two and a half years ago, right after I was invited to testify at the AHRQ First National Summit on Patient Safety and Medical Errors. My son Cal was highlighted in a USA Today feature article, and then that day I received all day phone calls from parents throughout the United States.

So, we got together and we formed PICK, and PICK's mission is to eradicate this preventable devastating condition by partnering with the healthcare system, by implementing a universal

systems-based approach. We believe that by implementing a universal bilirubin screen with the use of the Bhutani nomogram, we can significantly reduce kernicterus.

To demonstrate our partnership, PICK's partnership, I want to show you a video that we produced just this past January with a generous grant from Partnership for Patient Safety. This will show eight moms who have children with kernicterus, two kids with kernicterus are on this tape, and then what we refer to as our dream team. These are all the government agencies that have joined PICK, partnered with PICK, to eradicate this condition.

[Videotape shown]

MS. SHERIDAN: In preparing my remarks for today, I was inspired by the mission of the Health and Human Services Department, which reads, "To protect the health of all Americans and provide essential human services especially for those who are least able to help themselves."

I think newborns would fall under that category.

Much of the debate today has been about prevalence on kernicterus, and I guess it all

depends on perspective - is the glass half empty or is the glass half full.

Frankly, the answer to what is the prevalence of kernicterus is we have no idea how much kernicterus is out there. Anybody who is guessing is doing just that, you are guessing. We know of 125 children in the pilot kernicterus registry that has been shared voluntarily by doctors, families, and attorneys.

That is like I think Tom said the tip of the iceberg. These are kids that are so severely affected that they are hard to miss although my son wasn't diagnosed until he was 18 months old because either the doctors wouldn't or they couldn't. It's a tough diagnosis to give.

But, you know, I was actually somewhat disturbed that in the binder, it referenced prevalence at 1 in 250,000 because that is a guess. What about the rest of the kids in that spectrum? No one will argue with me that when there is any kind of disorder, you have got the very severe down to the very mild. We are not capturing the rest of that population. We have got the very severe in this pilot registry.

But even if we accept the guess at 1 in

250,000, I ask you, is that acceptable? You know, I ask you, what is rare, what is rare? It is not acceptable in other industries. It compares to the number of children that choke and died on toys in 1998. Twelve kids died because of choking on toys. Yet, millions of dollars were spent on recalls, labeling, and the reengineering of toys because of those deaths.

It compares to the number of children that died annually from strangulation from venetian blinds, yet 800 million of those were recalled because of that.

There was a popular toy made by Playschool that was called the Klackeroo. I actually saw a big poster in my pediatrician's office about the recall, how dangerous this was for children, that we call this 1-800 and we could get reimbursed for this toy, so I called the number, and it was the National Product Safety Commission.

I asked about the history of this toy, and there was a web site for me to go to, everything about this Klackeroo, millions were being recalled, and I asked about the deaths and injuries. They had 12 reported complaints from parents, no deaths, on injuries, 2 pieces were found in babies' mouths.

So, 12 in the other industries is intolerable. Millions of dollars are spent to protect our babies. Why are our babies and our children safer in other industries than they are in the healthcare industry? It doesn't make sense to me.

So, when we talk about rare, even though 1 in 250,000 kids, I think it tragically underestimated. In other industries, it would be outrageous.

Action by our regulatory agencies, the FDA, the National Consumer Product Safety Commission, their actions, their bans, and even their fines on industry is not due to prevalence, it is due to the perceived risk. It is due to the potential harm to Americans.

So, nobody knows the prevalence, but let's, instead of trying to make the number 1 in 500,000, 1 in 700,000, why aren't we looking at the other way around? Instead of saying of those 125 kids in the pilot registry, you know, some of them may not be, well, some of them may be, and what about these other kids that have mild auditory neuropathy and mild cerebral palsy, instead of saying well, it is probably not due to kernicterus,

why don't we turn that around and say, gosh, that could be due to kernicterus, and the reason is because bilirubin is a toxin.

Bilirubin, like Tom said, is a brain poison. It's a naturally occurring neurotoxin. Sure, there might be some antioxidant benefit, but, you know, a glass of red wine to end the day is also good for you, but two bottles a day is too much. So, you know, bilirubin hurts babies.

This morning I heard the AHRQ evidence-based report, and I read that report, and something in that report, it talks about that the preponderance of kernicterus cases occurred in infants with serum bilirubin levels over 20. This is evidence. This was in the AHRQ report.

Yet, the AAP recommends exchange transfusion at 25 and even 30. I must ask this committee, why is the healthcare system complacent about the dangers of hyperbilirubinemia, the documented dangers of a neurotoxin? How can we knowingly and willingly take these babies into a known and documented danger zone?

And like it was expressed earlier, how do we know what the long-term effects of this exposure of hyperbilirubinemia is now that kids in the 1990s

to present, they have been exposed to hyperbilirubinemia at higher levels for longer periods of time? We do not know the effect of this on their long-term development.

As a matter of fact, I feel that Cal, Cal was born in '95, the AAP guidelines came out in '94, the kinder, gentler approach, and, of course, the AAP had no intention of the reemergence of kernicterus.

But how did this complacency, how did this complacency happen, and now, from this, I have always felt that Cal was an in an undisclosed clinical trial, nobody knew what was going to happen to our children with these longer duration and higher bilirubin values.

I don't believe there is evidence of safety at the level of 25 and 30. Sure, some kids don't get kernicterus, but there are a lot of kids who do get kernicterus.

As a mom, the complacency about hyperbilirubinemia is very concerning. In comparison, other toxins, such as lead, get a lot of attention, financial support, and vigilance.

I looked at the comparison with lead because I wanted to see what industry does with

other toxins. They are both not good for children, they are preventable types of brain damage, and there is no known threshold for the toxic effects of either.

Right now in the United States, it is estimated that 800,000 children have elevated, what they call BLLs, blood lead levels over 10 mg/dl. By contrast, 2.3 million children develop elevated bilirubin levels each year, and 1 in 700 develop bilirubin over 25, which is well into the danger zone.

There has been 1 death from lead poisoning in the past decade. That was issued in a MMWR put out by the CDC. There have been 6 documented deaths that we know of from kernicterus. As we know, they don't do routine autopsies on newborns, so we don't really know the full number, but we do know that 6 have died in that same period of time.

So, why is it more important to focus on lead, and not kernicterus? I think we need to raise the level of awareness on the toxicity of kernicterus, it hurts babies. Also, the CDC has announced or they have determined that BLLs over 80 can cause hearing loss and brain damage.

So, as a response to that, the HHS's

Healthy People 2010 Initiative has set a national goal of eliminating BLLs in excess of 10, a level far below the danger zone.

This illustrates the need to institute a goal for eliminating bilirubin levels over 20 when exchange transfusions and vigilance in testing were used and kept bilirubins below 20 historically, kernicterus effectively disappeared.

I want to tell you a little bit about my son Cal. He is a bright and happy little boy. He loves Pokemon. He loves playing with his sister. When asked what he would like to do when he grows up, his answer is to be the best daddy in the whole wide world.

He also aspires to be a film maker. Sadly, however, Cal is trapped in a body that simply doesn't work. He has athetoid cerebral palsy. He has uncontrolled movements of his arms and legs. He can't walk. His speech is very impaired. He has neurosensory hearing loss. His eyes crossed when he was 10 months old that were surgically repaired. His front teeth have enamel dysplasia problems. He drools. When he gets sick, he is reduced to the functional level of a 6-month-old.

Cal can't go potty by himself. He is not invited to birthday parties. He can't tie his shoes. As a matter of fact, I don't think he can even itch his head.

I have titled my presentation Warning, Bilirubin is a Toxin: Who is Keeping Newborns Safe From the Hazards of Jaundice? I chose this title because, like the visiting nurse was saying, parents have no clue that bilirubin is a toxin and that parents are totally unaware that this could hurt their baby.

When we get a toy, when we get a package, when we get wrapping paper, when we get tape, when we get household products, when we get shampoo, they all say warning, this could harm your baby. Why babies don't come with this warning tattooed on them?

I ask you who is going to keep our babies safe from the neurotoxic effects of jaundice. I am afraid that the answer right now is nobody.

I mentioned that after the AHRQ testimony, USA Today did an article on primarily my son, but how two medical errors had affected our family. It was that day that I was called by several families throughout the United States thinking they had the

only child with kernicterus. As a matter of fact, I got a call from a daddy from a NICU in Alabama. It was 9:00 a.m. in the morning, I had just got this paper out, and his daughter was in the NICU with a bilirubin of 33.

USA Today got such read response that they issued this within 10 days, and they interviewed other moms about their children and their brain injury. As a matter of fact, the day that this came out in USA Today, 6 of us moms were on a plane headed to Chicago to meet each other, and we actually attended an AAP preconference workshop on hyperbilirubinemia and kernicterus.

When we were there, we decided this was an emergency. We met two other families with children with kernicterus while we were there. So, we formed PICK, Parents of Infants and Children with Kernicterus.

We recruited the nation's top bilirubin researchers. We developed a mission objective, a timeline. We actually kind of launched it like you would a small business. This is our web site which is being updated actually today. That film that you saw will be on our web site. There is going to be an interactive nomogram and stories about

children who suffer brain damage from kernicterus.

We hosted the first parent health care workshop that some of you in this room were at. The moms invited all of the HHS agencies that we could think of along with researchers, Boston Children's Hospital, Harvard School of Public Health. We showed them the problem. We showed them videos of our kids and their medical records.

We proposed a solution by the researchers, that was a universal systemwide approach to make sure all babies received the same level of safety. We thought by the implementation of a universal bilirubin screen, the use of the nomogram was the first step.

The Joint Commission within two months issued a sentinel of an alert. USA Today again issued another article. CDC, a month after the Joint Commission issued their alert, issued an MMWR on the return of kernicterus, and the National Quality Forum, if you are familiar with them, they issued a list of 27 adverse outcomes that should never happen in the United States, and PICK campaigned for kernicterus being one of them, and it is the only pediatric issue that made the list. They defined kernicterus as damage from bilirubin

or bilirubins above 30.

The Boston Globe covered this, as well, and several other periodicals and magazines and newspapers.

I wish I could tell you that Cal's story is unique. I wish I could tell you that he has the only case of kernicterus in the United States, but the tragedy is that Cal's story is not, as you know.

When I met the moms all in Chicago when we formed PICK, we realized that our stories were all the same. Our newborns left the hospital well babies without a bilirubin test, just like 80 percent of the babies in the pilot registry.

We were told not to worry, we were told that this was normal. The parent education consisted of a handout put in the diaper bag. All of our children of the original six PICK moms were born in large, accredited JCAHO-accredited hospitals with NICUs. Most of the pediatricians that managed our children's bilirubin were AAP fellow and board certified.

The moms that I know, we all questioned our babies' symptoms - the lethargy, the poor suck. We even took our babies to pediatricians and to the

hospital. We categorized unfortunately as over-concerned first-time mothers.

I am going to go off on a tangent because people earlier were asking question about cost-benefit, and I want to share some numbers with you. When we met with the government agencies, we did our own analysis, and actually we did an analysis on the cost-benefit of testing all babies, doing a bilirubin test that costs around a dollar. It may vary per institution.

The cost of kernicterus is staggering, as you heard. My son's life care plan--and this is without fluff--this is without powered chairs and remodeling my home to accommodate these, is $10 million, and that is because my son needs attendant care. All of these kids will need attendant care for their lifetime.

In 1998 dollars, for attendant care for a certified nurse assistant, that was $7 million right there. Now, some of those kids you saw up there are on feeding tubes, they are on baclofen pumps. They aspirate, they have to be suctioned. They are on massive doses of drugs. They need R.N. care, and those kids' life care plans are $25 million.

The cost of phototherapy to our nation, if you go to the AHRQ Hospital Care Utilization Project, HCUP, or is it the Health Care Utilization Project, they can give rough numbers. It is not perfect data. But the amount is what is billed to patients. Phototherapy, they showed I think it was '98 or '99 numbers, around 100,000 kids, primary diagnosis, this is primary diagnosis, so other kids are coming in septic or other problems, primary diagnosis was hyperbilirubinemia, around 100,000 kids at a cost of approximately $700 million a year. That is not cheap.

Our children, the public school system, Cal, in Idaho, instead of $50,000 for his education for 12 years, will cost the education program half a million. So, you can do the math, because they have to use special bus transportation, special ed., physical ed., there is therapists, assessments, they are very expensive children. As a matter of fact, they rate, I think the highest that the CDC does on the economic burden of disability, our kids are the most expensive.

You saw the partnerships that we have formed. NIH, March of Dimes, Healthy Mothers, Healthy Babies have joined us. Of course, our

mission is to prevent kernicterus. In analyzing and just knowing all the moms and kids with kernicterus, we are concerned that this is not going to disappear with the status quo.

The AAP still recommends visual assessment of jaundice. This is guesswork. And their guidelines unfortunately are not followed. I mean Tom mentioned that study he did I think on phototherapy, that of the kids that the AAP recommended phototherapy, 55 percent didn't even get it.

So, although the guidelines went through a very long thought process, pediatricians simply do not follow them, and to change doctor behavior will take decades. Bilirubins are not routinely taken. Neonatal blood type and Coombs are no longer done or they are no longer the standard of care.

Home Health, to be honest, is disappearing because of financial constraints. Timely post-discharge follow-up doesn't happen in the real world, and kernicterus cases are not being reported because of gag clauses, like it was alluded earlier that kernicterus unfortunately ends up in litigation, and parents and doctors are gagged quite often to come to a settlement.

Our littlest citizens are being harmed by the subjective and unscientific approach to jaundice management. Guesswork must be eliminated. Our systems-based approach must be implemented. Right now in the United States, any newborn is still at risk of developing kernicterus. Newborns are not safe.

Who is responsible for that? Nothing has happened since my son was injured. A reporter asked me, well, what did I expect. I expected all hospitals to stop everything they did, implement a universal screen, implement something like an aircraft would do if a 12-inch screw was found faulty, they ground all planes, they change it, the public is safe. Eight years later, nothing has happened.

All 50 states routinely screen for PKU and hypothyroidism. Babies are screened now for their hearing. Why aren't we screening babies, why isn't there a universal screen for bilirubin? How many tests must be done to prevent that one case of kernicterus as some of the data showed? I think it's a disturbing way to look at how we need to prevent kernicterus, to be honest. All of them is the answer. We need to screen all of them.

I recently read an article in Public Health entitled "A Conversation on Medical Injury." It said that to trigger the level of reform that is so clearly mandated here, we cannot rely on the healthcare professional or stakeholder organizations. We, the public, must demand it.

As parents of infants and children with kernicterus, we accept this responsibility. We accept this responsibility to partner with you and to trigger the reforms necessary to eradicate this. We ask the same of you.

We, the parents, unite to prevent kernicterus. We unite to demand national implementation of effective understand management standards, policies, and interventions to prevent what has happened to our babies, and we unite for a call to action to keep our newborns safe from the toxic hazards of bilirubin.

I am going to start showing you a list of children in the pilot kernicterus registry. They are not anecdotes, they are our children. I cannot say with any certainty how many more suffer in darkness because their condition was never diagnosed.

I speak for the parents of the 125

identified in the pilot registry at Pennsylvania Hospital. I speak for the parents of the countless children who have remained undiagnosed and for parents of unborn infants who will soon be diagnosed with kernicterus, but most of all, I speak for the children with kernicterus, who are prisoners of their disabled bodies and cannot speak.

As you deliberate tomorrow, I hope you will be inspired by the mission of HHS, particularly the part about protecting those unable to protect themselves. You and your sister agencies have a remarkable history of protecting children from other hazardous products and substances.

The time has come to apply that same commitment to protecting our babies from the hazards of jaundice. As you read this list, I appeal to you please do not attempt to minimize the occurrence of kernicterus. We do not know.

Please do not attempt to minimize the human devastation or the financial impact that kernicterus has on babies, families, and society. Please provide the same level of safety and protection that you would with other toxins and

hazardous substances and commit to putting kernicterus back in the history book where it belongs.

I challenge you to ask yourself when you meet tomorrow would you allow your own newborn's bilirubin to exceed 20? Tomorrow will be a big day. You will be making significant choices regarding jaundice management. I ask that you put the newborns' safety at the top of your list, dismissing the status quo, personal agendas, professional aspirations, and cost-cutting mandates from employers.

Statistically speaking, what is statistically significant when it comes to a human life? What is more important than the safety of a newborn?

I close my remarks with a reflection of the wisdom of a child. But who knows you have the power to protect others, he said, quite simply, like you saw on the film, prevent this. I have to tell you that I was there during the filming, and the producers simply asked Jess if he had anything to say to the world, what would you say, and that was his remark. It was totally unsolicited, totally unplanned, but straight from his heart.

So, in looking at these names and these numbers, or not the names, numbers, I ask you how many more names do we need before we take immediate sweeping dramatic action.

Thank you.

DR. CHESNEY: Thank you very, very much. You made many, many points for all of us to consider and reconsider.

Our next speaker is Dr. Marshallyn Yeargin-Allsop, who is a medical epidemiologist with the Center on Birth Defects and Developmental Disabilities at the CDC. She is going to describe for us the CDC's kernicterus surveillance activities.

Kernicterus Surveillance

DR. YEARGIN-ALLSOP: Thank you very much for the opportunity to update you on CDC's activities in the area of kernicterus surveillance. I have heard Sue speak a number of times, and she is a tough act to follow.

[Slide.]

I would like to just present an overview, a framework, a public health framework for developmental disability surveillance because surveillance of kernicterus is put into that

framework of what we do in the area of developmental disabilities.

The first step in this process for us is to develop population-based surveillance systems, and the purpose of those systems is to monitor prevalence rates, trends, and prevention programs.

The surveillance systems can also provide a registry of cases, and these cases can be used for the purposes of service provision or provision of treatment. The cases from the surveillance system can be used, as well, to create epidemiologic studies, studies where the cases are compared to non-affected children or controls in order to identify risk and protective factors and the results from the epidemiologic studies can address public concerns.

An example would be looking at whether there is an association between maternal smoking and mental retardation or cognitive impairment in the children.

The third step in this process is to design prevention programs, and these programs promote health education and prevention strategies and also inform public policy.

[Slide.]

I like to compare the complexities of surveillance of kernicterus with the complexities of surveillance of developmental disabilities, and we have about a 20-year history at CDC beginning in the early '80s. We were looking at the establishment of surveillance for a number of developmental disabilities, so based on our 20-year experience, we think that we can speak well to the complexities, as well as the challenges of developmental disability surveillance.

The first point is our surveillance is based on outcomes that describe functioning in children. However the case definitions and the conditions are attributable to an impairment in physical, cognitive, speech or language, psychological or self-care areas. So, we have this comparison of functioning with a level of impairment.

The second point related to the complexity is measurement issues. For example, we look at surveillance of mental retardation, and our case definition for mental retardation is an IQ test score based on a standardized test.

Now, that is objective criteria that we used, but we also do surveillance for autism, and

when we look at autism, we are looking at a range of behaviors, so we have more subjective criteria that may be implemented in order to look at surveillance of autism. The behaviors are based on the DSM-IV criteria from the American Psychiatric Association.

So, the point is that measurement issues are not straightforward when we are looking at outcomes related to developmental disabilities.

Our surveillance in metropolitan Atlanta is population based, and we have tried to implement this in other areas of the country, as well. That means that we define a geographic area and we try to count every case within that geographic area.

Although there may be some limitations of that, we feel that our population-based surveillance has been informative, such as the prevalence rates of autism that we just reported, and it is viewed as a landmark study because we don't have any other population-based data from the United States.

In summary, all of these issues can make generalizing results from our population-based surveillance system difficult or impossible to interpret, so we always issue some caution we are

trying to generalize from limited population-based data to say national figures related to prevalence.

[Slide.]

Let's look at the complexities of kernicterus surveillance and how they might be similar to surveillance for developmental disabilities. Kernicterus presents as a range of impairment and associated conditions. Kernicterus is defined as brain damage that is associated with athetoid CP, hearing loss, vision impairment, dental dysplasia, and sometimes mental retardation.

As we have heard and as we are probably aware, there have been changes in the level of awareness and the use of the diagnosis over time. We believe that some of the younger physicians may not have ever seen a case of kernicterus and may not be aware of the dangers of high levels of bilirubin in terms of causing brain damage.

There is also variability in how cases of kernicterus are diagnosed. We don't have a gold standard in terms of the number of physical findings or the number of behaviors, the number and the pattern that are necessary to establish a diagnosis of kernicterus, and that means a clinical diagnosis of kernicterus.

Of course, there is early onset, but often the diagnosis is delayed because these features appear over time.

[Slide.]

From a historical perspective, there has never been any systematic population-based surveillance of kernicterus in place to monitor kernicterus or hyperbilirubinemia. Sue said it best. We don't know the prevalence of kernicterus in this country.

We do have some case reports from convenience samples or select populations, such as from select hospitals, self-reported cases. We have information from medical insurance records, but these do not represent a systematic approach to looking at the prevalence, and there is no accepted standard for surveillance definition, such as what would the cutoff be for surveillance of kernicterus.

[Slide.]

Therefore, a true population estimates are not known to date. We do have I believe now it is more than 100 cases reported from 1984 to I think January of 2002, and these are case reports from a convenience sample. They have been very

informative. These are numerators, they do not have denominators because these are children of different ages from different geographic areas, and therefore, we can't really attach a rate to the cases that have been identified. So, we can't really answer the question of whether kernicterus is on the rise.

[Slide.]

In summary, we have issues related to the case definition of kernicterus. There is debate about what an appropriate cutoff would be from an epidemiologic standpoint. It is a low prevalence condition, however, it would require a substantial population in order to detect cases.

There is a lack of recognition because it's an acute event with specific features, but the permanent damage and the long-term clinical features do not appear until sometimes even years after the insult, and also the litigation may be a possible deterrent for clinicians identifying cases.

[Slide.]

So, what has CDC done in this area? Well, as Sue pointed out, there was a call to action from PICK. In early 2001, there was a meeting and CDC

was invited to participate, and we became aware of the problem of the reemergence of kernicterus.

When we left the meeting, we thought that we could go back and establish the prevalence of kernicterus looking at some existing datasets. So, our first look was looking at the national hospital discharge data, and we looked at years 1989 to 1997, and although there were many children with codes of hyperbilirubinemia, there was no way to distinguish between those children who had severe hyperbilirubinemia from those milder cases. We also found that kernicterus codes were not readily used in that we found no cases of kernicterus when we did our initial look at data from the national hospital discharge data.

We have an existing surveillance system in metropolitan Atlanta. It's the Metropolitan Atlanta Developmental Disabilities Surveillance Program. We looked at our data, and we looked at cases of athetoid CP. I think we identified eight cases, and none of them seemed to have an association with high bilirubin levels from our record review.

We explored the opportunity to make kernicterus a reportable condition. We found out

it is the Council of State and Territorial Epidemiologists that is responsible at the state public health level for determining what conditions are reported to CDC and therefore that we get national data.

We think that maybe our approach to them was a little premature because we didn't have a case definition, so since there is not agreement among the experts as to what an appropriate cutoff would be for reporting cases, we were not able to make kernicterus a reportable condition, and that is something we hope to do in the future.

Our last attempt was to go to an organization of managed care organizations and to say that if we developed a cooperative agreement, perhaps some of the HMOs would be interested in looking at the rate of kernicterus within those HMOs. I will just say that there was a limited interest.

[Slide.]

But the good news is we have a mechanism at CDC that allows for extramural opportunities for research, and through that announcement last year, we are able to look at kernicterus in two areas of the country.

The objectives of the announcement were that: applicants should seek to review cases of extreme jaundice in otherwise healthy full-term infants; provide a body of evidence to inform why cases of extreme jaundice may lead to kernicterus and why kernicterus may be re-emerging; to provide a forum of concerned scientists and healthcare professionals to convene and develop a strategic plan for a national kernicterus prevention program.

[Slide.]

Our awards went to the University of Medicine and Dentistry in New Jersey, the Robert Wood Johnson Medical School, and their objectives are to look at infant mortality and morbidity related to kernicterus, to design a surveillance system for kernicterus, to identify risk factors for kernicterus using a case control methodology, and using this to focus on early identification and management of hyperbilirubinemia, and to provide a support network for families affected by kernicterus.

[Slide.]

To date, they have submitted requests for IRB approval for their activities. There has been initial discussion and a process for

population-based surveillance with the New Jersey Department of Health, and they have analyzed some data on infant morbidity and mortality due to kernicterus.

They are allowing me to share with you some preliminary results from their look at kernicterus morbidity. They used New Jersey hospital discharge data for 1992 to 2001. They identified 82 cases of kernicterus. The denominator is the entire State of New Jersey, so this is population based, and their rate is 7.5 per 100,000 live births. That is their cumulative incidence.

They noted that there was significant variation by race and ethnicity with the lowest rate being among Hispanics and the highest rate among Asians.

[Slide.]

Our second award went to Pennsylvania Hospital, the University of Pennsylvania, and they are partnering with PICK, and their objectives are to establish surveillance, and their surveillance activity is related to analysis of the pilot study data that you have all heard a lot about today, to identify risk factors for kernicterus, to establish

a Prevention Task Force or Steering Committee that would advise on the management of hyperbilirubinemia and to launch a national prevention campaign.

[Slide.]

To date, Pennsylvania Hospital has had a teleconference of their Advisory Board. They met along with our other grantee and with CDC to begin to develop a consensus on the definition of kernicterus for public health purposes.

They are current establishing the database that would allow them to systematically report results from the pilot study, and with PICK, they have collaborated on the educational video, and you saw part of the video just a few minutes ago.

[Slide.]

In terms of future direction from the CDC perspective, we are always looking to partner with others in our goal on elimination of kernicterus and raising awareness of this as a public health problem.

We are planning a forum for developing consensus on a surveillance case definition, and the goal of that is to identify a mechanism for population-based surveillance at the state level,

as well as at the national level.

[Slide.]

I would like to thank Dr. Rachel Afgen, who is our point of contact for our kernicterus activities at CDC, for our collaborative partners, as well as our other partners, and for all of the children and families that have been affected by kernicterus.

Thank you.

DR. CHESNEY: Thank you very much.

Our next speaker is Dr. David Stevenson, who is the Harold Faber Professor of Pediatrics and Senior Associate Dean for Academic Affairs at Stanford University Medical School. He is going to review for us the metabolism of bilirubin and the metalloporphyrin heme oxygenase inhibitor drug class.

Metalloporphyrin Heme Oxygenase Inhibitors

DR. STEVENSON: Thank you very much.

It is a pleasure to address you, a little bit different than the last two presentations, but hopefully, this will add to the information that will be of use to people this afternoon and tomorrow.

[Slide.]

Let me begin by giving a quick primer on neonatal jaundice. This is a favorite slide of mine and some of my colleagues in the room have seen this many times, but it is a very useful way to begin this kind of discussion.

Neonatal jaundice can be understood by analogy to a sink. If you let the processes of bilirubin production be represented by the turned on spigot and the processes of bilirubin elimination be represented by the drain, then, you can understand the problem of transitional jaundice as a problem of an imbalance, and if the rate at which bilirubin is produced exceeds the rate at which bilirubin is eliminated, then, the level in the sink begins to rise.

This is exactly what happens in period of time after birth. If there are relative increases in bilirubin production or relative decreases in the ability to eliminate bilirubin, then, you can exacerbate that normal transition, and it is just about that simple in terms of the physiology although the biology is fairly complex controlling these processes. So, neonatal jaundice is a normal transitional phenomenon.

[Slide.]

The turned-on spigot can be represented by this cartoon of the reactions that are involved with heme catabolism. Some of the most important early work on this biochemistry was done by individuals like Dr. Kappas, many others before me.

But this is a very ancient system in nature. It is present in both plants and animals. It is a process which is probably essential to life on this planet, that is, life making use of oxygen and exposed to light.

It's a two-step process. This is a cartoon because there are many more oxidations and reductions that take place than represented in this slide.

The first step is the rate-limiting step in the process. It is catalyzed by heme oxygenase and involves absolute requirements for oxygen and for NADPH, which is donated from the cytochrome p450 system.

In this first step, the alpha-methene bridge is broken, carbon monoxide, a trace volatile molecule is produced equal molar amounts with biliverdin and iron, the latter of which is recycled.

Biliverdin is reduced in the cytosol. The

other reaction takes place at the microsomal level. Biliverdin is reduced in the cytosol again with absolute requirements for NADPH and biliverdin reductase to bilirubin, so there are actually equal molar amounts of bilirubin and carbon monoxide which are produced.

Historically, carbon monoxide and bilirubin have been thought of as waste products, but as it turns out, every part of this reaction probably has some relevance in normal biology, just to put it in context.

[Slide.]

The point that I would like to make is that all substances are poisonous. Only the dose differentiates a poison from a remedy, and we have had some of this discussion earlier today, but it is an important point to make. It does not lessen the importance of understanding, but a compound can be toxic under certain conditions that we encounter clinically.

But it is also important to remember that some of these compounds like carbon monoxide, which I have used as you will see as an index for production of a pigment because it is produced in equal molar amounts, bound to hemoglobin,

circulates in the bloodstream, and is continuously excreted in your breath, so it is a window on endogenous CO production which mirrors bilirubin production.

We have to remember that CO is also an important biological signaling molecule, and a lot of people are now investigating its role in neurosciences and vascular sciences.

[Slide.]

They are doing that because of the fact that, just like NO, it can interact with guanylyl cyclase and activate CGP to cyclic GMP and have a whole host of important cellular functions.

The relative potency of CO for doing that is much less, but the potential for the body to make CO is much more, and I will make a comment about that later, as well. So, even this part of the biological system is important to understand in terms of the spigot which produces carbon monoxide, biliverdin, and then when the second step goes to bilirubin.

Also, it needs to be understood that carbon monoxide may be involved in the inhibition of other enzymes with iron/sulfur centers, so its impact on other aspects of metabolism needs to be

understood, so even the CO that is produced and is excreted at a cellular level, it may have a very important role biologically, just like bilirubin which can serve as an antioxidant in the intracellular environment may be involved with maintaining the redox state of the cell and even in regulation of gene expression.

[Slide.]

So, my world has gotten more complex. Most people think of me in terms of bilirubin, but I have become increasingly interested in carbon monoxide, and you will see the reason for making these comments at the beginning because it has relevance to what I will be talking about primarily, which will be the metalloporphyrins.

The main reaction we have been talking about is this one right here, down in the middle, where heme is catabolized by heme oxygenase. As you can see already there, there is an indication that the metalloporphyrins have the potential for acting as competitive inhibitors and can block that first step, thus putting our hand on the handle of that biochemistry, and they can do that very efficaciously.

The CO is produced, bound in blood, and

then excreted in the breath, and you can measure either as a continuous excretion rate or as an end-tidal carbon monoxide concentration, corrected for the ambient exposure. This is all quantitative and mathematically related, so they are good indices of what is going on.

But you can see all the other possible sources. The two I will bring to your attention, one is light, light actually can cause photo-oxidation as you have heard, and one of the products is carbon monoxide. Also, lipid peroxidation is another source of carbon monoxide. Both of these can occur in the absence of heme. So, that would be a confounding event for some of the things that I might be interested in measuring in the newborn period.

[Slide.]

Fortunately, the endogenous sources of CO are well understood, and this goes back many years, and many people besides me have looked at this, but heme degradation in the newborn period under most of the conditions that we encounter, particularly in the kinds of babies we have been talking about today, most of the sources of CO comes from heme degradation.

So, from the senescent red cells, it is about 70 percent of that 86 percent, or from ineffective erythropoiesis approaching 10 percent, then, other hemoproteins around 21 percent.

You can imagine what hemolysis does to these relative percentages, because if you have an increased rate at which the red cell mass is breaking down, you will have marked increases in bilirubin and carbon monoxide production. You can see that quite nicely.

There are non-heme sources of carbon monoxide, as I mentioned, but they are not really of great consequence for these estimates that we are making. Remember, the CO in the breath is an index of bilirubin production, it is not a direct measure of the production because it includes these other sources.

Lipid peroxidation and photo-oxidation are variable in their contributions, but on the average contribute roughly that amount, and they are really important in conditions that we encounter in smaller infants where proportions might become greater, and this would become a more important source to consider under those circumstances.

We were the first really to demonstrate

those independent sources of CO in these heme-free environments in vivo and in vitro.

[Slide.]

We have been measuring carbon monoxide excretion rates in animals for literally the last two and a half decades, and this shows you some of the systems that we currently use for rats, mice, and monkeys, so we do larger animals, as well, again mainly for the purpose of looking at bilirubin production under a variety of conditions.

[Slide.]

This is a typical diagram of a system that we would use. This is a rat in a collection system attached to a reduction gas detector which can measure CO in parts per trillion, and this technology actually allows us to adapt these measurements to development of a new hemoxygenase assay which is now used by many people, a gas chromatographic assay using that kind of detection system. Also, we can measure over small numbers of cells and tissues, which allows us to extend the work into those model systems, as well.

[Slide.]

We will point out something which is important for the presentation this afternoon.

This is one of the earlier experiments that I did literally almost 20 years ago. It is the percent recovery of injected heme over time as carbon monoxide. Percent of recovery of heme is along the y axis and the time is on the horizontal axis.

You can see that when you give a known amount of heme as damaged red blood cells and then sample the breath over an interval of time, which in this case was about 8 to 12 hours, you can collect 100 percent of that heme as CO produced. This is the most valid and accurate way of assessing in vivo hemolysis that exists.

This is a little bit of history here. That gap in the data is just because we used to have hand cranks and I had to run down the hall to a bathroom, and I didn't get back in time for that crank. Now it is all automated, so we don't have to worry about those kinds of things. But this validated this approach in this system.

[Slide.]

We also devised systems early on for studying human neonates. This is a big system for a baby, so babies were in the same kind of systems as the smaller animals, and we were able to do large numbers of studies. So, this is the way the

world has looked to me for over two decades.

This world can be seen even before someone becomes jaundiced, and the points I will make here are some important ones in the context of this discussion and about the compounds that we are going to be talking about.

This is the adult. This is the term infant. This is the excretion rate of carbon monoxide on a per kilogram basis. You can see that all term babies on the average produce about 2 to 3 times as much bilirubin on a body weight basis compared to an adult.

So, increased bilirubin production is in the background of all the different patterns of jaundice that we see including pathologic jaundice in the newborn period. That is an important concept to remember.

It doesn't mean that everybody who has increased production, relatively speaking, is going to become jaundiced, in fact, many people are able to conjugate well, so they avoid that circumstance. So, it is not the best predictor, as you have heard Dr. Ip talk about when you use it in isolation, but it is the best way to understand what is happening with respect to an individual's biology.

This is what a hematoma does, polycythemia, so a larger red cell mass breaking down at a normal rate. Smaller preterm infants, they have shorter red cell life spans and have increased production rates, so increased production is a part of the near-term infant problem with jaundice. Here is your infant of a diabetic mother. That is probably ineffective erythropoiesis most of the time, sometimes polycythemia.

Here is your ABO hemolytic disease and your Rh disease in which you see the most brisk hemolysis.

So, you can see all these things even before someone becomes jaundiced, usually by about 12 hours of age with this current technology, or in a jaundiced infant, you can know whether an increased production is a contributing cause to that problem beyond what is normally the case in every baby.

[Slide.]

We have simplified the technology and have shown that rather than having to do things in those big chambers, which were quite cumbersome and had to have drills to get the kids out and things like

that, which was pretty challenging, but you can now do automatic end-tidal sampling corrected for the ambient, and you can see a very good correlation with the standard index, which is the carboxyhemoglobin level measured by GC.

[Slide.]

This just shows you in a recent publication that we did, and this a part of a multinational, multiethnic study in which some people in here also participated. This is what the distribution of carbon monoxide production looks like as indexed by the level in breath, so it is a mirror of bilirubin production, which is what you are looking at, at about 30 hours plus or minus 6 hours.

You can look at a group of individuals, and this included children with hemolytic disease--there they are out there--you can identify the high producers of the pigment quite easily. If you wanted to, you could arbitrarily say, well, the part of the population that is of interest to me, if they are having trouble with bilirubin, is the part of the population that is, let's say, 3 standard deviations above the mean or something of that sort, so you can actually look at production

as a way of targeting your population, but remembering that all babies have increased production to a certain extent.

[Slide.]

Then, you can look at this in the context of the nomogram that you have heard so much about. We were recently looking at the same multiethic, multinational study, and we have now learned that on the average, since there is general impairment and conjugation in the period after birth, that these percentiles in the nomogram are, in fact, informed in part by production rates.

So, if you look at the average end-tidal carbon monoxide concentrations in the different percentiles, you will see that they go up as you go up in the nomogram. The babies that we haven't talked a lot about are the ones who are already outside the nomogram early on, and they have increased production.

In other children who are still within the nomogram and you have a hard time figuring out what is going to happen with them, you can identify some of them who may or may not have problems, but you will at least know who is hemolyzing, and they will go out sometimes later.

Then, you have kids who have normal production rates and tend to go out much later, and those are your poor conjugators, those are your Gilberts and your G71R mutations in the Japanese and other Asians.

So, combining the information about production, which reflects what is happening with the hemoxygenase in a person's body and the relative breakdown of heme, with how a baby is actually performing with respect to that challenge, can provide you with a lot of important information.

[Slide.]

That is the background which establishes the rationale for what Dr. Kappas and Dr. Drummond and Dr. Valaes, who helped him later in that series of investigations ultimately involving human neonates, that was the rationale for getting a handle on that spigot.

There has been no question that over the last two decades with a tremendous amount of systematic and exhaustive and very thoughtful work done at Rockefeller and also over the same period of time after we were introduced to this area of biochemistry at Stanford, we have been able to

clearly establish the efficacy, and much credit goes to Dr. Kappas and his group for making that original observation and confirming it over many, many studies, in vitro animal studies and ultimately human investigation.

What you are doing when you block the step here is you are inhibiting the production of carbon monoxide and bilirubin, and that is what we need to remember.

[Slide.]

If efficacy is easy to establish, choosing the right drug has been a part of that challenge. Of course, the choice has been made, and it has been made for a lot of good reasons, and some of those, Dr. Kappas and others may want to comment on. It is clearly the most potent of the potential drugs, and thereby can avoid perhaps many of the other potential side effects of these drugs by using a much lower dose.

But the thing to see here is there are many options. Most of these are inhibitors of hemoxygenase, and they differ by virtue of their substitutions on the porphyrin macrocycle and the different metals in that ring, and it is hard to predict how they are going to behave with respect

to their various properties, but without actually evaluating each of them, there is no easy way to get a relationship between the structure and their activity at least chemically.

[Slide.]

One of the first things, of course, you have to ask, and I will just show this again. The Rockefeller group showed this, as well, and we did it after them. This was cannulation of a bile duct in an infant treated with one of the first drugs that was tried clinically, tin protoporphyrin, which was much less potent than tin mesoporphyrin, and the thing that I have been asked over and over again, and Dr. Kappas has probably been asked this, as well, don't you just accumulate large amounts of heme.

What happens is you convert to a circumstance where heme is excreted in bile in approximate proportion to the degree of inhibition that you get, so you are not going to accumulate heme in the body, at least in the aggregate.

There may be transient elevations in specific tissues, but overall, this is not a heme accumulation problem. This is, in fact, a way to eliminate heme from the system and also iron if you

were to give dosing over a long period of time, but, of course, what is being proposed in this circumstance is single, low-dose intervention, so iron loss would not be a consequence of that kind of approach.

This shows you how quantitative these kinds of approaches can be. It was done in a rat model in the system that I showed you earlier. So, this can be molar accounting for these two compounds.

[Slide.]

There are some other effects of the metalloporphyrins. I am not going to review these in a lot of detail, but I will mention them. We have been able to show that some of these metalloporphyrins can inhibit lipid peroxidation. Depending upon the dose, many of them can inhibit nitric oxide synthase and cyclic guanylyl cyclase, but if the dose is low enough for some of them, then, you can avoid that and they can become much more selective with respect to their impact on hemoxygenase.

Photo-oxidation has been something that has challenged all of us, and I think led to the decision to use the more potent tin mesoporphyrin

compound compared to the tin protoporphyrin compound because you can get it down to a level where it will not have those kinds of reactions or at least the chances for anything like that happening will be minimized.

[Slide.]

So, this is what we are talking about. A lot of these porphyrins can be excited by light interacting with oxygen to generate singlet oxygen, and singlet oxygen, of course, is very reactive. It can cause cytotoxicity and damaged cell membranes. No one wants that to happen in this circumstance. These compounds can be used in other circumstances to take advantage of this part of their electrical behavior.

[Slide.]

So, we have established criteria for potential antihyperbilirubinemic drugs in this class, and the approach that we have taken is that we can't fulfill all of these, no drug does that, but the idea would be that you would identify a compound with a biocompatible central metal, potent hemoxygenase inhibition, that is the primary feature, negligible degradation, which sort of goes with that, negligible photoreactivity, and

negligible HO-1, which is the inducible form, up-regulation of that gene.

[Slide.]

So, our approach has been in a four-step approach. My intent here in this is not to go over a lot of the systematic and exhaustive amounts of data that we have produced for these many different compounds, but just to give you a sense of how this approach is undertaken and then sort of give you a summary at the end of where I think we are.

The first is in vitro screening in two parts and then followed by in vivo screening. So, the first part is really the screening for HO inhibition, degradation to CO, that is, how do these things serve at all as a substrate for the enzyme, which you would not expect if they were good inhibitors since this is a competitive reaction, and then their photoreactivity.

[Slide.]

So, here is just an example of the kinds of data that we can get. Again, in some of these slides, the compounds are not always the same because we were doing them in different batches, but here is the natural substrate heme, and you can see the amount of HO activity when you administer

the substrate, and you can see that for tin mesoporphyrin here, the second one in, it has marked inhibition.

This is a single high dose, so you aren't able to discern among the different compounds at a high dose like this. A later part of the testing will allow you to look at a range of dosing, but just to screen for their potential as inhibitors.

You can see the naturally occurring zinc protoporphyrin, which is probably the least potent of these compounds, but naturally occurring, and then another example which we will track through in a few things, chromium mesoporphyrin, because it has some interesting properties, but you can see that we can easily see if they are serving as competitive inhibitors in this assay.

[Slide.]

We can also then quickly look to see whether they can be degraded by the enzymatic system, and again, these are slightly different metalloporphyrins, but some of the same ones are included here, and you can see that we can quite definitively demonstrate that they are not degraded, which means the ring is not broken and the metal is not escaping.

[Slide.]

Then, our photoreactivity determination is done using this assay. It uses cool white light at around 30 microwatts per centimeter. We take advantage of the fact that carbon monoxide is a product of photo-oxidation and we can actually look at the different metalloporphyrins in that context.

[Slide.]

The system looks something like this with the vials being on top of that, and then you can get a picture of how these compounds look.

[Slide.]

You can see here now important features which were a challenge for the Rockefeller group, but potency won out and they can avoid this kind of a problem. You can see the tremendous photoreactivity of the tin compounds with zinc mesoporphyrin being in this assay, more photoreactive, but the potency allows the drug to be used at such a very low dose that in vivo, that is not going to be of any consequence.

In this assay, zinc protoporphyrin also appears to have some photoreactivity in vivo, that has not been demonstrated, but there are some compounds that appear to be photo-inert, like the

chromium compounds, for example.

[Slide.]

Here is zinc bis glycol. This is a derivative of the naturally occurring zinc protoporphyrin since it's a synthetic molecule, and I show this just to show you how paying attention to these properties is important for picking a drug.

This is a very potent metalloporphyrin, as well, and like the tin compounds, it is also photoreactive, and you can see that in this in vivo testing with different concentrations of the drug exposed to light, you can see the mortality caused by these exposures, and you will see at these lower levels, there is no mortality whatsoever, then, there a sudden increase, and then over here on the end, this is in the dark, so it is the light impacting the interaction of this molecule in the presence of oxygen that can cause this kind of a problem.

This compound can also be used in the less than 5 range, so you can avoid that kind of toxicity in vivo. This compound has not been used in humans and is still being investigated in animals, but it has some other interesting

properties, which I will mention at the end.

[Slide.]

The second kind of testing is HO inhibition in a range of metalloporphyrins. Again, I know Dr. Kappas is going to say something about the tin mesoporphyrin itself, so I will show you another one.

[Slide.]

This is chromium protoporphyrin and chromium mesoporphyrin. You can see how in this assay, by looking at different doses, we can characterize the relative inhibitory potency of these compounds.

[Slide.]

We can also look at the potency of their inhibition against the two isoforms. The HO-2 isoform is the constitutive form, is not inducible by most of the ways in which we induce this enzyme, and then HO-1, the one that would be regulated by exposure to heme, and things of that sort.

You can see that tin mesoporphyrin is the most potent compound for both HO-1 and HO-2 inhibition, but there are some other ones that are right up near the top. Just for people's information, chromium mesoporphyrin and zinc bis

glycol are very important inhibitors.

Then, as you go down the list, they vary in their rankings depending upon the compounds. You can see zinc protoporphyrin, the naturally occurring metalloporphyrin, at the very bottom. It still is an inhibitor, but it is one of the least potent.

[Slide.]

The next thing we do is we test them in vivo, and this is an example of those kinds of experiments. This is the VeCO over time, the control animals at the top, chromium protoporphyrin and chromium mesoporphyrin. Both of these are done at 4 micromoles/kg, so very low dose, and you can see the relative increased potency of the mesoporphyrin, chromium metalloporphyrin here to inhibit bilirubin production as measured in the living animal.

So, for each of the metalloporphyrins, you can do studies like this and see in vivo that they are, in fact, doing what you want them to do. We also checked their tissues, and we can confirm the patterns that we saw in vivo in the tissues.

You can also do important things to look, like in this case, as it has been done by Dr.

Kappas at least for the tin compounds, we don't see any effect in brain, so brain stays out of the circumstance here.

[Slide.]

The last thing I want to show you is how we take it to monkeys. This was done for zinc protoporphyrin, which is the first one we worked on, the least potent of the compounds. Monkeys are just like people, they have relative increased production rates as babies. That is in the left sort of bar graphs. They have transient hyperbilirubinemia, and their hemoglobins are roughly the same as the adults, they aren't quite so different as they are in the human circumstance.

[Slide.]

This is what their pattern looks like. It is lower and it is shorter, but it is roughly the same kind of pattern, so they are a good model. If you give them undamaged red cells, you can look at a model which is almost identical to the child with increased bilirubin production from hemolysis, and then see how these compounds work.

[Slide.]

This just shows you how the least potent compound works. This is carboxyhemoglobin, an

index of bilirubin production on the left, saline in the yellow, erythrocytes that are damaged plus the solvent in the middle, and then erythrocytes plus the solvent and then 40 micromoles of ZnPP, that is 10 times the dose you would have to use compared to these more potent metalloporphyrins.

You can see the marked reduction in bilirubin production.

[Slide.]

Then, of course, bilirubin levels are not directly related to production rates, it involves conjugation, so it is not exactly as dramatic, but you can still see the overall impact on bilirubin in circulation in these animals in the hemolytic condition, so it is almost exactly like you would be encountering in the clinical circumstance.

So, this is a very good model for what you get when you use a drug like this to treat a human neonate who might have increased production of the pigment as a cause of their jaundice.

So, the efficacy has been very well established, and the potency of the current drug that has been picked is well established and very good, and it can keep you out of the range where it is going to cause other kinds of problems.

There are other options, other follow-through drugs if people were interested in developing such compounds.

[Slide.]

The final thing that we do is we do in vivo side effect testing for HO-1 regulation because we want to see if this impacts gene expression of hemoxygenase. Again, there are different ways to do this, but we decided to take advantage of a new technology which is in vivo bioluminescent imaging.

[Slide.]

Because light penetrates tissue and it can come out of tissues, this is an example of an internal light source, a firefly there on the right box in the upper part, but you can also take a promoter of interest, in this case, it was the HO-1 promoter, and basically create a transgene, the HO-1 luciferase transgene, and then under the right conditions have these animals report to you when their gene expression occurs. So, you can see the impact of these drugs on gene expression in living animals. It was one last check to look at safety issues.

[Slide.]

The way this works is you can either tag a cell or tag a gene, and you can image them. You can digitize, quantify, and archive, and people are using these kinds of things now for all kinds of developmental biology. It is perfect for gene expression, pick your gene of choice, and then build your transgene, build your transgenic model, and you can then look at gene expression in real time basically.

[Slide.]

The way this works is you get a reference image grayscale, collect in low light. You get a low light image with a pseudocolor generated by your computer, collected in a dark box. You can superimpose them and you can see where the light then emanates from the animal. There are now benchtop animal imaging systems for that purpose.

We use this system because I was interested in jaundice and the effect of these metalloporphyrins on the system. I used this system because there is tight regulation due to toxicity of carbon monoxide, iron, and bilirubin, there is tissue-specific expression, it is developmentally regulated, it is a key molecular target for therapy, and ex vivo assays are slow and

provide only a snapshot, so it's a better way to look at the biology.

[Slide.]

We built our HO-luc fusion and created our transgenic animals. This allows us then to also do an analysis of about how, in fact, up-regulation occurs mechanistically. You can look at the different things that might cause induction of that gene, and you can easily see your animals in these systems.

[Slide.]

This is from a homozygous mating. That is a heterozygous mating. You can identify your transgenic animals who make light in response to activation of their hemoxygenase gene.

[Slide.]

Then, we are able to study important phenomena like this one, this is an example. HO-1 transcription early in life in the brain. We can see that it has a developmental pattern. That is something important that we need to understand. We need to make sure that medicines like this don't alter those patterns in adverse ways.

We can confirm these reporting systems, these optical reporting systems with more

traditional approaches looking at protein levels in the brain just to confirm that that is happening. We can look at any tissue. I am just giving brain as an example here.

[Slide.]

Here is where we use it to look at the metalloporphyrins. So, there is zinc metalloporphyrin, tin mesoporphyrin, zinc bis glycol. You can see that there are differences in the activation or up-regulation of the gene in response to these compounds.

None of them are persistent. The tin mesoporphyrin response is slightly more protracted than, say, the naturally occurring zinc protoporphyrin, probably because it is a more potent inhibitor, but it is not protracted, and the zinc bis glycol has essentially no perturbation whatsoever in this gene regulation. Just to give you some examples of how this tool works for looking at the response of this.

[Slide.]

Using this kind of technology, you can begin to see the differences in enhancer involvement for that up-regulation, so you can see the differences between the compounds. There is

zinc protoporphyrin, the naturally occurring one, which is distinct and very different from the elements that are important for regulation of the gene in response to tin mesoporphyrin. There is cadmium chloride on the right side as sort of a positive control.

So, the gene activation by different metalloporphyrins differs in magnitude and involves different HO-1 promoter regulatory elements, which again might help you with some drug selection issues as more drugs are developed.

[Slide.]

The other thing we were worried about initially was that there might be an effect on gene programming. This is what cadmium had done. We had seen massive responses and up-regulation response to cadmium, and then it would dissipate and disappear like we saw with the drugs. Then, when we retested the animals, they had an attenuated response, so there was some kind of programming that was going on that the mechanism needs to be fully explicated for cadmium.

The preliminary work that we have done does not demonstrate, at least to this point in time, for the compounds that are being considered

for human use to have that kind of a programming effect, which I think is important information. That work is still in progress, but at least the preliminary information looks good in that regard. Another example of how we use this technology.

[Slide.]

So, here is my summary and my last slide. Tin mesoporphyrin, after a lot of very systematic and exhaustive studies conducted in vitro in animals and later in humans, is the drug of choice currently. It is very potent and at the dose that is being used can still achieve that kind of efficacy, and looks also that it can be used in a way to avoid a lot of potential problems.

It is a synthetic compound, it is non-biocompatible with respect to the central metal. It has very high potency which allows it to be used at a very low dose, and it is most likely not going to affect other enzymatic systems.

It has high phototoxicity, but that can also be avoided for the same reason. It is not orally absorbable although more recent information we have suggests that if you can bypass the stomach, it may be absorbable directly from the intestine, which would be a handy thing if you

package it the right way, and it is currently being used in clinical studies.

Just for some other reference points in terms of the things we have studied, and none of these have been used in humans yet, and haven't done anywhere near the amount of work that has been done on tin mesoporphyrin by the Rockefeller group, but there is a lot of information available.

Zinc bis glycol is a synthetic compound. It has a biocompatible central metal. It's a derivative of the naturally occurring zinc protoporphyrin. It has very high potency comparable to tin mesoporphyrin, very high phototoxicity comparable to mesoporphyrin, but it can also be used at a lower dose, and also can be shown not to affect the enzymatic systems except the one of interest, which is hemoxygenase.

This one happens to be orally absorbable, so just a small drop could accomplish what you want to do in the oral feeding.

Chromium mesoporphyrin is synthetic, has a biocompatible central metal. It is very high potency again, it has no phototoxicity, it is photo-inert, it is orally absorbable, and also may not affect the NOS or guanylyl cyclase systems.

Finally, the naturally occurring compound, not the greatest potency, but it does work and it also is metabolized. It has a naturally occurring and trace essential metal, moderate potency, very low phototoxicity to none in vivo, it is not orally absorbable however.

So, there are a lot of other compounds that I could talk about, but it gives you a good sense of how I look at this biochemistry, this developmental biology, and how it translates in terms of applicability to the kinds of choices that have been made by my colleagues and what other potential compounds might be available for what appears to be very powerful agents for controlling hemoxygenase and doing pretty much what they were designed to do, which is to get a handle on that spigot and control the production rate of the pigment.

I will just stop at that point and see if you have any questions.

DR. CHESNEY: Thank you very much, Dr. Stevenson.

I have been cautioned about the importance of a break, which I was willing to have you all work right through the break, but I have been

cautioned against that.

As I have to go upstairs and build a transgenic model, so I can give you a reporting system when I return, I think we should all take a 10-minute break. I hope this doesn't inconvenience any of those of you here for the open public session, but if everybody could be back in 10 minutes, we will pick up then. Thank you.

[Break.]

DR. CHESNEY: For the next hour we have our open public hearing. We have nine people who have indicated an interest in speaking. Just two issues. First of all, as Tom read at the beginning of the session, and I quote, we ask in the interest of fairness that any of you who are speaking in the open public hearing, disclose any current or previous financial involvement with any firm whose product they may wish to comment on.

The second point is that people in the open public hearing have been given different intervals of time to speak, and we would really appreciate it if you could do everything possible to stay within your time limit. We absolutely want to hear from everybody, and we want to get as much information out of today as possible, but if you

could stay as close to your time limit as possible, we would be appreciative.

Our first speaker is Dr. Attallah Kappas. He is the Sherman Fairchild Professor and Physician-in-Chief emeritus at the Rockefeller University. He is a leading authority in metabolic and genetic disorders, and I understand won the NIH's first annual award for excellence in clinical research.

Dr. Kappas.

Open Public Hearing

DR. KAPPAS: Thank you, Dr. Chesney, and I thank David for the elegant, extremely full and really beautiful review of the subject. It has, however, put me in a spot. He has covered the biochemistry of it from bottom to top, leaving the clinical part of it to me, and since I am not a pediatrician, that is not so easy a task.

I have had to cut and paste my presentation from a longer lecture because I had not been scheduled for this meeting until yesterday.

[Slide.]

For those who need addresses and so on, this slide.

My laboratory group has for 35 years focused its research on the biochemistry of heme and heme-dependent processes and on related clinical and pharmacological issues. Twenty-two years ago, we discovered the potentability of certain synthetic heme analogues to inhibit heme catabolism, and we have intensively examined the biological and pharmacological properties of those compounds since.

In the course of this work, my colleagues, principally Dr. Drummond, Dr. Valaes, and Dr. Martinez, and I developed an inhibitor which can effectively resolve, we believe, many of the ambiguities surrounding the problem of newborn jaundice.

[Slide.]

Heme conversion to bilirubin is catalyzed by two enzymes, the rate-controlling enzyme is hemoxygenase. Newborns temporarily produce bilirubin faster than they can dispose of it. The jaundice, which is mild and transient, which they experience, peaks at about 96 hours, well after they have left the hospital.

In some babies, however, the jaundice may become severe, unrecognized, and then unmanageable,

and major brain damage can occur. More subtle neurological impairments are now being identified. It could hardly be otherwise in the fragile, immature, and developing biological system which the newborn brain represents.

Central issues in this problem are the unpredictable nature, unpredictable course of jaundice in some babies, the undefined susceptibility of individual babies to bilirubin toxicity, and the uncertain blood levels at which bilirubin is toxic to the brain.

Phototherapy is quite successful as you all know from personal experience. Its side effects and drawbacks are also acknowledged.

Its underlying medical logic in particular seems to us presents a problem. Light treatment is initiated only after the blood bilirubin has reached a level perceived to threaten the brain. This exact level is not known for certainty, and whatever it is, it may be reached after the baby is beyond medical care.

[Slide.]

We focused our research on the enzyme which controls bilirubin production and we ultimately developed an inhibitor of its activity.

We named this inhibitor, a synthetic heme analogue among the group that David presented to you, Stannic-mesoporphyrin or SnMP for short. It is now known as Stannsoporfin.

It acts, as shown on this slide, to prevent heme from binding to the enzyme site at which bilirubin production is initiated. Its pharmacological and toxicological properties have been intensively examined over a number of years.

[Slide.]

In the studies along these lines which we have conducted, the inhibitor was shown to rapidly and effectively suppress bilirubin production in all of the models of jaundice in experimental animals, shown on the left. In clinical studies, in adult, a single small dose reduced blood bilirubin levels by 30 to 50 percent for a period of 10 days.

The inhibitor acted similarly in adults with liver disease associated with jaundice and ultimately was shown to suppress hyperbilirubinemia in children and to interdict development of severe newborn jaundice in the population shown on the right.

[Slide.]

The overall results in five controlled, randomized, blinded where possible, clinical trials involving more than 400 newborns are summarized here. We had earlier determined the appropriate dose of inhibitor in careful dose-arranging studies in several hundred additional newborns. These studies were funded for a very long period of time by the National Institute of Child Health and Human Development, monitored by the FDA regularly, and closely supervised by senior neonatologist, in particular Professor Valaes.

Treated babies in these studies have had medical follow-ups for periods up to five years. No side effects of treatment have ever been observed. There were 279 combined control infants in these trials, 129, or 46 percent, needed light treatment to suppress progressive jaundice. A total of 443 infants received a single small dose of the inhibitor at a suitable time after birth. In these infants, blood bilirubin levels were significantly reduced and in 97 percent, the need for light treatment was eliminated, and there were not cutaneous reactions to treatment in these babies.

In a group of 80 newborns in whom

bilirubin levels had reached 15 to 18 times normal, that is, close to the level, 19.5 mg/dl, requiring phototherapy, the inhibitor rapidly blocked further progression of jaundice, and none of the babies needed light treatment.

In contrast, of 86 controls who did not receive the inhibitor, 22 percent required phototherapy. A direct comparison of the inhibitor versus phototherapy was made in other newborns in whom blood bilirubins had already reached the critical level requiring light treatment.

Forty-four babies received the inhibitor alone. In all 44, jaundice receded and none required light treatment. These babies left the hospital about 30 hours earlier than the 42 infants who did not receive the inhibitor, and they required considerably less medical resources to monitor their status.

The inhibitor entirely eliminated the need for light treatment in newborns with G6PD deficiency, a gene defect predisposing them to severe, unpredictable jaundice. Out of 58 babies in the control group, 31 percent became seriously jaundiced and required lights. None of the 225 babies receiving the single dose of inhibitor

developed jaundice requiring phototherapy.

The interdiction of severe jaundice in these infants simplified and greatly reduced the cost of their medical care.

[Slide.]

Inhibitor effects in these G6PD-deficient newborns are graphically shown in this figure. The 58 babies who did not receive the inhibitor continued to accumulate bilirubin in their blood during the second day after birth, as shown in the top line, and ultimately, many required light treatment.

The bilirubin accumulation process was blocked in the 225 babies who received the inhibitor, and none needed phototherapy.

[Slide.]

A more severe hereditary disorder in children results in jaundice which is nearly always fatal. Affected children are unable to dispose of bilirubin and survive for a time with bilirubin levels of 20 or more times normal as in this 4-year-old girl. They ultimately die of brain damage unless they are able to secure a liver transplant.

These children are being studied

Rockefeller-Cornell joint program of research involving pediatric pharmacology.

A single dose of inhibitor can, as shown on the left of this slide, markedly reduce blood bilirubin levels for about 10 days. The effects is entirely analogous to what is observed in newborns.

Several doses, as shown on the right, in the same child can moderate the jaundice for many weeks. In these children, the inhibitor can offer, while they wait for a liver transplant, protection against the acute, severe exacerbations of jaundice which prove fatal to them.

[Slide.]

The inhibitor can also replace the full blood exchange transfusion, a light, last resort procedure when lights do not control severe jaundice. Seventy-five hours of intense phototherapy could not stop the relentless progression of jaundice in this infant. Blood exchange was rejected on religious grounds by the parents.

With emergency FDA approval, the inhibitor was flown to the physician caring for the baby in South Dakota, and a single dose was administered as shown by the arrow. Blood bilirubin levels declined

rapidly and the threat of brain damage was eliminated as was the matter of taking legal action against the parents.

This experience is well known now in the Jehovah's Witness community and has been repeated a number of times over.

[Slide.]

Periodic reappraisal of clinical interventions is essential if science is to advance medical care. Phototherapy in use for 40 years could not be reappraised properly because there simply was no serious alternative to which its advantages and its drawbacks could be compared, thus, pediatricians have become bound to a single therapeutic option, and to the logic that newborn jaundice can only be treated when the bilirubin level directly threatens the brain. What this exact level is remains elusive. This is an unsatisfying and, as you know, sometimes dangerous logic.

The use of an inhibitor to temporarily reduce bilirubin over production, a key source of this problem, while the bilirubin disposal mechanism matures in the infant, has a more secure basis in science. It also now has a firm

foundation in a clinical experience comprising multiple successful trials for more than a decade in which more than 800 newborns to date have been treated and studied.

The inhibitor can be used early to control jaundice in select populations, such as G6PD-deficient newborns, or it will interdict jaundice at any time point in the evolution of this process as the physician chooses.

Finally, I think we need to remember that there are underprivileged societal settings in this country and abroad in which prolonged unrecognized or untreated newborn jaundice can, because of its prevalence and the paucity of medical resources, constitute a serious public health problem.

The method we have developed provides a simple and rapidly effective means for resolving this problem.

Thank you.

DR. CHESNEY: Thank you, Dr. Kappas.

Our next speaker is Dr. Bhutani, who is a neonatologist in the Department of Pediatrics at the University of Pennsylvania School of Medicine. He is a member of the current AAP Committee on the Management of Neonatal Hyperbilirubinemia. He has

been an investigator of the BiliChek transcutaneous bilirubin monitor and the author of the nomogram for detecting severe hyperbilirubinemia.

DR. BHUTANI: While we get started, I would like to wish everybody a good afternoon. My name is Vinod Bhutani. I am a baby doctor from Philadelphia. I am also an investigator and a rookie in the area of bilirubin for the last decade or so, and as a part of that, I received mentorship from Dr. Lois Johnson, who has been a great instrument of teaching to me personally.

In addition, we have a grant from the CDC to look at the database for the kernicterus registry, and I am unsalaried investigator for the WellSpring clinical trial. I am not going to be mentioning those things in this brief kind of set of comments.

[Slide.]

The issue of saving babies from brain damage is something that is inherent to all pediatricians and neonatologists and to ensure that a baby has a full safe week, we protect babies from six-year, from hypoglycemia, from sepsis, from intracranial bleeding as a vitamin K injection, as well as from trauma.

Ever since a concern has been raised whether bilirubin causes brain damage, we now know from our kernicterus registry based on the year of birth of the child the number of cases that have been reported to the registry have increased 11-fold from this day in 1990, and that is in the handout that is available.

The handout is detailed, but I will just stick to a few slides and a few points.

[Slide.]

The question that Susan Sheridan asked, and we have asked ourselves, is in trying to prevent adverse outcomes and concerns for patient safety with newborn jaundice, what is the level of bilirubin that is high. The one that I get stuck at is the one which is how sure are we that serum bilirubin levels are actually safe or will be safe.

In an attempt to answer that question, many of our studies have focused on a structured approach to the management of jaundice, so that we can make it easier for the practicing pediatricians who have to implement the various guidelines that are passed down to them.

[Slide.]

As we review the cases of kernicterus in

our registry, we have used the Institute of Medicine matrix to analyze the care that these babies have received as their families and at all levels related to patient safety, patient centeredness, effectiveness of care, and more importantly, on the timeliness of care. There have been significant lapses, as you will see in the handout.

[Slide.]

The primary root cause analysis tell us and shows us the there has been an underlying major loss of concern for the neurotoxic potential of bilirubin, limitation on the visual recognition of jaundice, and the failure to recognize the severity of hyperbilirubinemia corrected for age in hours.

In that respect, a nomogram was meant to be of help. Many have attempted to read more into the nomogram than there may actually is. This nomogram represents, in the simplest form, the rate of bilirubin rise that occurs in the first 72 hours. It provides at the magnitude of the severity of bilirubin and then it can be also used as a predictive strategy, but the rate of rise is important.

If one looks at the 95th percentile track,

the rate of rise if 0.2 mg/dl/hr, which compares at the 75th percentile to 0.15 mg/dl/hr, and at the 40th percentile to 0.1 mg/dl/hr.

As you review the cases that were reported to us in the kernicterus registry, the readmission bilirubin values, once the babies were discharged, some being admitted within the third day, fourth, or the fifth day, the ranges of bilirubin on admission ranged from 21.5 to 50 mg/dl.

Clearly, these babies had high bilirubins before they were discharged. In these babies, the estimated rate of bilirubin rise ranges from 0.25 mg to 0.6 mg/dl/hr.

If you compare the rate of rise of 0.25 mg/dl/hr for the 95th percentile track, and margin of safety is extremely small given all the issues that we know about bilirubin measurements.

[Slide.]

This is a baby with a high bilirubin value as one can see. The babies that we worry about are the babies between the 75th and the 95th percentile track, who have a 1 in 5 chance or a probability of having a severe hyperbilirubinemia once they have been discharged. The other 87 percent generally do well, but we do not yet have better predictive

strategies to differentiate these 13 percent babies from the remainder 87 percent babies.

[Slide.]

To this end, we look at the limitations of the visual recognition of jaundice, and we have compared with a pooled analysis of data, babies who were screened by the jaundice-based screening techniques and those by bilirubin-based screening techniques, and these are again in the handout in detail.

[Slide.]

The pooled analysis shows that with bilirubin screening, you can reduce by 50 percent the peak bilirubin values of 20 and above, as reported in the literature. You can reduce by 50 fold, the occurrence of bilirubin above a level of 25, and you can potentially have a zero occurrence of the never [?] event of bilirubin value above 13 mg/dl.

[Slide.]

We view jaundice in two simple forms for pediatricians. One, the early onset of severe hyperbilirubinemia, a value above the 75th percentile track before 72 hours of age when the bilirubin binding to albumin is impaired, so these

babies are vulnerable to lower levels of bilirubin and toxicity, and then the late onset that Dr. Stevenson mentioned, the conjugation defects, who are above the 95th percentile track and are more than 72 hours of age.

The concern is of the baby before they go home, those who are above the 75th percentile track.

[Slide.]

If you follow these guidelines and this level of concern, I think we can meet the goals of all the stakeholders and bilirubin, those of the clinicians, those of the public health officials, those of the society, and those of the family for a safe experience with newborn jaundice.

Thank you very much for this time.

DR. CHESNEY: Thank you very much, Dr. Bhutani, and for giving us the extra slides that we can peruse tonight.

The next speaker is Dr. Murray Goldstein.

DR. HATLIE: Madam Chair, I am actually not Murray Goldstein. I am Martin Hatlie. Murray Goldstein's chair was empty next to me for the whole meeting, so I stepped up in the interest of time.

DR. CHESNEY: Do you want me to introduce you?

MR. HATLIE: That would be nice, unless Murray is here and we just don't know who he is.

DR. CHESNEY: I am so sorry.

Martin Hatlie, Esquire, is President of the Partnership for Patient Safety and a nationally recognized authority on patient safety and medical professional liability issues. He founded the Partnership in 2000, which is dedicated to advancing the reliability of healthcare systems, and he is a member of the Harvard University Kennedy School of Government's Executive Session on Medical Errors.

Thank you.

MR. HATLIE: Thank you, Madam Chair.

I was given a sliding scale of time today, 5 to 10 minutes, so I will stay within the 10 minutes and try to keep closer to 5.

I am a lawyer. I got to patient safety through years of being a lobbyist on litigation issues for the AMA. I am not really going to talk too much about that today, it is not the topic, and frankly, many of you may not care, but I wanted you

to know that about me because you will see that I come from a different perspective and had the privilege of working with organized medicine as this notion of a systems approach to safety and a safety kind of science has been developing really starting in the mid-1990s although I will say that it did start in anesthesia quite a bit earlier, probably the mid-1970s, and the CDC and the FDA were very, very involved in partnering with the anesthesia field to make that happen.

So, when we did start a National Patient Safety Foundation out of the AMA in mid-1990s, it was really the FDA that probably had more system and safety knowledge. This is out of the Center for Devices and Radiological Health than any other part of government that we can find.

I am going to jump around in my slides a little bit today. You have some more material in your written materials than you are going to see up here today, but I want to leave you with four points at the end of my presentation and for the purposes of sort of reinforcement and repetition, I am going to start with them.

One is that low prevalence from a system and safety point of view is really not a

justification for inaction. A lot of industries really are pursuing high reliability, and, Madam Chair, that is a term of art for your list or extraordinary safety, really focus on their low prevalence especially high severity injuries as treasures, they call them. They are essentially things that tell you a lot about your system, if you can't prevent those high severity injuries, then, there are some systemic things that you really need to be looking at, and every one of these cases becomes something that industries that are serious about safety spend quite a bit of resources on to really investigate how that could fallen through the cracks.

The second is that an intervention that relies on either vigilance or memory, or both, really again from systems thinking and human factors thinking is not optimally safe. Those are ways in which we know human beings fail no matter how hard they try, and no matter how competent, it is not how perfect they are.

Vigilance including visual assessment, memory including know when and how to apply a guideline are things that just are not going to get you again to that extraordinary safe stratosphere

that you want to go to.

The third point is that evidence-based medicine, while a very valuable tool and really important for a number of reasons in medicine, is not a particularly sensitive safety tool. For a number of reasons that have really been articulated best probably in the literature by two pediatricians, Don Berwick and Lucian Leape, in an article, a dialogue actually, in JAMA last summer, they really focused on a number of reasons why evidence-based medicine isn't something that is going to be particularly helpful to you in making safety happen. It's slow, it's costly, it's not good at sort of targeting latent risk or emerging risk in a system, so you need other things to complement that certainly.

It is not that it has no value, it has great value, but you need more. It should not be a rate-limiting step.

The final point I want to make, really based on comments this morning, that I really want to leave you with, although I will elaborate all of these a bit more, is that accidents, including the kinds of stories that are captured in registries like the Pilot Kernicterus Registry, are incredibly

robust safety tools.

The aviation industry has spent terrific amounts of resources in really capturing the kinds of stories that are captured in registries like this one, voluntary registries that have a lot of narrative, a lot of richness of story telling where you can thematically analyze and understand why things went wrong and how they went wrong.

There is much more emphasis from a safety point of view in that kind of data than in counting numbers and just looking at frequencies because that doesn't give you the kind of narrative, the kind of richness where you can really understand why processes failed and what went wrong.

We really are going to move through these slides pretty quickly.

I also want to stress, though, by saying that complacency is a word that has come up here a couple of times, and the IOM report that really brought safety into the public consciousness at the end of 1999 did charge the healthcare system with being complacent.

By that, they didn't mean careless, they did not mean callous, what they meant is that there is a sense in some industries that we are doing as

well as we can do especially where prevalence is low, that we are sort of at the best place that we can be at, and again, organizations that are highly reliable are often seeing that their safety initiatives, their big leaps forward in safety come from organizations that are already leaders in the field, they are already at the top of the game. They might be organizations that either themselves would say or their peers would say you don't need to be focusing on safety because you are already doing as good a job as anyone that we know of, those organizations that again really aim for perfection and they are often motivated by the Hippocratic Oath. That really resonates with a lot of other industries, first, do no harm, let's aim for perfection. Those are the organizations that are going further.

The best case study I can leave you with, and it is not in my slides, is the Alcoa case study. It comes out of the Harper Business Review. It's a wonderful, wonderful story that you will find very applicable to what you are doing here, but really focusing on first doing no harm, looking at your processes, aiming for perfection, and finding a lot of cost savings along the way.

This is Patient Safety 101. I would recommend James Reason's book which is cited in your slides, and Charles Perrow's book which is cited in your slides, or the IOM report, you can pick up all of this stuff.

These are all the different places that safety science comes from. It is not just the medical literature. There is a lot of knowledge that is being captured from other fields.

These are the basic models. If I leave you with nothing else today, this will be some of the things that are certainly percolating through the safety literature right now.

This is the Swiss Cheese model. This is coming from James Reason's work. It really I think is applicable in many ways to the kinds of issues that I heard you discussing today.

One of the basic paradigm shifts that we see in systems thinking about safety versus the kind of thinking that I think is driven by our current liability system, if nothing else, is that things are constantly on the verge of happening. Accidents don't just happen when there is a breach in the standard of care. They are constantly on the verge of happening. You are constantly

managing them and keeping them from happening through a series of defenses that you all have in your systems.

The fact that the prevalence of kernicterus is as low as it is, and the fact that you are managing hyperbilirubinemia as well as you are, suggests that your defenses have worked pretty well.

What we see, though, in safety thinking is a paradox, sort of the better that you do at safety, the more you lose track of the kind of risks that are there. Frankly, if you are trained to look for a certain kind of risk, if you are trained about the dangers of hyperbilirubinemia, but you don't see it for 15 years, you tend to move it off to the side of your red error screen.

So, one of the hole to one of these defenses is just the kind of complacency or lack of alertness that comes with not seeing something for a broad period of time. A number of organizations, we use different kinds of simulation training to really keep that foremost in the minds of the people and keep those kinds of risks alert.

The phenomenon, the human fact researchers call "the coming of attention," we just don't look

for things, we don't tend to see things that we don't see frequently and aren't familiar with.

Another thing I want to mention from this slide is that certainly in Dr. Newman's presentation this morning, he went through a number of things in history that have changed over the course of our management of this disease.

One of the things that we know from systems thinking is that any kind of change introduces different kinds of risks. So, for example, one thing that resonated very much with me today is the movement of the management of hyperbilirubinemia out of acute care settings into ambulatory care settings.

When that happened in the mid-1990s, again with 20/20 hindsight, perhaps there was a need to do different kinds of education with families, different kinds of risk management strategies to reflect that change in the way in which we now see this kind of risk emerging.

Frankly, it is one of the holes that PICK is trying to fill. It is the hole in really bringing forward the partners, the families as partners, the lay caregivers as partners, and they have a more active role to play if this is a fact,

something that is going to emerge in outpatient care settings.

We have talked a lot about--this is, first of all, the Sharp and Blunt Ends model, another one of the basic models from Safety Science. We have talked quite a bit about the guidelines that are in place here and the fact that kernicterus does continue to happen even if the prevalence may be low.

The purpose of this slide is to really show that where care is given, which is the sharp end of this triangle, practitioners are often balancing three different things, guidelines in this case, it's their goals, what they think is going on.

Probably in this case, a good example would be can you diagnose kernicterus, can you diagnose hyperbilirubinemia, are you trying to balance it with other kinds of things that you are differentially diagnosing, and also the issue of attention, and attention is really interrupted in most healthcare settings by distraction and by fatigue.

So, a lot of the work that happens in managing safety involves managing that attention,

that focus of attention. It is one of the reasons why vigilance and memory really are not good strategies to rely on because they get interrupted by all that action at the sharp end of the system.

The sharp end, frankly, what happened to the sharp end is shaped by the blunt, and the blunt end includes different kinds of systems thinking including the legal system, including the guidelines, including the kinds of technologies we have in place. Anything that we can do to minimize vigilance, reliance on vigilance, or minimize reliance on memory, or simplify or standardize are frankly things that will help people perform better at the sharp end, and that is really the major take-away I think from this slide in the time that we have today.

Hindsight bias. I haven't heard it much today, I have heard it in most situations where we have talked about this sort of thing, and that is the statement that if doctors only followed the guidelines that they have up there, we really wouldn't see kernicterus.

In fact, it is a very, very well known phenomena in the literature that hindsight, that when you look back on a situation, you tend to make

judgments like that, it's internalized blame that it was the doctor that was at fault. In fact, because of all that complexity at the sharp end of the system, there is many things that are going on and really focusing on whether doctors should be or should not be following guidelines is not going to get you where you want to go.

Again, you want to focus on technologies, strategies, to simplify, to standardize, and to decrease reliance on vigilance and memory.

How do we apply safety science to optimizing the prevention of kernicterus? One of the major lessons that we know from looking at many years of experience in safety science and other systems is that systems never run perfectly, they are prone to failure and degradation, we should not be relying on guidelines and protocols as our major line of defense because that assumes optimal system performance, and the system rarely performs optimally.

Reliance on vigilance and memory, we have talked about already, but there is frankly just not strategies that are going to really get you to the high reliability sector on this issue.

How do we apply safety science to

optimizing the prevention of kernicterus?

My time is up. Lots of people have to be involved. Simplification and standardization are important tools.

Many of these other strategies are cultural strategies, we are not going to talk about them here, but it really is a whole series of training and communication stuff.

Evidence-based medicine, I am going to leave you with the slides here. They include a number of quotes from Berwick and Leape from that series of articles that I talked to you about, but essentially, evidence-based medicine is not something that either aviation or anesthesia has relied on terrifically in creating safety.

It is much more of a problem-solving technique. It is every story in the registry that can be analyzed thematically and really looked at with the kind of problem-solving that frankly, commissions are very good at doing.

So, you have the steps in place to really move forward and really getting to the next level in safety and reducing the prevalence that you have of hyperbilirubinemia, whatever it is. It is really just the approach that could be different

than the traditional approach that is important here.

I am going to stop here. There is many more things that I could say, would love to say. If you have any other questions about any of this, I will be at the cocktail bar at the end of the day and I would be happy to talk to any of you.

Thank you so much.

DR. CHESNEY: Are you sponsoring the bar? I don't think the FDA is.

MR. HATLIE: No, I think the hotel is, I think it is something that they are giving us for free. Thank you very much for the extra time, I appreciate it.

DR. CHESNEY: We will be there. Thank you very much.

Many of us have become devout Don Berwick fans and for those of you who have not seen the video, Escape Fire, I think if you want to understand process and medicine and errors, that has a very profound message to it.

Our next speaker is Dr. Duane Alexander, who is the Director of the NICHD and has been since February 5th of 1986. His own personal interests and training have been in developmental

disabilities, and I was interested to learn that in his first position at the NICHD, he directed their national amniocentesis study that established the safety and accuracy of amniocentesis for prenatal diagnosis.

Dr. Alexander.

DR. ALEXANDER: Thank you all for the opportunity to speak to this group on this very important topic.

The study that I organized after the amniocentesis study was a phototherapy study assessing the safety and efficacy of phototherapy for treating jaundice. I never got to finish that one because I went on to the National Commission for Protection of Human Subjects instead, but this is obviously an issue that has been of interest to me for a long time and to the Institute.

During its 40 years of existence, a major focus of our attention has been on improving pregnancy outcome and ensuring intact survival of newborn infants and prevention of disability. I should state for the record that I have no financial relationships to WellSpring or other pharmaceutical companies, nor does the Institute.

Bilirubin encephalopathy has long been a

major problem for newborn infants. The biggest advance came before NICHD was established with the development of Rhogam, which eliminated a huge proportion of neonatal jaundice and problems associated with it.

Then came phototherapy. The Institute addressed this. It took care of much of the problem with premature infants when our collaborative study demonstrated its safety and efficacy in reducing the need for exchange transfusion and reducing the incidence of kernicterus, and it rapidly became standard treatment.

Unfortunately, it is also clumsy and complicated, it takes a long time, it interferes with access to the infant, and it is not 100 percent effective, so we really have needed a better intervention if one could be developed.

Sumner Yaffe, the former Director of the Center for Research for Mothers and Children at NICHD, came to me one day with a potential solution. Based on his conversations with Attallah Kappas, who you just heard speak, Dr. Kappas reported on development of a new series of compounds that they were working on that could

represent a one-time injectable drug that would interfere with the formation of bilirubin until a baby's enzymes matured sufficiently that it could excrete it.

They had tested several different formulations, tin, zinc, proto-, meso-, and settled on tin mesoporphyrin as the most effective and the safest, as well. We believed, based on the evidence that we saw, that this could potentially be the long-sought magic bullet that could finally end the problem of hyperbilirubinemia and kernicterus.

We worked with Dr. Kappas to organize some clinical trials. These were done by contract in Greece and in Argentina. They included studies of term breast-feeding infants, G6PD-deficient infants, ABO incompatibles, term infants with hyperbilirubinemia.

In every study, tin mesoporphyrin administered once resulted in lower peak bilirubins in the treated infants than in the controls, and reduced or eliminated the need for phototherapy. The only infants in any of these studies that have been reported who required phototherapy after receiving tin mesoporphyrin were some very small

preterm infants.

In addition to this, there was no evidence of any adverse effects in any of studies. Results like this don't come along very often. So, the number of patients, however, in our studies, was not large, it numbered in the hundreds rather than in the thousands, so these data have to be regarded as preliminary certainly rather than definitive.

They also were not reported in sufficiently rigorous way to meet all the FDA requirements, so more studies were needed. We urged Dr. Kappas to license this compound to a pharmaceutical company, which he did, and the studies have begun.

The promise of this treatment is so great that it is important that these studies needed to provide data for a judgment on approval, need to be moving ahead rapidly, so that tin mesoporphyrin can be studied for its preventive efficacy, as well as its therapeutic efficacy.

We, at NICHD, believe that this is one of the most important new drugs being studied for pediatric use and that it is the only intervention on the horizon that holds out the prospect of completely eliminating the problem of

hyperbilirubinemia and kernicterus.

We are sufficiently enthusiastic about it that we have a protocol ready to implement in our neonatal intensive care unit network to test its additional applications of tin mesoporphyrin once it is approved for use in term infants, so that we will know its efficacy and safety before it gets broader application after licensure.

If this proves useful, we will go on to evaluate other possible applications. We hope that a way will be found to move current studies forward expeditiously, so that the full promise of this drug for ending the problem of kernicterus will finally be realized.

Thank you very much.

DR. CHESNEY: Thank you.

Dr. Goldstein is here, but I think we will give him a chance to catch his breath and move on to Dr. Andrew Moosa, who is Director of Newborn Nurseries and the Infant ICU at St. Francis Medical Center in Linwood, California.

DR. MOOSA: Thank you, Dr. Chesney, thank you, Tom Perez for allowing me to speak today.

As an initial waiver, I want to say that I have no relationship with WellSpring, I am not

being reimbursed, I am not involved in the clinical trials, I am not salaried, so I have no conflict of interest.

Dr. Lucey asked me who was I representing, so I said I was representing the practicing pediatricians who day and night take care of babies and children. I am from Southern California, the Los Angeles area. Somebody has to speak for the South since Dr. Newman and Dr. Stevenson represent the North, which is more affluent, which is more sophisticated, but I am from Southern California.

Dr. Newman mentioned to you the Kaiser study in Northern California. Kaiser is a very special place in the sense that they have very good control of what goes on with both the physicians and the patients, et cetera. It is a marvelous system. But in those of us who practice outside the system, I practice in a hospital of 520 beds. We have 7,000 deliveries a year.

When we look at those numbers, and a lot of our population is the working poor, who earn $20,000 or less a year, many of them are single parents, they don't have vehicles to come back to the hospital. With the new HMO systems, in spite of the federal mandate that the kids will stay in

the hospital, the newborns will stay in the hospital for 48 hours, the mothers are sent home earlier by HMOs or they choose to go home because they have got three or four other kids at home and they need to go home.

We then say, well, you had better come back and get a bilirubin in two days, three days, they don't come because they don't have transportation. Our system is very difficult. It is very different from the Kaiser system or other systems in the west side of Los Angeles as opposed to where we practice.

I practice in southeast Los Angeles. Then, we have been tracking. One of the things I also do is I head California's program for hospital accreditation. In that role, I go up and down to California hospitals and we survey them for accreditation.

One of the things we are looking at now, and one of the things front and center, both in Washington and in Sacramento, is patient safety. We are now looking at the babies who come to the hospital or show up in the emergency room from the time they are discharged from the hospital until 21 days of life.

In my hospital last year, I pulled the figures out, we had close to 7,000 deliveries. The exact number was 6,987 babies. Out of that, 535 babies came back to the emergency room in the year 2002 for jaundice and poor feeding. We have not been looking at those figures.

I don't have the numbers of how many were readmitted to the hospital. Now, that is a major problem for us because when these babies go home, a large number of our babies belong to parents, as I said, that really can't afford to come back to the hospital, can't afford the taxi fare, can't afford or do not want to come and get the kids stuck two or three times when the bilirubin is up, and they really don't want the kid in the hospital, they want the kid to go home.

Then, when you say to the mother, when we call the mother say, you know, how come you didn't bring the baby for the blood test, they say, well, my other two children are sick or I don't have transportation, or my husband is working on the night shift or day shift, whatever, it is a problem for us.

So, I have 37 pediatricians. This year I happen to be Chairman of the Department of the

Department of Pediatrics, have 37 practicing pediatricians in my department. You know, they are looking for a better way to take care of these kids who are jaundiced. We are now using the carbon monoxide studies for the Bhutani graphs, trying to find out which babies the bilirubin is going to go up, et cetera, and we are having difficulty with that, because we know these kids, it is going to go up, we want to measure the bilirubin in two or three days. They don't come.

So, what I am saying to you as a practicing physician out there, the practicing pediatrician out there, we need some help. If there is a compound available, a pharmaceutical agent available out there that can help us with these kids, because they are really, in the real world, they are not going to get two and three blood tests of bilirubin to come back.

Somebody said, Dr. Bhutani said it costs one dollar to get a total bilirubin, Dr. Lucey said it costs $35.00 in Vermont, so I don't know what it costs where, but it is not cheap, and to get the thing done, we are allowing these kids to stay at a risk that is there.

Dr. Newman asked a very important question

during his talk. He said how can we reduce the occurrence of kernicterus. For me, as a practicing pediatrician, my question would be how can we eliminate kernicterus.

Thank you for allowing me to talk to you.

DR. CHESNEY: Thank you very much.

Our next speaker is Dr. Jerold Lucey, who is a Professor of Pediatrics and Neonatology at the University of Vermont, and has been a mentor for many of us with respect to his years of writing, teaching, and advocating for infants and as the long-time editor of the Journal of Pediatrics.

DR. LUCEY: I paid my own way. I am a friend of Dr. Kappas, but he doesn't have to pay me for that.

Being almost the last one on this program is sometimes an advantage. You can always say, well, everything that has been said worthwhile has been said already, and I think I can plead that somewhat, but I am probably the only one in the room that goes back to the Shaw, Diamond, and Allen era in Boston when they invented the level of 20 mg percent.

I have done hundreds, I think I stopped counting, exchange transfused at number 500. So,

let me say something about exchange transfusions. Nobody has made clear the fact that there is about a 1 percent mortality rate with these, and it happens in well babies, and there have been articles written about it in the old days, but nobody ever really solved the problem of why these babies died.

I can remember probably every single one of the ones that died on me because they stunned you. You went out and talked to a mother, said we are going to do an exchange, and there is a very low risk, and then, boom, the baby's heart stopped during the thing and they couldn't get it started. So, that is still there, and I think there aren't a lot of people who are very adept at doing exchange transfusions anymore.

So, that is an effective therapy all right, but it has with it a little risk.

Now, the first time I met Dr. Kappas was when he presented his first paper on hemoxygenase inhibitor and right away I knew the days of phototherapy were limited, because here was something that you look forward to, a shot that you could give.

I have been responsible for the

introduction of phototherapy in the United States, doing a randomized trial in the late 1960s, and, first of all, people didn't believe it. I started out thinking light would never work myself, as a matter of fact.

It was done because I had a Chilean research fellow who they were doing it using it all over in South America and Italy and France, but I am monolingual and I never read any of these articles. When my research fellow came to me, he said why aren't you doing phototherapy, I said, oh, it doesn't work.

If you look at the early papers as far as evidence is concerned, that first paper didn't convince very many people. It came out in '58 and nobody in the United States started using it until after we at least did a randomized trial in '68.

Then, there was 10 years, you know, phototherapy would never pass the FDA regulations, I think, at this point, or take years to do it. In those days, all you had to do was prove that the therapy was effective, and people started using it because it was a device, and obviously, the device was safe, nobody ever got too hurt by a light bulb unless they touched it or something.

So, there was a therapy that came in and then there was just an academic debate that went on for a decade because actually there wasn't a way of telling where did the bilirubin go, where did the yellow go. That took about 11 years to be worked out, and there is still people who worry about phototherapy.

You will be presented tomorrow, I gather, when you are making your deliberations on tin mesoporphyrin about what are the long-term effects. Well, to get long-term effects, it takes a long time. Bill Oh summarized all the limitations of phototherapy. There is certainly several of them. They can be handled, but if you wanted to be a purist, you could say, well, nobody has ever followed those people for 30 or 40 years.

Well, please remember that very few, I don't know of any drugs that have been followed where somebody who introduced and then followed the people for 30 years. That is just not possible. So, I think you are going to have to take a chance.

When I got interested in light and realized it worked, my idea was that we give it to everybody, because I had the idea that if you walked around on the outside and didn't get hurt,

and that was 10,000 times more radiant energy than you got from the light therapy, then, this is probably going to turn out to be safe.

So, if you read the little paper carefully, you will see it was proposed as a way of preventing jaundice in newborn infants. It hasn't been used that way anymore because people got worried about separation from mothers and the effect of blinders, and everything, and we backed off, and that may be one of the reasons why you are seeing more--I mean as phototherapy went down, maybe the incidence of kernicterus went up, but we started seeing more anyway.

Then, I got really disenchanted with the field because I didn't see any way out how you could ever do a study in which you would allow a level to go up to something that was toxic and then have a control group, so there aren't any real possibilities for much of a control study with a high risk group out there.

I wrote a thing called, The Bilirubin Mess. There never was a level, there never will be a level, which I still believe. Judging the toxicity of a certain level versus the baby in the situation, I just don't think is a practical

approach.

Other people have held onto the idea that maybe you should do unbound bilirubin, scientifically, quite sound, practically, not apt to be very practical.

So, I would urge you to look at new proposal before you as far as the treatment is concerned and that we proceed on two levels. One is use the new treatment, approve the new treatment, use it and then start doing some other studies with it, and try to selectively treat as few babies as you can by using some variation of Dr. Bhutani's graph for picking out babies.

Thank you very much.

DR. CHESNEY: We have two more speakers, Dr. Timos Valaes, a clinical instructor in the Pediatric Program at Boston University.

DR. VALAES: It is an advantage and a disadvantage to be one of the last speakers. The advantage is that you know, you have heard what everybody else has said. The disadvantage is that you cannot have prepared slides of anything because then you will repeat what some of more eloquent people have already said.

First of all, I guess I have to do my

disclosure part, and I am Professor Emeritus at the Tufts University School of Medicine in Boston, and I have been involves with the tin mesoporphyrin studies in Greece from 1988 to the year 2000.

During this 12-year period, I spent 50 percent of my professional time doing the studies. The studies were, as you heard, supported by National Institute of Child Health and Human Development and when the contract was over, the WellSpring Pharmaceutical Corporation became the custodian of the computerized database and also paid for the last months the nurse practitioners that was involved with the five-year follow-up. So, that is my contact with the company.

When they asked me while I was traveling if I am interested in attending this meeting, they volunteered to pay my travel expenses from Boston to here.

Having said that, I must say that I have not yet recovered from the emotional impacts on me from the speech, the presentation rather than the speech, of Mrs. Sheridan. The reason I am so involved and impacted by her presentation, that in my earlier professional life, I had the bad luck of having seen more than 300 cases of kernicterus.

This was after my training in England where I was part of the revolution there in taking care of the Rh disease babies and see the marvelous disappearance of kernicterus from this cause by the timely use of exchange transfusion.

Then, in '59, I went to Greece, established an exchange transfusion service at the State and University Maternity Hospital in Athens, and we eliminated kernicterus in that institution, but this left the rest of Greece without the help of phototherapy, sending us very late, as I said, hundreds of babies and where we could do nothing to save them or alleviate their condition.

Then, phototherapy came and the problem was no longer there, and then I decided to come to Boston, not because I was looking for the problem, no, I was looking to get away from it.

Having said that, I think I need to iterate a few things. Neonatal jaundice is a self-resolving condition and all we do with whatever measure we take is to buy time for the small minority of babies that are going to develop kernicterus.

Kernicterus can be prevented, but cannot be treated, and every epidemiologist knows that if

it is prevention, you have to treat many more patients that will eventually develop the condition, if not for the preventive measure.

It is also very well established that if a preventive measure succeeds in eliminating the disease, then, the medical profession and the public start questioning whether really the preventive measure is necessary. This is exactly what happened with kernicterus. We have been trapped by our own success in eliminating kernicterus.

What happened, we allowed, or as pediatricians, for a drastic reduction of the in-hospital observation of babies, and we are now experiencing another thing again. The safety margins for exchange transfusion or for phototherapy or for tin mesoporphyrin for intervening have been compressed, and this compression means that it is not only the levels of bilirubin between these different things that are reduced, but is also the time available for us to make the intervention, particularly if the baby is already home and there is no beeper in the baby's system to tell the physician when the target call for action has been reached, and there is a lot of

delay, and that is really what is happening everywhere.

I have produced a mathematical model to show how really bilirubin level, a time key anytime during the first week of life has been reached. As you see there, there is a cumulative rate of bilirubin production involved. It is not one rate, it is a cumulative, because this rate changes, it decreases throughout this period of time.

The cumulative intrahepatic circulation of bilirubin is one side and then the cumulative rate of bilirubin elimination, and that again is not one rate, it is a continuously changing, fortunately increasing rate of elimination.

Phototherapy intervenes in this process by increasing elimination. Tin mesoporphyrin is acting on the other side by decreasing production, and it does it very efficiently and for enough time, at least 7 to 10 days, so that you only have to give it once.

There is an historical paradigm available to us, how you react to a situation like this. There is a condition known to all the pediatricians known as hemorrhagic disease of the newborn. It is a developmental situation. The baby is born with a

low level of vitamin K dependent clotting factors. They go further down, particularly in breast-fed babies, and this tendency can be reversed by a single dose of vitamin K.

In the '40s, there was a lot of discussion, the commonality is, first of all, that there is not one level of clotting--low level of clotting factors that will be for certainly related with clinical manifestations, and there is a continuous change of these factors different from one baby to another, similar to what is happening with bilirubin, and there was a lot of discussion in the '40s and '50s whether you should be giving vitamin K, which corrected the abnormality definitely well proven, to the mother, so that the baby is protected during a traumatic delivery, to the baby orally, and the problem there was that there was not an oral preparation, but who cares, you open the ampule of the intramuscular preparation and you pour it into the baby's mouth.

But then in 1961, the American Academy of Pediatrics stepped in and pushed aside all this controversy, and without any single sort of new study that was reported as pushing them in this decision, decided that every baby should get an

intramuscular injection of vitamin K, and this was enough and sufficient to make the complete disappearance and make early and classical analytic [?] decision of the newborn eliminated, and it is a historical sort of condition for most of the pediatricians.

Now, what I said had happened, with the British and some other people first, questioning why should every baby get an injection. They started saying it is not necessary and they stopped giving it, but to cut the story short, the American Academy of Pediatrics again intervened, I think it was two or three years ago, and said no, let's forget about all this discussion and go back to the intramuscular injection and continue the practice that was there.

Now, of course, this is a different situation we are talking about because now we have to introduce a new practice, and not really stick with the old one.

Thank you. I didn't see any light, sorry.

DR. CHESNEY: We don't have a light. That would be an excellent suggestion. I don't think they anticipated quite so many people for the open session. I thought you made some very excellent

points.

Our last speaker is Dr. Murray Goldstein, who is the Medical Director of the United Cerebral Palsy Research and Education Foundation and former Director of the National Institutes of Neurological Disorders and Stroke, and a former Assistant Surgeon General.

DR. GOLDSTEIN: Madam Chairman, I apologize for being late. I apparently misunderstood the time frame of your agenda. You have already introduced me, so I shan't introduce myself.

I guess I need to say I have no personal social, working, or other relationships with any industrial organization relevant to this discussion.

First, I would like to take a moment to congratulate the staff of the subcommittee. The thoroughness of its concise staff paper of May 14, summarizing the state of present knowledge on hyperbilirubinemia of the newborn, and, two, the significance and specificity of Dr. Cummins' charge to the subcommittee.

Having been in government for a number of years, I appreciate both the technical excellence

of these documents and the sensitivity with which they were written. Great staff work.

I have already submitted a brief document on kernicterus for this committee's consideration and on the role of hyperbilirubinemia of the newborn as an important etiologic factor in athetoid cerebral palsy. This information is in your folder, and so I won't spend time repeating it. However, I do need to point out that athetoid cerebral palsy is one of the severest forms of cerebral palsy and is characterized by a serious lifelong interference with activities of daily living.

Also, in the past, it was one of the more common manifestations of cerebral palsy. The important findings of a generation ago in early diagnosis and therapy essentially removed kernicterus from the screen of medical attention.

I daresay there are very few medical house officers today who have ever seen a case of kernicterus. Also, I would guess they probably will have difficulty recognizing it if it was presented. In essence, as a medical research and public health community, we have assigned kernicterus and its consequences to the category of benign neglect.

As presented here by previous speakers, the reasons for this benign neglect may no longer be appropriate. Although kernicterus is still a rare disorder, it appears to threaten to re-emerge.

As my paper indicates, there are a number of clinical care, medical research, and public health measures that now demand additional attention from both government and nongovernment sources.

To be specific about the role of the FDA in this new agenda, first, I urge the subcommittee to advise the FDA to give targeted and priority attention to the use of its authority to meet its agency-designated responsibilities under the Orphan Drug Act.

This Act was passed to stimulate and support needed research development on (a) improvement in the diagnostic criteria and methodologies for early identification of hyperbilirubinemia in the newborn; and (b) the development of more definitive clinical interventions for the treatment of this disorder.

I had the privilege of being one of the people who helped design the Orphan Drug Act and was a member of the Assistant Secretary of Health's

subcommittee that designed the specifics of it. Unless that Act has been changed, and I don't think it has been, I believe the need for its use as an instrument of the FDA is imperative, and it was designed to do such.

I also suggest that the subcommittee recommend that the FDA use its administrative procedures for expedited review to evaluate the results of this research and development activities.

These actions on the part of the FDA would meet its unique responsibilities for addressing this potentially serious problem of infancy. Although kernicterus is not a public health problem of the size of SARS or AIDS, to the parents of infants and children with athetoid cerebral palsy, one case of kernicterus is one case too many.

Madam Chairman, thank you for your attention and I would be pleased to attempt to respond to any questions the subcommittee may have.

Thank you.

DR. CHESNEY: Thank you very much.

We need to move on to Dr. Nelson's presentation next and then we will be addressing Questions 2, 3, and 4. As a personal favor, in

order to reinstate my credibility as somebody who sticks to the time, which I have lost already, I am going to ask Skip if he could shorten his presentation by some amount of time.

Thank you.

Ethical Issues

DR. NELSON: What I would like to present today is four sets of reflections on four different issues. It is not meant to be a complete presentation of the ethical issues in drug development in this area, but to stimulate our conversation. I think they have been touched on at different points in time.

You have the complete slides, so I will sort of, in the interests of time, move through them rather quickly.

[Slide.]

The first point I want to make is on surrogate endpoints, but for those of you in the audience, I don't have a biochemical pathway, but this is a regulatory pathway which, in your handout, is presented as a full page document as the last page of the handout, and it shows you how you move through 21 CFR 50 and 56 in the case of the FDA, or 45 CFR 46, and to orient my remarks

according to this regulatory pathway, the first question being sound research design.

[Slide.]

The first point we need to ask, as we are looking at drug development is sound research design, and the issue I want to raise if the choice of endpoint, surrogate endpoint.

[Slide.]

The primary goal for the treatment or in fact prevention, since I will have some reflections on prevention, of hyperbilirubinemia is to prevent kernicterus and other irreversible neurodevelopmental impairment in case some of the concerns about other impairments at lower levels of total bilirubin are confirmed.

The association with total bilirubin level suggests that the control of this level may be an appropriate surrogate endpoint, but even within that, we still have other possible surrogate endpoints - bilirubin above 20, bilirubin above 25, bilirubin above 30, maybe something lower, peak or maximum bilirubin comparing two interventions or an intervention against a non-intervention control, or decrease in the use of other treatments, such as exchange transfusion and/or phototherapy. All of

those are surrogate endpoints.

[Slide.]

A set of quotations from an article by Fleming and DeMets in the 1996 Journal of Annals of Internal Medicine where they looked at surrogate endpoints, and these are several points they made about the use of surrogates:

"The surrogate must be a correlate of the true clinical outcome and fully capture the net effect of treatment on the clinical outcome;

"To be a valid replacement endpoint, a surrogate must provide a high level of accuracy in predicting the intervention's effect on the true clinical endpoint;

"The primary goal (in these definitive phase 3 trials that they were discussing) should be to obtain direct evidence about the intervention's effect on safety measures and true clinical outcomes."

So, I am not going to answer the question, but the question is what is the appropriate endpoint to use in some of these studies. I think it is fairly clear it is not kernicterus. The question then is what is it.

[Slide.]

So, now some reflections about the justice of healthcare distribution, and I am going to actually present some data from California. I think it might even be Southern California, but I am not sure.

[Slide.]

But the point is raised by this notion of equitable selection. Now, usually, equitable selection means if you have a research trial, that you equitably select those who go into the trial, so I am using this, though, to raise some more general questions about equitability.

[Slide.]

What struck me in looking at the AAP's document on neonatal hyperbilirubinemia, which looks like it was also reflected in the same list that Dr. Bhutani put up, is that the root causes of kernicterus, if you look at them all, early discharge with no early follow-up, failure to check, failure to recognize, underestimating, lack of concern, delay, failure to respond, all of these are behavioral aspects, all of these are systems issues that appear to be totally unrelated to phototherapy, unrelated to the giving of a medication.

Now, I am not presuming to say what the answer is to correct the deficiencies, and I also agree with the comments that you don't look for a behavioral solution. Practicing in an intensive care unit, we need systems to correct this, but question is what is the best system for correcting these root causes - is it drug development, is it universal screening, is it some other process.

[Slide.]

Now, the issue of equitability was raised for me in looking at an article that came out in Pediatrics just recently, again based on data from the 1999 California Maternal and Infant Health Assessment.

In looking at the adjusted odds ratios for either early discharge or for inadequate follow-up with early discharge described as less than two days after vaginal delivery or less than four days after cesarean section, and the particular question was, in spite of the fact that we had a federal law stipulating that they had to be provided, who didn't get it.

[Slide.]

At least for early discharge, the only variables that fell out as important was maternal

income, and that was the adjusted odds that you see there in terms of predicting who got discharged early, odds ratios for untimely follow, and I see the formatting here didn't work quite perfectly, but basically, maternal race or ethnicity, Latina, maternal income again, Medicaid insurance, or the primary home language being non-English, those were the predictors of untimely follow-up. So, those infants who were born to mothers that had these criteria were those that were at risk for not having appropriate follow-up.

Now, that may reflect a number of different factors that were outlined by our speaker from Southern California, but this is the population that, in fact, is at risk. So, it would also be the population that is at risk for whatever intervention we decide to design.

[Slide.]

The authors point out that this is an inequitable pattern.

[Slide.]

Now, what is interesting to me is if you rely on the IRB system to help with these kind of public policy decisions, you will be sorely disappointed because actually in the regulations,

the IRBs are told that they shouldn't pay attention to the impact of research on public policy, and this is a direct quote from both FDA and it also is mirrored in the HHS regulations:

"The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility."

But the question before us is, does that fall under the FDA's mandate in terms of promote and protect the public health.

[Slide.]

Let's talk a little bit about treatment versus prevention. In reflecting on this, it struck me that the paradigm has always been one of prevention. It was mentioned by a number of speakers. There is no treatment for kernicterus.

So, the choice of total bilirubin of 20, I was taught, and it was, of course, in Boston in the early '80s that part of the reason for this number of 20 was the balance between the risks of kernicterus and the risks of exchange transfusion. Now, whether or not that was ever carried out in a

systematic way, who knows, but that at least was the argument for picking 20, that if you did it at a lower level, you are exposing an inappropriate number of infants to the risk of mortality and morbidity from the exchange transfusion.

Now, the choice of the lower level for phototherapy reflects a judgment of the greater safety of phototherapy versus exchange transfusion, and it had the particular therapeutic goal of preventing the need for exchange transfusion, again, a surrogate outcome.

The intervention then, in reflecting on this, is designed to prevent the need for phototherapy, if you chose that as a surrogate outcome, should prove at least as safe as phototherapy, assuming equal efficacy in limiting peak bilirubin level.

[Slide.]

So, the risk-benefit that we need to look at depends very much on the endpoint that we select, whether we pick preventing kernicterus, preventing the need for exchange transfusion, some maximum bilirubin level whether it is 20, 19, 18, 17, 16, 15, whatever number we pick is going to mandate then a different balancing of the risks and

benefits for each endpoint.

The safe and efficacy tradeoff, nothing is ever perfectly safe and 100 percent effective. There is going to be a balancing.

The risks of developing kernicterus and/or other irreversible neurodevelopmental impairment should be at least equal to the risks of an intervention at any given bilirubin level, again assuming that it's 100 percent effective. If it's less effective, then, of course, perhaps the risks of the intervention need to be even less.

[Slide.]

Now, this reflects to some extent the notion of equipoise, the position within which we are truly uncertain whether we are uncertain as an individual or at least uncertain as a community of experts about the comparative merits of the two different interventions.

[Slide.]

In trying to take this notion of equipoise into this setting, I tried to ask myself what does it mean to say I am in equipoise or we are in equipoise in this setting. It is that level of bilirubin at which the risks of the intervention are comparable to the risks of irreversible

neurodevelopmental impairment, what are the risks of that bilirubin level again assuming effective intervention.

Other ways of stating this is that the risks of whatever intervention we are considering using, whether phototherapy, exchange transfusions, or medication, to stop the rise in bilirubin needs to be comparable, balanced with the risks of the impairment of that bilirubin level, below bilirubin at that point, the risks of the intervention exceed the risks of the actual condition itself.

[Slide.]

Now, the treatment paradigm is perhaps applicable for a subpopulation of newborn infants at known risk. It struck me as interesting that most of the early studies were done in infants with increased production, so I asked myself whether going forward we should begin to make distinctions between, if you will, a condition of production versus slow elimination and begin to parse out the population of infants that are at risk for elevated bilirubin in that manner and begin to wonder should there be differential interventions based on that.

This, of course, if went that direction, would have a big impact on the kinds of target

populations that we would select for our interventions, whether it is newborn infants with increased production or so-called healthy infants who may have an elevated bilirubin due to slow elimination.

[Slide.]

This has been touched on a bit. One of the major issues that we need to talk about is at what risk for what, and, of course, the numbers needed to treat for any given intervention at any given bilirubin level will impact then on the risk-benefit assessment of that particular intervention, and these are just numbers that were taken from the reports that were part of today's documents.

So, there are really two questions: what is the acceptable false positive rate for selecting infants at risk for an elevated bilirubin, say, above 10 at any given bilirubin level? Another way of asking that, which was an earlier question by Norm Fost is what is the acceptable false negative rate, if you will, upon discharge if you are trying to exclude infants for coming back for follow-up for bilirubin. All of these are questions that we will need to struggle with, the answers of which

are not, from hearing the discussion, obvious to me.

[Slide.]

Finally, what about the ethical and regulatory issues in study design. Now, briefly, when we look at pediatric research, if that child is not going to have the possibility of direct benefit, there is limits about what we can do as far as risk, and even if the child is going to benefit, there is limits about the justification for that risk exposure.

[Slide.]

I am not going to spend a lot of time on the non-therapeutic risk in the interests of efficiency, but basically, this notion of minimal risk, which is debated about how it should be interpreted, but basically, tries to get a handle around the risks that if there is no benefit to that infant, we should restrict those risks to no greater than minimal risk, of if we consider that infant to have a condition, maybe a minor increase over minimal risk.

So, when you look at some of the components of a study, certainly blood sampling and PK data, you know, regardless of whether or not a

parent wants their infant to be stuck with a needle, that's a separate question, or would consent to that.

I think most IRBs would consider that if the sampling follows closely sort of the routine sampling you would have for the following of a child with hyperbilirubinemia, that they would consider that sampling either no more than minimal risk or even a minor increase over minimal risk, but either one would likely be approvable by an IRB if it followed kind of what our standard practice is, and generally, blood sampling is considered minimal risk even if it went above that to a reasonable number and volume and frequency. So, I don't think that is the issue.

[Slide.]

The issue is going to be then judging the intervention itself. The regulations, although they predate this notion of equipoise in the literature, I think roughly try to capture this notion of equipoise or balancing, and this is taken from the regulations themselves and it particularly is 21 CFR 50.52, which is the FDA version of the pediatric regulations.

The IRB is supposed to allow a trial to go

forward if there is two things that that trial satisfies under the assumption that that infant has the prospect of direct benefit.

The first is that the risks must be justified by anticipated benefits. That is within each arm of the trial, so that the risk of the intervention and the anticipated benefit of that intervention is relatively matched for that particular arm.

So, for example, if there is a placebo intervention, you are going to assume then that the risks of the placebo and the benefits to that infant are roughly balanced, and that is what I call internal equipoise. Each arm of the study has to have that kind of balance.

But then there is another relationship that I call external equipoise or even equipoise between the arms, which is this risk-benefit relationship needs to be at least as favorable as available alternatives, and it is sometimes lost in the discussion of this, that it is not only the two arms of the trial itself, but it is also what that infant may or may not be getting that they would otherwise receive, so that you need to have a sense that there is balance between the interventions and

the arms. That needs to be the balance within this case. I could give examples, but I would probably come up with ones that are not pertinent to bilirubin.

So, the question is are the risks of the intervention justified by the anticipated benefit. This relates as much on the selection of outcome - the risk of a medication to avoid phototherapy, the risk of phototherapy to avoid a bilirubin above 20, the risk of a medication to avoid kernicterus. Each one of these has a different risk-benefit balance, and each one of these, depending on how you designed a trial, to put one arm against the other, would have a different sense of whether we would be more or less certain about the balancing between those interventions.

Then, again, the risk of medication versus the risk of phototherapy at any bilirubin level, for example, if you decide to treat at 17 or 16 or 15, what would you say to a mother who is asking what is the risks of phototherapy at this level versus the risks of a medication, and could you say that medication in the trial or at least in the trial where you are randomized perhaps to phototherapy or medication, is, in fact, in

equipoise.

That is a question that we would need to ask and answer in the affirmative for a trial to be able to go forward.

[Slide.]

So, to justify a risky or less safe intervention requires a greater anticipated benefit, and not simply the ability to achieve the benefit whether achieving that benefit is worthwhile. So, that is a question we have to ask.

I think I am leaving you with my final question, which is sort of a whirlwind tour through my remarks, which is I think the important question that we need to ask and answer, and I suspect we will not be able to answer it today, but whether we end up in the same position both looking at the issue of sound research design with respect to surrogate endpoints, but also looking at the sort of ethical analysis of equipoise, is that really the key issue here is appropriate outcome selection to reflect genuine benefit for the selected target population, so we need to define in the course of answering that question, not only are outcomes that we think are appropriately selected for the design of a trial, but what benefit we anticipate

achieving by having selected that outcome and then what population we think that is appropriate to then target out interventions towards in order to make a change in that outcome.

Thank you.

DR. CHESNEY: Thank you very much.

I think this is such an important issue, are there any questions? We could probably entertain a small number of questions for Dr. Nelson before we go on with the official questions.

DR. FREEMAN: May I ask a question of Dr. Nelson? If the FDA is not to be involved in policy, in social policy questions, and the IRBs are not to consider social policy questions, then, if you are going to use a medical intervention to avoid phototherapy and the consequences of hyperbilirubinemia, and since as the problem has been presented to us with phototherapy, it's the women getting discharged early and the difficulties coming back, how do you factor that into the equipoise?

DR. NELSON: Maybe I stated it too quickly. I think the IRBs are directed not to look at issues of public policy, but personally, I think that although FDA may or may not agree, I think is

within the purview of this notion of promoting the public health, and where that comes in is trying to decide what's the appropriate safety and efficacy profile since, you know, what does safe enough and what does effective enough mean in the context.

As I recall that first slide that went up, that Dianne Murphy showed where the different balancing is, where do you balance that relative to the volume of individuals that a certain drug would be targeted for and the indications. So, I do think that is within the purview of trying to decide from a public policy perspective what is the appropriate intervention.

The only question I am raising is when a lot of the root causes for this are systems issues that are unrelated to the drug. Maybe a drug development program would answer that, maybe it wouldn't, maybe universal screening would answer that, which is what I heard a number of our speakers argue for, maybe some other systems approach within the healthcare setting would begin to address that.

I was simply raising that question for our consideration.

Discussion of Questions 2, 3, and 4

DR. CUMMINS: First, I want to thank everyone for sitting through quite a complex series of presentations and also comments during our public hearing.

We don't have our questions available to you as PowerPoint files, but you do have a handout in front of you in the packet that was set out in front of you today, that have all the questions on them in the second page following the agenda. Tom is trying to load them now, but we can also start to walk through them.

We actually decided to skip Question 1 and go straight to Question 2, and we reordered the agenda today because we felt it was important that Dr. Nelson's talk go before Question 2, and I will read that to you now. It's a multi-part question and we would like you to really discuss the various issues that are raised in this question.

Question 2. In the context of current medical practice, including phototherapy, should drugs be developed for an earlier intervention to prevent hyperbilirubinemia in newborn infants?

In answering this question, we would like you to please discuss the following:

Your understanding of the relationship

between bilirubin toxicity and neurodevelopmental outcome;

How you define the population at risk for complications of hyperbilirubinemia;

The intervention sequence and what that might be, should it be more screening--and these are just examples, there might be other interventions that we have not mentioned--but examples might include more screening, additional monitoring and assessments, phototherapy, hydration, pharmacotherapy, cessation of breast feeding, changes in infant nutrition, home nursing visits, and why would you propose that intervention sequence.

Let me just also say for those of you that are new to this process, what we will do is we will discuss each of these questions for about 15 to 20 minutes, and then we will move on to the next one. That is how the question process works.

With that, I will turn to Dr. Chesney and open the committee up for discussion.

DR. CHESNEY: So, we are being asked the question of should drugs be developed for an earlier intervention and to take into consideration our understanding of bilirubin toxicity and

neurodevelopmental outcome, who are the high risk populations, and with respect to the intervention sequence.

Comments?

I should also tell you that it has been suggested to me that we do a round robin after Questions 3 or 4, so that we hear from everybody, so everyone will have to come to grips with this issue at some point.

Dr. Mattison.

DR. MATTISON: I guess there is no reason to think that therapeutic strategies including medications should be excluded from consideration in dealing with strategies to prevent hyperbilirubinemia, but it seems to me that the question has behind it a set of qualifiers or steps that may need clearer explication, for example, and it has been brought up repeatedly in the presentations, one of the areas that appears to be missing in terms of thinking through the issue of hyperbilirubinemia is the actual strategy for identifying those kids.

So, while drugs might be a good strategy, it seems like the basic public health surveillance that we often use to identify our problem hasn't

yet been put in place.

So, I am not answering the question, I am backing away from it perhaps.

DR. MURPHY: I think you are giving us the level we are trying to lay out of all the issues that you have been presented today - what would be the role of drug development in this environment and how do we deal with these issues of definitions of occurrences, definitions of when we intervene, outcomes, you know, those all are things that you have heard about in various forms today, that you would try to synthesize that into some thoughts about how one would go about considering developing a product in this arena when you have to address some of these issues of what is the relationship because we have to be able to know what the endpoints are, and to be able to get to the endpoints, you have got to know where you are going to intervene.

Again, it is trying to bring back all those issues you heard today to an approach developing products in this present environment. So, you were right, it is trying to synthesize all that into a few bullets.

DR. CHESNEY: Dr. O'Fallon and then Dr.

Danford and Dr. Hudak.

DR. O'FALLON: The question here is really a mixture of a whole lot of stuff and I think we have to sort out what the major themes really are. I think the very first theme is a matter of, as you said, identifying the patients, the babes, the children that are truly at risk.

So, there is a whole diagnostic issue that needs to be dealt with, and it has nothing to do with treatment, it has to do with diagnosing and characterizing that.

The second part is okay, if we are going to treat, it sounds like there are only two treatments right now, the treatment quiver has only two arrows in it, and a third one sounds like it would be very appropriate to have a third one, so, yeah, go ahead and develop it for something, but how to do that and how to test it brings up all the issues that Dr. Nelson was bringing up, all of the design issues, choosing an endpoint, you know, and what you are going to buy by it, and another thing that was brought up earlier this morning and has just been sitting there, but the negative predictive value of these treatments.

It is very important, it seems to me, when

you have a rare disease, a rare condition, that the testing be capable, it is very important to prevent a lot of kids that don't need it from getting something.

The other part of it is, that has to be dealt with, are the long-term effects. I think those of us with more gray hair in this room, the problem is that we have been around and we have seen, I can name you several treatments that I was told at the beginning, oh, this is wonderful, there are no long bad effects at all to it. Yeah, sure. They do show up and so there are issues here that have to be dealt with.

So, it seems to me there are basically four things going on here, and we have got to sort them out and get answers for each one of them.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: I would like to address the first bullet point under Question 2, my understanding of the relationship between bilirubin toxicity and neurodevelopmental outcome.

Despite the wonderful presentations of a large volume of information today, I would characterize my understanding of that relationship as poor. I would point to the large numbers of

children in Northern California presented to us with bilirubin levels in the classically scary ranges who seem to be neurodevelopmentally fine.

I would also point to the allusions that our speakers made to perhaps some neurodevelopmental issues of more minor importance occurring in children whose bilirubin levels were well within the ranges we would accept as safe.

I don't know what the relationship of that is, and the implication of that, as I looked at Dr. Nelson's slide, bilirubin levels are not necessarily a very good surrogate for kernicterus as he laid out what makes a good surrogate. That is a very difficult point for me right now.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: I guess I will make some relatively simplistic answers here. I think the first question about the relationship between toxicity and bilirubin and outcome is there is apparently a lot of biological variability. Some babies can sustain a higher bilirubin level than others without damage, others wind up apparently having some toxic effects at lower levels, and there is no way of knowing ahead of time how a baby is going to behave in that setting.

I think the evidence is persuasive and undeniable that babies don't get kernicterus without having bilirubin levels that are higher than we like to see in most cases with the exception of certain babies with comorbid conditions like sepsis where they might get effects that lower levels or the blood-brain barrier perhaps is impaired.

So, I think that we have to grant from all the evidence we are not going to get any better knowledge about this issue at any time in the future, that, yes, there is a relationship between high bilirubins and the risk of kernicterus, and it is very variable and it is very unpredictable.

The issue of should there be drug development, I think the answer to that is yes. I think we are all struggling with how to sort of phase that into testing and what are the study designs, but the basic answer is yes. If we had a drug that had no side effects whatsoever, I think that would be--and we knew that for a fact--that would be a no-brainer. I think every baby in the country would get a drug to prevent hyperbilirubinemia at birth, just like they get vitamin K and erythromycin ointment for the eyes,

and things like that.

The question is understanding what the level of acceptability of risk is with that sort of intervention, and that's a big question. If you consider we don't know how many cases of kernicterus there are in this country out of 4 million babies every year, but if it is 1 in 200,000, that is 20, if it is 1 in 100,000, it is 40, if it is 1 in 50,000, it is 80, so even if you say that it is 100 babies a year, and think of that, that is a very, very small percentage.

So, if you say all right, what happens if there is a complication from your treatment, that is on the order of 100 out of 4 million, you will never find that in a randomized placebo-controlled study. You will have to wait and hope and pray that you do not experience that once you go to the route of having prophylaxis in every baby. There will be no way of knowing until you do that.

But we do need a treatment. Exchange transfusions are not nice, they are complex, the expertise is deluded, there are neonatologists out there practicing who have never done an exchange transfusion, I daresay.

There is a mortality, there are other

morbidities, and exchange transfusions do not necessarily prevent kernicterus either. I just reviewed a legal case from a very well respected busy tertiary nursery where a baby came back at two or three years of age with sort of what you would call I guess, not the full-blown kernicterus, but a little bit of choreoathetoid CP and hearing deficit, and this baby was sitting in an intensive care nursery getting bilirubins monitored every 4 to 6 hours, and because people were reluctant to do exchange transfusions, the bilirubin went up to 32, and this kid had an exchange transfusion, but then did have the clinical sequelae.

So, I think that certainly if there had been a drug available to prevent kernicterus in that baby, it might have been used at an earlier point in time, that baby might have done much better, and that would be a relatively limited population.

But I think yes, we do need a drug, we do need some development. The real hard questions are who do we treat, when do we treat them, and what are the ways that we can develop to sort of improve the system, so a lot of these babies don't slip through the cracks.

DR. CHESNEY: Yes, Dr. Oh.

DR. OH: I am willing to stick my neck out and say that the answer to the question should be yes, and I tell you the following reasons. One is that although we don't know the exact incidence of kernicterus, the fact that we do see them, particularly with the data, in the population-based data from New Jersey, suggests that we do have a problem, and we also don't know what the threshold number is for the bilirubin that will cause kernicterus.

On the other hand, understanding the pathophysiology of kernicterus, we know that although there is no threshold number that we are worried about in terms of producing kernicterus, we do know that the higher it is, that might exceed the so-called binding capacity of albumin for bilirubin, the more risk you are taking.

So, anything that we can do--and we also know that phototherapy itself has some problem in terms of keeping the levels at a certain range on the basis of perhaps, not so much the effect of the therapy itself, but the behavior and system involved that might cause problems in terms of allowing the bilirubin to a certain level--and that

anything that we can do to try and keep the bilirubin level down as low as we can will be I think a benefit.

I think it will be a good surrogate, not so much a surrogate for the outcome, but in terms of keeping it low enough, so that we are in the comfort zone, so to speak. But I hasten to add that any kind of drug trial, any development of the drug should be very well designed to not only look at the acute, but also the long-term potential side effects of a drug that may have some problem that we don't know about.

Right now we don't know what the potential complication is for this particular drug we are talking about, and any drug trial should have the safety aspect looked at very carefully before, you know, so that we will come out with data will show that, not only that it has some benefit, but the side effect is minimal, going to the point about balancing the risks versus benefits.

So, that is my comment on the issue. I think the important thing is that despite the guideline and maybe because the guideline being too gentle in terms of managing the bilirubin, in spite of the phototherapy that we use, we are seeing

kernicterus in our population, and I think that we need to develop another intervention to try and improve our ability to handle the bilirubin in the newborn period.

DR. CHESNEY: Thank you.

Dr. Lau.

DR. LAU: I think there is still quite a bit of debate as to whether bilirubin is a neurotoxin, but I think in terms of causality, but I think the evidence for association is fairly strong.

Then, there is also strong evidence to suggest that by lowering bilirubin with the treatment of phototherapy, we would reduce the incidence of kernicterus.

For the other question about defining the population, my perspective is often from the evidence-based approach of reviewing the literature is backward, that is, I often end up with studies rather than prospectively designing trials, so the approach that we often take in looking at the validity of trials would be what is known as the peephole process or looking at a patient population, what intervention were examined, and what are the comparators, and then what are the

outcomes.

I think we have discussed a lot of those issues today, and those are not easy things to tackle in a population, I think obviously we are not thinking of treating millions of babies, and defining the population is going to be difficult, but I think we may have some tools from some of the work done by various investigators to try to define a population.

The intervention, I think that is more well defined and there is only one drug being considered. The comparators, that also would be somewhat difficult to define exactly what it is being compared with.

The outcomes, this condition is not a disease. I think there is also going to be quite a bit of uncertainty, how best to define that.

DR. CHESNEY: Thank you.

Dr. Wilfond, I think was next, and then Dr. Stevenson.

DR. WILFOND: With regard to the question of kernicterus, it is unclear to me what is going on with that, however, I am not sure, I feel comfortable without even knowing that making some other reflections.

I think that the slides that were presented, that suggest that the causes of kernicterus are behavioral make sense, and in that regard, it would seem like having a drug wouldn't necessarily address that problem.

However, I am still in favor of the idea of drug development conceptually because if we look at the choices that Skip gave us for what we might want to make as a comparison, if we believe at some point it is a reasonable thing to do phototherapy on some people, if we had a drug that was sufficiently safe and sufficiently expensive to reduce the number of individuals who had phototherapy, that would be a good thing.

So, I think it is going to depend upon, in the end, its safety and its ultimate cost, but I think the objective would be to decrease phototherapy.

DR. CHESNEY: Thank you.

I have Dr. Stevenson, Dr. Glod, and Dr. Fost next.

DR. STEVENSON: I just want to weigh in on the issue of bilirubin toxicity although I think that in the human circumstance, it is hard to do an experiment that would do prove that causative link

definitively.

For those of us that work in the animal model, there is no question that bilirubin is toxic, and you can create conditions of a variety that mimic what we would see clinically and see the impacts of those factors like infection, and so forth. There are biological ways in which that can be understood.

We haven't spent a lot of time talking about those models today, but there is a whole area of biology that is focused on that, so I don't want people to think that there is any doubt about bilirubin as a toxin from a biological standpoint under certain conditions and at certain levels.

The comment that I would like to make besides that, though, is to sort of remind people that there is an undeniable biology here, and part of that has been addressed by a drug like phototherapy light, and that part of the biology is the limited elimination that the newborn has.

We don't use that medicine very well, but we can probably use it better and more efficiently. But the other part of the biology is really the production of the pigment, and I told you that all newborn babies have a higher production compared to

adults, about two or three times higher, and for many of the individuals who find themselves on these unfortunate lists, being near term or individuals that develop other conditions, like G6PD, they have very high production rates of the pigment.

So, there is an undeniable logic that an additional arrow in the quiver is required, which addresses that part of the biology, so as a scientist, the logic for that is undeniable.

The issue then becomes one of putting that in the context of your other arrows and when do you shoot them, and I think that some of you are touching upon those more difficult questions about how best to identify the individuals that would be the target of that kind of intervention.

I think that the kinds of drugs that are represented by this new class of heme analogues, that are competitive inhibitors, suggests that there is a way to use them that can target them very precisely. They may even work in more precise ways than phototherapy works, and could be very, very useful in the circumstance.

So, the last thing I would say, to make this thing come full around for you, is that

because of the unpredictable nature of the onset of this condition, and the fact that when you see it, you are deep into it, and unlikely to be able to prevent it, because it is happening. There may be some debate about if you get it early enough, you may have some reversibility.

Then, you are faced with there being the best quiver solution, the best arrow in your quiver, because by that point in time, you are already dealing with something that is upon you. It is hard to use as a preventive tool because the bilirubin is not there to actually undergo the photo isomerizations.

So, the chemical approach is actually a more logical approach if you are interested in prevention and avoiding something that is, as you have heard, very hard to predict.

So, I would just like to leave you with those thoughts.

DR. CHESNEY: Dr. Glod.

DR. GLODE: I sort of have two lines of thinking I wanted to bring up. The first one would be that at least from my sense of top priority, the question would be that the priority is prevention of kernicterus and perhaps other subtle forms of

neurologic impairment, and the question would be do we currently have effective therapies that we believe can at least prevent the tip of the iceberg, the kernicterus that we recognize.

It seems to me from the discussions today that the phototherapy and exchange transfusion are effective therapies. If there were another effective therapy that was proven to be more effective or equally safe to those two, then, I would certainly favor its development, but I would favor that it be studied in selected populations of children with hemolytic anemias predominantly.

The second issue has to do with the paradigm that was brought up today. The one we heard most often was the vitamin K deficiency paradigm, and all babies get an injection of vitamin K. But I would like to bring up the other paradigm of the newborn screening, which deals with rare conditions, but really does not, except from a public health point of view that we can't effectively identify and track patients, so we have systems set up.

We don't say we can't prevent cretinism because it is impossible to do a newborn screen and follow it up. We say we can do that, and so we

have systems in place, at least in Colorado, through out state health department and through our section of Pediatric Endocrinology, that we follow up everybody with an abnormal thyroid screen. We just don't give all babies thyroid hormone, and we follow up all babies with abnormal PKU, et cetera, where we are able to do that effectively and prevent those rare but devastating conditions.

So, I just think we should be able, even though again maybe it is not within the purview of the FDA, but somehow we should be able to develop public health policies that identify high risk children based on the nomogram, and they get a letter sent home with them, they are reported to the state health department, they are followed up on, they get another bilirubin, they get interventions, and we prevent kernicterus.

Now, I am again not against developing another drug, but I am really worried about giving it to 4 million children and the safety profile issue, but I am all in favor of preventing kernicterus by identifying babies and treating them early.

DR. CHESNEY: Thank you.

Dr. Fost.

DR. FOST: We are all concerned about studying history so we don't repeat it, but the question is which historical examples are relevant. There are several examples of newborn screening and treatment that I worry about, that I am concerned we don't repeat.

The first would be PKU screening, the granddaddy of all newborn screening and intervention programs, and there are several echoes with this story that concern me.

In 1960, we had a rare disease, its biochemistry was very well worked out. It was very clear by 1960 that if you reduced exposure to phenylalanine, you could ameliorate and even prevent retardation, and there was great passion by advocacy groups, including affected families and Dr. Guthrie himself, and the president John Kennedy.

So, we mandated PKU screening in every state, and it was 10 years before we realized that the screening test was too sensitive, that is, that 95 percent of the children with high blood phenylalanines, not just Guthrie's, but confirmed by whole blood assays, did not have PKU, but had a benign form of hyperphenylalaninemia that were

destined to be normal.

Second, that restriction of diet could be just as harmful as excess, that is, the toxicity of the diet was not appropriately anticipated, so many of these normal children were not only made retarded by the diet, but were killed by severe protein malnutrition.

We don't know how many. We know that it took a decade, and it wasn't until 1972, '71, '72, that the Institute of Medicine formed a panel, and we now understand it perfectly, and we now know how to identify the subset of children with elevated blood phenylalanines who are really destined to become retarded, and we now know exactly the right dose of the diet.

All this sounds very worrisomely similar to what we have now, that is, we have a cohort of children who have an abnormal screen, whether it's visual or biochemical. We don't know exactly what subset of them is destined to have anything very bad happen. We know that kernicterus is very bad, but I agree with Dr. Danford, it's a little unclear whether the vast majority of these children are going to have anything very bad happening to them.

We have an intervention that looks very

promising, whose biochemistry is well understood, but we just don't have a lot of data on the safety of it and maybe not as much as we would like on the efficacy either, although that seems a little bit more clear.

There are five other examples. I mean bicarbonate for respiratory acidosis, hyaline membrane disease, the biochemistry was well understood, the kids were all dying of severe acidosis, just give them bicarbonate, the Aschner [ph] regimen, it will be fine, and it was 10, 15 years before Mike Simmons did a randomized, controlled trial, and said it was killing kids, it was causing intracranial hemorrhage in some, and now nobody gives it, but there was no prospective, careful trial for a decade.

Oxygen. For a century we inspected the kids, these obviously need oxygen, then, we got more fancy, we measured it, give them oxygen, it can't possibly hurt, and look how devastating the consequences of hypoxemia are.

Then, finally, we learned that it had a dose-response curve, you could give too much, and so on.

Antibiotics. I mean sulfonamides, there

are half a dozen examples, and the number of normal children who have been killed by these things is probably in the tens of thousands.

So, it is not that we don't care about the small number of cases of kernicterus or PKU, or whatever, the question is how to capture those and reduce them even further or eliminate them, and not harm a lot of other people in the process.

So, it seems to me doing studies that, as Skip put it, that would maximize the benefit-risk ratio for each child in a study, so a child who has a discharge bilirubin of 5, I assume has nothing to gain from being in a study of a new drug that might prevent kernicterus. One that has a discharge bilirubin of whatever the number is, a much higher number, 15, obviously has a lot to gain by being in this trial, and it might avert something that maybe is more risky, I don't know if phototherapy is more risky than this drug or not.

It seems to me the first challenge, is drug development good, of course, it is good. I mean it is self-evident that if we have a drug that is equally effective as phototherapy or exchange transfusion, and it is cheaper and safer, of course, it should be preferred, but that is what we

are trying to find out.

So, in trying to find out, it seems to me we should be as narrow as possible in the beginning, so that the children who are entered into these studies have the most to gain and the least to lose, we have the least number of kids in these studies who are at almost no risk of developing a problem.

Those are just some of thoughts about that. I want to say a second thing, which is the elephant in the room that we are sort of not allowed to talk, which is cost, not an FDA concern, not an IRB concern, it is nobody's concern in this country, so we have these expansive technologies, we have these innumerable examples of drugs that are developed for very narrow purposes, in this case, to prevent a disorder that affects a mere several hundred children a year, terrible for each one obviously, but we know that that is not how it is going to be used once it's approved, and that the FDA is virtually powerless to stop the expansive use of it.

We know how the pharmaceutical companies manage to influence that even though they are legally not supposed to be marketing off-label

uses, but it has happened so over and over and over again that, as the background materials suggest, the concern always is that even if we were able to reduce the number of children with kernicterus, what will the cost be, that is, how many millions of children will get this drug who have nothing to gain from it, and what will the toxicity be.

Now, if it's like vitamin C, we prevent lots of scurvy with vitamin C or like vitamin K, if it's virtually riskless, then it won't matter. If it's free, it won't matter, like vitamin C or virtually free, but if it costs a lot, either in terms of toxicity or in money, then, we have a problem.

The cost in terms of toxicity, FDA is authorized to pay attention to and will. The cost in terms of money, they are not, so we might have another, what, I don't know, billion dollar drug on the market that does nothing for 99 percent of the people who get it? And we continue to have a healthcare system in which 40 million people are insured, one-third of them children, and we say we can't afford to do anything about that, but we can afford to give everybody 10 protoporphyrin.

So, those are the two things that worry

me, the one that we can't do much about. The first one, we can do something about, which is to make sure that studies that are designed are done in a way to maximize the benefit to the children who are in the study, so that eventually, hopefully, the use of the drug could be limited to those children who have something to gain from it.

DR. CHESNEY: Thank you.

Dr. Newman and Dr. Freeman.

DR. NEWMAN: I want to comment on these two examples that have been used, the vitamin K and the newborn screening. I appreciate Dr. Fost's PKU example, which I hadn't heard before.

It is a little bit misleading to compare, oh, all we need to do is do a bilirubin level that costs a dollar or two dollars and ten dollars, it could be like newborn screening. If you picture, if your screen for hyperthyroidism had a specificity of 40 percent, because the recommendations for the systems approach to hyperbilirubinemia screening are that the top 60 percent, it is only the bottom 40 percent we are reassured they don't need another bilirubin level, the top 60 percent, they all are labeled as having a bilirubin problem and need to come back and all

need a mandatory second bilirubin test.

So, that is sort of the problem for me, which is that it would be wonderful if we could do a test before they left the hospital, that said yes, you have a problem, you don't need to worry, and it had anywhere near the sensitivity and specificity of our newborn screens, but they don't.

One of the speakers said prevalence should not be an issue. Prevalence is an issue when you have diagnostic tests that aren't very good, and you have high false positive rates, and the lower the prevalence, the higher the number of people you are going to need to treat and the more false positives.

The trouble here, the AAP, in their new guidelines, are not recommending universal bilirubin screening, and it's for this reason, the test just does not seem to be that good, it is not clear what to do with the result.

DR. FOST: Can I just ask you one question? That is why asked Dr. Ip this morning what the negative predictive--I understood one of his graphs to show a negative predictive value of 99.5 percent. That is pretty darn good.

DR. NEWMAN: Again, if you are in the 40

percent who have, you know, the bottom 40 percent. The trouble is the positive predictive value, if you have a bilirubin level that is in the top 60 percent, and therefore you are labeled, but, of course, most of those will be the false positives.

I think the vitamin K is a really good example because, you know, several years ago, many of you know there was an alarm about whether vitamin K caused cancer. There were a couple of studies in Bristol, in England, that really suggested that intramuscular vitamin K in newborns doubled the risk of childhood cancer, and the first one, people didn't pay that much attention to, it was a data dredging thing, and it was appropriately believed that it should be confirmed by another study, and the drug company, in fact, funded another study, which found the same thing, a more than doubling of the risk of childhood cancer after intramuscular vitamin K in Bristol.

Subsequent studies mostly have not confirmed that, but I think that is the kind of example, that is the sort of thing that worries me is, you know, how are you going to find stuff like that and how many years later might it be, and how big a study for how long do you need in order to

say, oh, yes, this is a drug that we can give to hundreds of thousands or millions of children to prevent something which is very rare.

DR. CHESNEY: Dr. Freeman.

DR. FREEMAN: Dr. Norm Fost made many of my comments, and I agree with him. As a neurologist, I fail to believe that kernicterus is an all or none thing. There must be toxicities of bilirubin at lower levels even though we do not detect them. So, I don't know what level is toxic or what level we should treat.

I am also concerned about costs and the cost to society. I am very persuaded by Dr. Moosa's talking about the number of poor women who leave his place with no ability to follow them up and how do we deal with that.

Yes, it would be very nice to have a medical treatment that avoided phototherapy. I think we can, by and large, we have avoided exchange transfusion, but we need something to avoid phototherapy in this population.

On the other hand, I am very concerned about the unknown toxicities of whatever medication we do, and would like to see any trial, carefully monitored, in a high-risk population, so that we

can pick up these rare toxicities of whatever drug we develop.

DR. CHESNEY: Dr. Fuchs.

DR. FUCHS: I am glad somebody finally mentioned bullet point 3. I think that is the hardest thing because as a medical community, we don't control a lot of that, things you mentioned already, that people are not coming back as it is for when you asked them to come back for bilirubins, or the other thing about going to Home Nursing visits, home nurses will not go into the inner cities to follow up these children either.

So, there is a lot of issues that we, as the medical community, can't control because of the whole system, whether it's HMOs or other things, that I think it is going to be very hard to answer the intervention sequence when we don't have a lot of control over that until, like you mentioned, the more screening, until there is a better test, the same thing. You can ask for additional monitoring, but if you can't get them back, then, the system has failed.

DR. CHESNEY: Dr. Smith, and then Dr. Ip.

DR. SMITH: I am a chemist, so I believe that chemicals are saving the world and will

continue to save the world, so, of course, we need as many arrows in our quiver as we can possibly get, but two things I heard today have me thinking.

One was Ms. Sheridan told us that really the difference between her two children was a bilirubin test, and I think it is shocking that regular monitoring of Cal didn't happen.

Then, Dr. Valaes told us that in Greece, that as soon as they discovered phototherapy--I wrote the words down--the problem was no longer there. I, as a chemist, of course, as many drugs as we can have available, the better, but I am kind of wondering if there is a problem.

DR. CHESNEY: Dr. Ip, and then Dr. Aschner.

DR. IP: The way I think about the issue is, as a practicing pediatrician, without even thinking about your qualifiers to your question, if I am presented with a drug that is as safe, as good as phototherapy, would I use it over phototherapy, the answer is clearly yes.

So, to answer that question, yes, we should develop this drug. Now, I don't know if you folks, some of you have the FDA background document, a thick, thick book, if you turn to page

28, there is a graph. It's at Tab 6. It is basically an analysis of all the newborns who have idiopathic jaundice who develop kernicterus. It's the case reports, the reviews that we did for the AAP report.

If you look at the distribution, actually, 91 percent of these cases had bilirubin 25 or greater. There were three cases between 20 and 25. I am just doing some rough calculation. So, if you are going to try to capture that particular population, if you are looking at 25 as the cutoff, you would be treating about 6,000 kids, but if you are using 20 as the cutoff, you would be treating 80,000 kids. That is something that we need to decide how many kids are we willing to treat and experiment with it.

DR. CHESNEY: Thank you.

Dr. Aschner.

DR. ASCHNER: I am coming from a little bit of a different background. I guess my first comment would be that I am almost not sure that I have seen enough data to make a good correlation between the level of bilirubin and kernicterus. In trying to think more about it, I would say that there may be other issues in addition to bilirubin

levels that might be important in terms of determining whether a neonate would go on and develop kernicterus at the molecular levels, cellular level, in terms of extrusion of bilirubin from the brain and other parameters.

Now, looking at a drug, I think obviously, I would be in favor of developing a drug, but thinking again about toxicity and the potential that millions of children will be exposed to it, I would like to know much more about the safety of the drug, and I am just going to posit a simple question for everybody to think.

Let's just consider, for example, that a drug has a 5-point IQ reduction in the general population, what would that do to our society in terms of exposure to a drug in 4 million children over 10, 20 years, and I am not exactly sure actually how you would go about doing a randomized study to pick up the effect.

DR. CHESNEY: Dr. Gorman, Dr. Nelson, Dr. Stevenson, and then maybe we will stop at that point and ask the FDA folks if they have enough information on this issue, that we can move on.

DR. GORMAN: I am another one who learns well from analogies or at least I am impressed by

analogies, and the analogy that moved me the most today was the lead analogy.

Bilirubin in the blood doesn't hurt anybody, bilirubin in the brain hurts people. In the procedures of any clinical testing, if there is any way to measure the bilirubin in the target organ rather than the surrogate marker that we use so poorly, and therefore are troubled with our results, would be a big advantage to ongoing studies short of brain biopsies or autopsies on clinical subjects or human subjects.

I am convinced that bilirubin is a toxin once it gets in gets in the brain.

I will also agree as a practicing pediatrician that if it was shown to be as effective and as safe as phototherapy, it would replace phototherapy as a terrible, you know, with a great rapidity. The practitioners in clinical practice would vote with their feet very rapidly and phototherapy would disappear if you could replace that with a single shot of any agent, be it this one or another agent.

Having said that, I will address the 600-pound gorilla or the 800-pound gorilla, or however big it was, in Dr. Fost's opinion, there

will be therapeutic creep. We will start this with a very small group of people. In the clinical trials, it will get tested with children with hemolytic disease and then perhaps children as they enter phototherapy as an alternative to phototherapy, and then it will be used to see if it can prevent phototherapy, and then it will be generalized to the population.

That is the therapeutic creep as I predict it if no untoward safety data come out shortly, and I would say that this is one of those times which is exactly why we need clinical research. I would rather know if this drug is unsafe early rather than later, because I see this drug potentially being used on 4 million children a year, 4 million infants.

The other thing that I think as pediatricians, we all see intuitively, there is a therapeutic window which makes this very difficult for this drug. It has to be used early, it can't be used later. It is again like lead, if I ingested lead, there will be those accusing me of that around the table, but if I ingest lead now, I will be at less risk than if I ingested lead at six months of age, so there is a therapeutic window for

this drug that is also very important.

Is there an adult equivalent to kernicterus with high bilirubins? I think the answer is no.

So, there is another issue about and will that same therapeutic window allow us to see toxicities of this drug that we would not otherwise see.

DR. CHESNEY: Thank you. Actually, it was an elephant, Dr. Gorman.

Dr. Nelson.

DR. NELSON: I agree, I think it's a toxin. I am trying to play with some numbers and I am not necessarily facile with them, but I am struck by the difference between the numbers that were presented out of California and then the numbers, although preliminary, from the New Jersey surveillance, having lived in New Jersey. I was born in New York, so maybe I am protected from that. But 8 per 100,000 compared to a lower number, and the question is if you assume that the bilirubin was greater than 20 in all of those that were at risk, I was trying to calculate what would be the incidence per 100,000 of those greater than 20 for kernicterus, and then add to that the

question of subclinical or irreversible neurodevelopmental changes that could be related to bilirubin.

That would give you a number and then the question is would you consider that an appropriate safety profile for any intervention that would prevent anyone from getting into that range of 20. You end up with a number, such as using New Jersey statistics, 320 per 100,000 if you assume all their cases of kernicterus occurred in those who had a bilirubin greater than 20.

Then, the question is what kind of trial would you need to see that incidence of neurodevelopmental impact, and it would (a) be big, but I suspect if we had a drug that we gave to 100,000 newborns and we got 320 cases of what looked like kernicterus, we would consider that highly unacceptable.

I don't really have a conclusion of these reflections, but the debilities sort of trade off the interventions. You may end up just in a simple situation where you are talking with the parents about the relative risks of each intervention, which is what happens now with exchange transfusion, phototherapy, and if the trust you,

they will let it go up into the 25 range, and if they are risk-averse on that, they may say exchange at 22 or 23, or 28 these days, so there is some variability in practice based on that conversation.

DR. CHESNEY: Skip, I am sorry, maybe it was because I was writing, I didn't quite get the 300--I understand the first part of how you were approaching this, but--

DR. NEWMAN: I may have the math wrong. Part of it is coming up with assumptions here. If you take the New Jersey statistics, 71/2 per 100,000, round it up to 8, then, the question is if you assume that all of their cases occurred in infants with bilirubins greater than 20, consistent with the report, then, what is the incidence in infants greater than 20 of kernicterus based on their statistics, and I get 320--400, so it is reasonably large in that population depending upon what you pick.

Then, you go down to 15 or down lower, then, you get obviously lower numbers, but the safety profile of any intervention, if the risk is 400 per 100,000, I mean I suspect there is a lot of drugs on the market that are not considered that safe that might not have that high an incidence of

serious adverse effects, similar to neurodevelopmental changes you see in kernicterus.

So, if the New Jersey numbers are correct as opposed to the California numbers--and that will be a debate I am sure once that comes out--that has a big impact on how you would evaluate the safety of any given intervention.

DR. CHESNEY: Dr. Stevenson, then Dr. Newman and Dr. Hudak.

DR. STEVENSON: This is a brief comment again about production. I have heard people talk about targeting, and people use categories of infants, ABO incompatible, ABO incompatible with a positive Coombs' test, and so forth, and so on.

Those are actually surrogates for actually accurate measurements can be made to understand what a production rate is in an individual, so if narrowness of targeting is what is going to allow something to be introduced, then, you can get that kind of narrowness by actually looking at the population from the perspective of the part of the biology you want to control with the drug, and that, in fact, improves the likelihood of benefit where productions are increased as opposed to any risks that might be understood to exist or possibly

exist with the drug.

The difficulty I have with even I guess making that statement--coming back to what Dr. Fost said--and that is that if all drugs have to be subject to this issue of the creep, which I think is important to understand, it makes it very difficult to introduce anything because that means that as soon as something is introduced, it will be used if it's easy to use, and there is not an obvious complication rate or it's not too expensive.

So, I think you have to be careful not to exclude things that might be of considerable value, just to say with appropriate instruction and maybe guidelines with respect to use, knowing that there are limitations on how you can control behavior.

DR. CHESNEY: Just two more. Dr. Newman and Dr. Hudak. Then, we will return to our FDA colleagues.

DR. NEWMAN: Just a quick comment on the data from New Jersey. Those are based on discharge abstracts, so it is based on a code, and ICD-9 code and a discharge abstract, and we use those at Kaiser as sort of a screen to see were there any cases of kernicterus, found I think 8 or 9 of them,

and all of them were false positives.

If you think about if the true frequency of kernicterus as something less than 1 in 100,000, even if the specificity of the coding is 99.99 percent, occasional digits being transposed, and the 773 instead of a 776, anything like that will give you a very, very low rate of false positive diagnoses.

So, the ICD-9 code discharge abstracts, I think you really can't use for something as rare as kernicterus. I think that actually the case for what the toxicity of bilirubin is, is at least I think clearer than has been suggested so far, and that is that really, it looks like kernicterus mostly occurs with bilirubin levels over 30, maybe very, very rarely over 25, and between 20 and 25, if it occurs at all, it would be extraordinarily rare, so I want to correct what one person said.

We recommend phototherapy for bilirubins in the 20, 25 range. That is not because those bilirubins are dangerous. The whole reason for phototherapy in that range is to keep the bilirubin from rising to a level where it would be dangerous, where someone would contemplate exchange transfusion.

So, if you are thinking about this question, you know, should drugs be developed to prevent hyperbilirubinemia, it seems like there are sort of three levels at which one might use the drug. One would be actually to prevent kernicterus in people who have hyperbilirubinemia, and that would be as an alternative to an exchange transfusion, as illustrated in the Jehovah's Witness child, which I thought looked very promising, and I would have no trouble saying this either should be used or a randomized trial be done instead of exchange.

The next step would be instead of phototherapy, and still the goal here I think is to keep the bilirubin from rising higher, to keep it from rising to a dangerous level while the baby's liver matures and it comes back down.

The number of babies in whom it would be indicated for that would be presumably a few percent, the number who get phototherapy.

The last indication would be to prevent the need for phototherapy, that is, to give it ahead of time, and, of course, that is so attractive because it deals with all the follow-up issues that are such a headache for everybody, but

then, of course, the potential number of people being treated would be way higher, and the number who would be treated who otherwise wouldn't need any phototherapy would be very high.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: Just a few comments. One is I think that although we haven't really looked at the evidence, we have been told that there have been no complications that have been seen in babies who have received this treatment, and there have been several hundred, I gather, in a variety of different studies.

I would say right now that given that the risk of exchange transfusion is a 1 percent mortality, that the issue of whether or not to do the exchange or give this drug if it were available is not an issue, I would give the drug based on the available evidence.

The other issue, coming back to Dr. Fost's point about screening tests, I think maybe just once again to put out something about advocacy here, we have in this country a very chaotic system of infant screening. Every state goes its own path. There are some states that do a lot of screening and do it very well, and other states,

such as Florida, where we are still back in the prehistoric age, and do about five different screens.

There are lots of different metabolic conditions that are amenable to treatment in infants that have frequencies on the order of 1 to 2,000, to 1 to 10,000, and we do not screen as a society for these conditions even though it would require a relatively minimal extra expense in the scheme of things, and these are things where babies have long-term deficits because they aren't identified.

Even if you were to grant that kernicterus has an incidence of 10 per 100,000, I mean we have lots of things that are very morbid to children that are possibly preventable that we don't pay any attention to.

The issue of complications, I think clearly I agree with everybody who suggests that we need to target a population, but I also agree with the issue of creep. If the supposition is that one case of kernicterus is too much, by definition, any high-risk group you target to treat, even if it's only 50 percent in the population, you are going to wind up reducing the incidence of kernicterus from

whatever it is by 70 percent, 75 percent, and you are still going to have that registry grow every year.

So, for those reasons, I think you would have some creep going on.

DR. CHESNEY: Dr. Cummins and Dr. Murphy, shall we move on to the next question, or would you like more input?

DR. MURPHY: I would like to just take that entire conversation and pull a few points out that maybe I have selective hearing, but I want to make sure that these are some of the main themes that we heard here.

People are interested in a therapy, drug therapy, that that therapy clearly needs studies, these studies would have to maximize--the word was maximize the study to those who can benefit, and to maximize the studies to define the harm, in other words, define the safety profile as a theme.

I heard also that surrogate endpoints--I am just going to say it because that is really what it is--we cannot do a randomized, controlled trial for an endpoint for kernicterus, that we have to do a randomized, controlled trial with a surrogate; that the committee is I think trying to tell us,

and this is why I am repeating this, that they think that the surrogate is preventing an increase in bilirubin; and that the randomized trials would be possibilities, again, I am trying to synthesize all this, would be prevention of exchange transfusion as an endpoint, or randomization between phototherapy and a drug treatment.

The definition of phototherapy intervention somewhere around--knowing all the other things--around 20, but knowing there is a whole nomogram, all that sort of stuff, but that's what I think I have heard so far. I have heard a concern about defining the trial design as a prevention for hyperbilirubinemia.

I mean we need the bilirubin there to work basically, too, in other words, not a trial that would be randomized to children who received a dose when they left the nursery and those who did not. I didn't hear a lot of support for that kind of a trial, because I am not sure what the endpoints on that would be.

Bob, were there any other points that you thought were coming out of this discussion? The definitions of predictability clearly underlie the problem here.

DR. JUSTICE: No, I think you summarized it well.

DR. MURPHY: Any comments that I got that wrong, incorrectly? Yes, sir.

DR. OH: I think several of us indicated that a safety feature should be incorporated in any drug development. I don't think I heard you say that.

DR. MURPHY: Oh, absolutely, yes. I was stumbling on it because I wrote in shorthand here, but basically, that any trial clearly needs to have safety as a major assessment. We do that anyway. I guess what we don't have enough time to discuss is what is the definition of what long-term safety is and how in the world you would do but I think that that is a real issue that you all brought up, and I was trying to say that, that that is something that we will have to struggle with because, in general, long-term safety studies are not usually asked for as part of an FDA approval.

You know, there are some exceptions, but it is a very big issue, and there is a national study, as you know, ongoing to try to look at how to do long-term safety studies.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: A think it is a question for Dr. Stevenson, because I heard him say one thing that follows on that slide you showed where you show the three black lines going up from the nomogram as to whether or not there would be any use for trying to distinguish within stratifications of bilirubin at different levels, whether 20, 25, 30, or 15, those who are at that level because they have above a certain percentile in production versus just above a certain percentile on bilirubin as a way of trying to make an additional distinction within the nomogram itself using carbon monoxide or some other testing.

DR. STEVENSON: That is a good question. I don't know the definitive answer yet. Dr. Bhutani is analyzing some of the data from the large multiethnic, multinational trial that we did.

As I mentioned briefly in passing, the nomogram seems to be informed in part, as would be expected, by production rate, so the higher you are up in those percentiles, the higher the average production for the individuals in those percentiles.

There are also individuals who seem to be producing bilirubin excessively, and what Dr.

Bhutani is exploring is whether that information is sufficient for identifying or targeting these individuals as the individuals that will also jump tracks and proceed to leave the nomogram all together.

So, I think the issue you bring up is an important one, that is, that it's a balance, it's a matter of impaired conjugation and production, but if you have excessive production and you are already behaving in a certain way in terms of your ability to handle the pigment, then, you may be self-identifying as a very narrow group of individuals who are uniquely disposed to being helped by something to control their abnormal production rates.

DR. NELSON: Do you think that when that data is analyzed, that it would reduce the false positives and that number needed to treat, that is of concern, in other words, those infants who, in retrospect, would not have needed an intervention, that if you combined bilirubin plus some measure of production, that you might treat three to get one instead of five to get one, for example?

DR. STEVENSON: I don't know, but my guess is that it would likely decrease that number, but I

don't know for sure.

DR. CHESNEY: Dr. Justice.

DR. JUSTICE: Yes, just one thing to add to what I heard the committee say, at least a couple of members of the committee suggested that the population be narrowed to a higher risk population, such as hemolytic anemias.

DR. CHESNEY: We have a plan for the last two questions, which have to do with safety and efficacy. As you know, the FDA has a legal responsibility to assure both safety and efficacy, and that is what these two questions are about. So, I will read these briefly and then we will have 10 to 15 minutes to discuss them.

Then, at the end, we will go all around the table, so everybody can have a last comment relative to whatever they feel they need to comment about.

Question No. 3. Assuming that hyperbilirubinemia only requires therapeutic intervention with phototherapy 3 to 5 percent of the time, what safety information would you require from a sponsor for a new molecular entity before it could it introduced into the newborn population?

Question No. 4. In today's healthcare

setting, does the benefit of drug therapy to prevent hyperbilirubinemia in the newborn population as a whole outweigh the risk to individual newborns, the majority of whom require no intervention?

Comments? Dr. Freeman.

DR. FREEMAN: I am very concerned about these two questions and about any study that you design particularly if it's limited to a defined population being able to pick up low-risk side effects of your medication, and I would urge the FDA to build in long-term studies after whatever drug gets marketed presuming that it will get marketed.

DR. WILFOND: I think that these two questions bring us back to the comment before about trying to maximize benefit to minimizing risks, and the problem with the questions, they are framing it as preventing hyperbilirubinemia, whereas, if instead these questions are framed as either preventing exchange transfusions, for example, I think the questions would be very different, so unless we decide what our goals are, and what our population is, these are hard questions to answer. The answers are different, I guess.

DR. CHESNEY: Thank you.

Dr. Nelson.

DR. NELSON: I guess a question for those more knowledgeable and perhaps Dr. Stevenson, whether you think there would be any possible surrogates that could be used to measure risk of certain adverse events, such as impact on neurodevelopmental outcome, whether tagged drug distribution studies that show none get to the CNS. As I recall, there was some of your slides that you went through rather quickly showed differential distribution of different drugs and different targets. In other words, if it doesn't get to the CNS, it would be less concerning to me, or maybe that's just being naive. So, that's a question.

DR. STEVENSON: It's a good question and obviously a concern. I think most of the information is probably known about tin mesoporphyrin, and that work has been done by Rockefeller. I don't remember the exact nature of the experiments that looked for traces of the compound in the brain, but my recollection of the report was that none was found.

Our work has been primarily looking for biological effects. We have not done labeling

studies. So, coming back to your general question, I am not sure if that would be possible to do in humans, and in trying to get to the issue, understanding what the risk might be or what surrogate you might have for looking for that risk, that is very difficult. We are learning now something that I think is very frustrating to most of us, and that is, when we look at long-term neurodevelopmental outcome as a primary outcome for a lot of our large trials, in ACC network, oftentimes things which we think are appropriate surrogates for long-term neurodevelopmental outcome, turn out not to be so.

The most recent example is in the TIP trial, the indomethacin prophylaxis trial, where as the smaller studies had suggested, there was a marked decrease in Grade 3 and Grade 4 hemorrhages in response to that prophylactic treatment, but there was no difference in the long-term neurodevelopmental outcome between the two groups.

So, when you try and pick even fairly gross surrogates for neurodevelopmental outcome, you may miss the mark, and part of that is related to the plasticity of the newborn brain, and there are many other things that will impact that brain

over the course of the first couple of years of life, and that is not just in terms of function, that's in terms of its anatomy, as well.

DR. CHESNEY: Dr. Mattison.

DR. MATTISON: In terms of the safety information, I guess thinking about it from sort of several different levels, I would be interested in really very well conducted traditional segment one, segment two, segment three FDA animal tox studied.

These are studies that are done to look critically at effects on reproductive performance and developmental function, pregnancy outcome, and so on.

The problem with the current designs, though, I think for the most multi-gen and the three segment tox studies, don't get at functional endpoints, so I think, you know, careful discussion with any proposed sponsor of a molecular entity like this, given that there are a range of developmental activities that have to go on in the newborn, I think would be really very important.

Having spent a lot of time thinking about developmental toxicity, I am also troubled a little bit by the fact that there is kind of the other side of the question that we haven't addressed, and

I am reminded of the vitamin A story, which is that no question at high levels, vitamin A produces adverse effects, but we also understand that vitamin A deficiencies are also associated with adverse neurodevelopmental outcomes.

Dr. Stevenson alluded to the fact that he seems a little perplexed by is there a level of bilirubin below which we wouldn't want to go, and from that perspective, then, it is not simply designing a dose that lowers the level of circulating bilirubin, it is understanding what happens at these lower levels in terms of neurodevelopmental outcome, they may not be related to the drug at all, but altered biochemistry in the individual, which I think also suggests a different way of thinking about the traditional three-segment and multigeneration tox studies in animals and might actually suggest the need to look at perhaps several different species in the developmental tox studies.

DR. CHESNEY: Thank you.

I wanted to ask a question and then I see Dr. Luban. Dr. Stevenson, I was struck in your slides by the contrast between the one naturally occurring mesoporphyrin, zinc mesoporphyrin--I hope

I have this correct--in almost every instance had the lowest of the effects that you were describing as something that we see as maybe good.

Teleologically, that gives me a little anxiety.

DR. STEVENSON: Zinc protoporphyrin is the naturally occurring protoporphyrin. Its role is still being investigated. Of course, it's an indicator of lead toxicity and probably reflects availability of iron for incorporation into hemoglobin, and so forth, but I think what I describe is simply a compound that has moderate effects and then has many of the other desirable features that, in fact, the other compounds do have, either at the dose they are being used or by their unique synthetic nature.

Those would be besides the efficacy, which can be established at a much higher dose, it has the lack of photoreactivity in vivo and other things of that sort. But it is a hard compound to work with, and is probably at the bottom of the list in terms of one you might pick from a drug development perspective because of that property alone.

I am not sure if I answered your question

exactly, but I think when you engineer the other compounds, you can end up using them at doses where you achieve the other desirable features that you see with that compound.

DR. CHESNEY: I probably didn't express it very well, but it just seemed a contrast between a naturally occurring compound and a contrived one. In some of the areas, it was so striking that you just worry about toxicity issues.

Dr. Luban.

DR. LUBAN: In my review of the two books, there were a few things that I was struck with, that I think we need to spend some time talking about apropos of Question 3, and the two systems that I think we need to send some time looking at in any kind of a long-term safety trial are the hematopoietic systems, since this is a hemoxygenase inhibitor, and iron metabolism particularly at the nadir of iron absorption could be affected.

The second, from a long-term adverse potential, is the RES system. Some of the data indicated lymphocytopenia, for example, in some of the children that were studied with this class of compound.

So, I am being very specific rather than

general, but I think those are two areas that we need to concentrate on.

DR. CHESNEY: Thank you. I think those are issues that we probably will address tomorrow.

Any other? Dr. O'Fallon.

DR. O'FALLON: I think somebody should say at this point the fact that we haven't--I mean we have been told that no bad things have been found in certain areas--I think it is very important to point out that not finding things in the number of people studied, it doesn't tell us anything, that in order to find relatively rare events, which we would certainly hope most of these long-term toxicities would be, or any kind of toxicity, we would have to study a lot in order to be finding them.

So, the fact that there is nothing out there yet is somewhat comforting, but not completely comforting.

The other thing is we have been listening, we have been told in two or three different ways that there are parents who simply are not able to even come back for a follow-up bilirubin test within a week after the baby was born. If we are going to be putting kids into long-term studies

where they are going to have to be coming back at year 1, year 2, year 5, that type of thing, in order to see what is happening to their intelligence levels and their blood counts, and that sort of thing, this is going to be difficult.

I think the drug companies have to be prepared to deal with this type of thing or we are going to have a problem. Well, I think that our results that we have already been told are already biased because there was so much missing data on some of the long term, and the question is who was missing, who didn't get tested, and we can't have that happen for a good study of these new therapies, because if by the treatment creep, we are going to end up treating a whole lot more kids that don't need it, we have to have a darn good idea of what kind of adverse events that are likely to be occurring five year hence.

DR. CHESNEY: Dr. Newman.

DR. NEWMAN: I think to answer the question about how much we need to know about safety or how big the trials have to be is partly informed by biochemistry and understanding these drugs and the biologic plausibility that they would have effects on various tissues, and I don't know

that much about that.

My kind of simple-minded thought would be, well, if we are going to use it instead of exchange transfusion, we should know that it's as least as safe as exchange transfusion. If we are going to use it instead of phototherapy, we should try to have somewhere around as much data that it is as safe as we have for phototherapy. For phototherapy, we at least do have the Collaborative Phototherapy Study, which was a long-term study following kids up to I think age six or seven to look at their neurodevelopmental outcome.

If we were going to try and use it to prevent phototherapy and be treating, you know, 5 or 6 or some number of kids for each one who otherwise would have gotten phototherapy, then, it seems like we kind of need to know that it is at least five times as safe as phototherapy, so that would be even a bigger study just to be able to reassure ourselves that we are not doing more harm than good.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: I think in terms of the specific answer to that Question 3, I think it is

pretty clear that whatever study is done, we need to have a minimum of a two-year careful follow-up including the full neurodevelopmental exam and assessment. I think that is what is standard for the NIH studies where we looked at entities like nitric oxide and other things. I think that would be expected.

The difficulty there is, of course, that even in the small networks where there is a lot of effort to getting these kids back, we take all babies regardless of likelihood that they are going to be coming back for follow-up, so we take the poor and the not so poor, and so forth. We get about an 80 percent follow-up.

If you wind up spreading this among many centers, we are going to have fewer babies at each center, and you don't have that sort of network to encourage patient capture. It is going to be very hard to get a very good follow-up rate, but nonetheless, one has to do the best one can do.

The other issue is in terms of the actual study design, we have talked about exchange transfusion. I think I would be very worried about limiting entry to those babies who are at high risk for getting exchange transfusion because if in the

control arm you had a lot of babies who had exchange transfusion, and if there is some consequence to an exchange transfusion in terms of neurodevelopmental outcome, you may falsely reassure yourself your drug intervention is reasonable. It may even look better than the group that got high incidences of exchange, so I think there are caveats there.

DR. CHESNEY: I don't think any of us ever want to do an exchange transfusion again.

How about if we start going around the table and letting everybody address the most compelling issue for them at this point. Dr. Luban, you have the good luck of being the first person.

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DR. LUBAN: Do you want me to go over Questions 2, 3, and 4 or just make a general comment?

DR. CHESNEY: I think the idea is more that you maybe address the one or two points that are most important to you, most compelling to you, that may have to do with any one or all three of the questions.

DR. LUBAN: Well, I think it would be

wonderful if we had an absolutely safe drug that could stop the need for doing exchange transfusions. Since as the director of a blood bank, I can tell you that I don't sleep at night when those are being done at my institution.

On the other hand, I can also tell you that the number of times that we perform exchange transfusions now is lingeringly small.

So, from my perspective, much of the treatment of Rh hemolytic disease has taken away exchange and what we are left with are the severe G6PDs, the tiny preemies with sepsis and multiple complications, metabolic diseases, and then the other class, which nobody has mentioned, which are the kids neither with ABO nor Rh, but with other antibodies, and those are actually growing in number rather than decreasing in number, particularly Kell, so that is a group of hemolytic disease of the newborn that no one has mentioned that we need to keep in mind.

There is something intrinsically gut-wrenching to consider treating a very large number of babies with a treatment modality without a known safety record for the prevention of a very limited number of severe adverse outcomes.

I will stop there.

DR. CHESNEY: Dr. Stevenson.

DR. STEVENSON: I can be very brief. I think exchange transfusions are dangerous, and that is something that needs to be avoided. It may be avoided through a whole variety of different ways, some of which don't have to include novel therapies.

I guess from my perspective, the rationality of the approach that lies behind this kind of targeted therapy is best complemented by a targeting of the group that might benefit the most.

So, I guess I would weigh in with respect to identifying individuals who are at greatest risk and who might benefit from altering this part of the biology which is contributing to the problem in their particular case, understanding that not everybody who has high production has high levels of bilirubin, they would not self-identify as being individuals that would require treatment.

A final thing is just that I think that it is important to understand that some increased production is a normal part of the transitional period after birth, the up-regulation occurs normally, and so it becomes a powerful lever if you

want to control something that you otherwise can't control.

So, I understand the interest in getting one's hand on that handle, but I think it should be done with appropriate respect for the complexity of that biochemistry, which I think people have, and try to maximize safety with that in mind.

DR. CHESNEY: Dr. Lau.

DR. LAU: My comment will be brief. I think that we need to be very precise about our language that is mentioned earlier, that hyperbilirubinemia is not a disease, it is a condition, and even in Question 4, it is stated as to prevent hyperbilirubinemia treatment, so we are not really trying to prevent hyperbilirubinemia, because we are already doing intervention on kids with hyperbilirubinemia, so what we are trying to do, we are trying to keep them from rising. I think we just need to be precise about our language.

DR. CHESNEY: Dr. Newman.

DR. NEWMAN: I have mostly said what I want to say. I just had one other thought, which is this whole issue of difficulty with follow-up and therefore, you know, patients getting their

high bilirubin levels, and I totally sympathize with that because we struggle with that, too, but I guess it bothers me a little bit that the direction where this might head is that if you are caring for a family that is poor and has bad access, then, you give them the drug, whereas, the families who are better connected with the medical system, you can just follow them and have a Home Health nurse go out to their house.

So, I guess there is some sort of troubling ethical issues there about who would be the people in the studies and then who would the drug actually be given to, and maybe as a society, we really should commit that we can do better than just sort of throw up our hands and say we can't do follow-up a day or two postpartum.

DR. CHESNEY: You articulate that so well.

Dr. Oh.

DR. OH: One final thought I have is issue of powering any of my control trial. Very often what happens is particularly using this surrogate as an endpoint. The sample size is not powered enough to look at long-term outcome, and that needs to be addressed in any kind of design in a study.

The other thing that I need to point out

is that since we are concerned about potential side effect, any trial--I am probably saying something obvious--should have a data safety monitoring committee, independent DSMC monitoring the study to make sure that the patients being enrolled are protected during the study period.

DR. CHESNEY: Dr. Smith.

DR. SMITH: I am in favor of development of a new drug. I am more concerned about what we are targeting as the endpoints for it. I have heard several people say--and I know nothing about these things--but several people have said exchange transfusion is dangerous. I don't think that anyone has said that phototherapy is dangerous. It is inconvenient, but nobody said it's dangerous.

So, I think we should pay particular attention to what we are addressing to replace rather than injecting 4 million kids with this.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: My comment actually follows on the prior comment. If we were to have as an objective trying to prevent exchange transfusions using a drug rather than phototherapy, we would not be subjecting 4 million kids, we would be subjecting that very small number who currently

gets phototherapy.

I think that really would be the way to go in terms of designing a trial that randomized children either to phototherapy or to a drug based upon clear criteria when we otherwise think phototherapy is appropriate with the objective of trying to avoid exchange transfusions and to establish efficacy and safety in that subpopulation.

DR. O'BRIEN: I guess my first comment is I am also struck by the fact that our safety systems issues, although not a part of this deliberation here, just as a comment, that I would hope that we could do a lot better than we are doing, and certainly was very struck by Mrs. Sheridan's presentation of what happened with her son.

I also would agree that starting certainly with the most at-risk infants and any way that we could sort of identify those that may have increased production where we know that the drug would be most effective presumably would be the way to start.

DR. CHESNEY: Dr. Aschner.

DR. ASCHNER: I like the idea of

developing a new drug especially I think I have been convinced for those who need it most. What I would like to see is much more studies on the distribution of the drug in different tissues.

I would like to see proper screening studies done in terms of various toxicological endpoints, and to echo what Dr. Mattison said before, I think I would like to know much more about what the consequences are of reducing bilirubin levels to levels that might be below optimal in the newborn.

DR. CHESNEY: Dr. Freeman.

DR. FREEMAN: I think Dr. Newman expressed my opinions. I have concerns on two sides. One, I think a drug should be developed, but I am concerned about even low incidence of toxicity and the need for these long-term studies in large numbers of patients, but I also am concerned about the way we treat the poor, the difficulties in follow-up, and the need for something to prevent phototherapy or the need for phototherapy in this population that is so at high risk.

I am concerned that as we design these studies, that we will be targeting a poor indigent population and how do we deal with the equities

involved in that.

DR. CHESNEY: Dr. Ip.

DR. IP: Am I allowed to comment on the confidential stuff I have been reading? I will reserve my comment until tomorrow.

DR. CHESNEY: Dr. Mattison.

DR. MATTISON: I guess I would just reiterate my concerns about functional developmental consequences and echo some of the comments that others have made with respect to frustration with the current system for screening and identification of these infants.

That is not a drug development question, it's an entirely different kind of system question, but my biggest concern is sort of long-term functional developmental impact.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: A couple of random thoughts. The pursuit of convenience is pretty obvious in our healthcare system. We want things that are convenient, but sometimes they also simplify, those same pursuits simplify the systems for both us and our parents to provide care for their children, so I am not sure they are always mutually exclusive.

It is clear to me that healthcare is not

the number one priority of a large number of our populations, so that systems we set in place, that seem logical to us, don't always seem logical to our patients.

I have a comment to follow up on Dr. Luban's. I think that I would be even more specific in my long-term safety profiling than you were. Who knew there were so many ways to make carbon monoxide in the body? Certainly not I. But I think that at 18 and 24 months, carbon monoxide production, since we are specifically targeting it and changing it, should be monitored, and the hemoxygenase system, in whatever way you measure it, in 18- and 24-month- olds should also be tested.

I would also like to echo something that Dr. Freeman said, which was that he thinks that there is a distribution that does not include only kernicterus with bilirubin's effect, and I would hope that a gross developmental screen, such as the one we do, would pick up a halo effect if, by reducing bilirubins, we look at confounding or contributing variables to other neurological diseases that we see and we can only poorly explain.

DR. CHESNEY: Dr. Ebert.

DR. EBERT: I am in support of the development of drugs for the management of hyperbilirubinemia, and I would see the role in therapy here being somewhat before exchange transfusion. Where exactly that fits, I think certainly that discussion has led us to believe that we are not sure exactly where that would be at this point.

I think probably first and foremost, we need to do a better job of characterizing patients who are high risk for progression to high bilirubin levels and/or kernicterus, whether that be through more intensive history taking and sampling of individual or ideally by developing a test that can be administered prior to discharge because of the concerns about follow-up of patients after they have been discharged.

I don't think that we can really determine at this point what the safety would be of this compound without first testing it in a group that is at higher risk for complications, try to at least at that point get a risk versus benefit assessment, and perhaps then with post-marketing assessments, Phase IV trials, as lower risk

populations are tested, we can continue to follow up with safety at that point.

DR. CHESNEY: Mine is more reflection. I think it is ironic that the healthcare system has put us in this situation because pediatricians, I think almost uniformly, decried the move to discharge at 24 or less than 48 hours, and it is because of that that we seem to be having a problem now, and it is also because our processes are imperfect that we don't seem to be able to get children back and to monitor what, on the face of it, should be a fairly simple thing to monitor, but we don't have the processes in face, so it is just a reflection.

Dr. Fost.

DR. FOST: I hate to wake anybody up at 10 after 6:00 with a new idea, and I also regret disagreeing I think with John Freeman, my teacher, and Tom Newman, whose work I admire so much in this area, but it seems to me there is something close to consensus developing around the table on a general principle that, first of all, that a new drug, there seems to be wide agreement that a new drug, if it were safe, effective, and reasonably cheap, would be a great help, and that, second, it

should be tested on children who have the most to gain from it.

If that is true, it seems to me that the ideal target population is those who are most underserved at the moment, that is, children in a developing country, who presently have no access to anything and for whom being in a trial of a reasonably promising drug against phototherapy would be a boon for the children in the trial, it would almost certainly have a benefit if we take high-risk children, that is, children with hemolytic disease or at high risk for hemolytic disease, that the benefit-risk ratio for that population would exceed anything we could do in the United States.

it might also, if the drug were cheap enough, lead to a treatment or a preventative for underserved populations since phototherapy is extremely unlikely. I am guessing, maybe I am wrong about that, certainly, home phototherapy.

So, it seems to me the ideal place to develop, to study this drug is in a population that presently has no access to any treatment for hyperbilirubinemia and that is at high risk.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: That's a great idea, I just wish it were possible to get follow-up on those kids. That is the key. I think everyone is in consensus that we need the drug development study. It is just the details that are the devil, and the power issues are critical and depending upon what you are looking at, the power calculation will be different.

I think we do need to look at the high risk group. I have no idea how you define that. Anything you do, by definition, is going to be somewhat arbitrary because we don't know at any given point what the exact risk is for getting from bilirubin level X to bilirubin level 30 without intervention, we just don't know.

So, it would be reasonable to pick by the nomogram, for instance, if you wanted to get a good number of patients in, you can either pick the hemolytic disease patients, who have a high incidence of having high levels, or you can sort of by the nomogram pick those who are at the 98th percentile anytime within the first 48 hours and assume they are the ones who are going to be most at risk for getting the very, very high levels, although we don't know that. So, there is

something about the natural history we don't know.

In terms of the follow-up, I think the point that was made about is there a 5-point difference in IQ that might result from this treatment, well, you can put a number on how many babies you need to study to reassure yourselves that there in no more than, you know, a 1-point difference or whatever. I think that sort of study design needs to be done because a 5-point difference in IQ, I think is a significant societal issue and needs to be carefully examined what the impact on that is.

You know, other outcomes, for instance, like what happens if this drug were to double the underlying incidence of aplastic anemia, how many patients are you going to need to determine that. I go back to the studies that were done on the rotazyme vaccine, and very well done studies showed it to be very safe and effective, and within nine months of it getting on the market, being used in a lot of patients, the issue of intussusception came up, and the drug was withdrawn.

So, I think there are clearly instances where something gets into widespread use despite the best study efforts at determining safety and

efficacy and there are problems that are detected, and I think it is just critical as we go along whatever path this goes down, that the FDA hopefully has the authority to make sure that there are the appropriate large registries once this drug gets outside into open clinical use.

DR. CHESNEY: Dr. O'Fallon.

DR. O'FALLON: My comments, I keep remembering my dad saying that it took a dentist to invent the railroad couple. You know, I am outside the medical community, I work with physicians, but I am listening to you, and it just seems to me in listening today that it isn't that hard.

You guys are all talking about eligibility criteria. As a statistician, I think that defining the eligibility criteria very precisely is an extremely important thing to do in each of these studies, and you guys are all talking about levels of hyper--well, I can't say it, but the level of bilirubin, you are talking about rates of bilirubin rise. There are ways to measure that. You talked about that.

So, I think you already know and could define a group that you could agree would be at real risk and should be studied first. So, I think

that can be done, listening to you. Then, the comment about the population, about going to Africa and some places like that, come on, guys, we have all these Americans sitting in our inner cities that have no medical care either, and I think that we should make an effort to include those guys in any studies, too, that the companies should make sure that they are spreading around the benefits and the liabilities.

The endpoint definition is absolutely crucial and again, what I am hearing you say, you say, well, should we give exchange transfusion when it hits 30 or 28. I think you have got to just define your endpoint as being some extreme value, and if the bilirubin hits that level in either group, they have failed, that treatment has failed. I think you can do that, define it some way like that, but it would not be to avoid either of these therapies because the physicians, you know, you are kind of a rebellious group, and you tend to say nobody is going to make me do anything, and you aren't always following the guidelines.

But if it comes down to the level itself, understanding the variability and the laboratory measurements, and all that, I mean there are going

to be problems, but that would seem to me as close to an objective endpoint as you could have.

The careful follow-up is so important and it has go to be long term, and it has to be very vigorous to make sure that everybody comes back, that we are not losing a large percentage of the patients out on the long-term follow-up, and that is going to be hard.

Then, oh, yeah, the modeling. We keep talking about the modeling, and I do a lot of that, I am a statistician. Folks, a model is only as good as the items that are in the--I call them the shopping lists, the independent variables, and we are finding out it is very humiliating to recognize that we are missing a lot of very important variables that nobody ever knew were important, and we all know that there are genes that are important, that we don't know anything about.

So, the modeling we take with a block of salt on each shoulder.

DR. CHESNEY: Dr. Fuchs.

DR. FUCHS: I think I echo a lot of people's opinion that this is going to be a long-term, several step process. I think the idea about comparing drug versus phototherapy to prevent

exchange transfusion is probably step number one with long-term follow-up, and that group, it could be the ABO group, the G6PD group, that is your target population as one option.

Then, when that is proven as safe or as effective as phototherapy, then, you jump back down and then you can get into your healthy newborns with whether you want to use with risk factors or without risk factors, it is going to take a long time no matter what you do.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: I think everybody probably agrees that ignoring extreme hyperbilirubinemia is dangerous and there are two ways to approach that problem to make it go away. One is to make the extreme hyperbilirubinemia go away, the other is to tune the system, so that we no longer are permitted to ignore it.

I wonder a little bit about the risks of developing a drug that could come into common practice that could be perceived as the magic bullet that prevents extreme hyperbilirubinemia, you have had your shot, you go home, nobody ever worries about hyperbilirubinemia and kernicterus anymore, and yet there will be system failures in

either the administration of the drug or the effectiveness of the drug in certain small populations yet to be identified where that drug will be a failure and the next generation of patients entering the kernicterus registry will be those who have received the magic bullet and the medical community has given themselves permission to forget about them.

That having been said, I really do think that we need to investigate the development of a drug like this. I agree with the remarks that the safety data that we need to accumulate will require a large, long-term expensive and difficult to interpret studies.

I would like to be assured that the drug that we unleash on society is safe as phototherapy.

DR. CHESNEY: Dr. Glod.

DR. GLODE: Just on a historical note. As you noted, Dr. Chesney, about the change in medical practice with early discharge, I do now recall that the most common conversations I ever had with mothers during my training was the conversation about how your baby could not go home because of the yellow jaundice, and, in fact, had that same statement made to me with the birth of my first

child, staying in the hospital because my baby's bilirubin was 12 and we need to check it tomorrow. So, it is a remarkable effect.

Back to again the priority, prevention of kernicterus, do we currently have effective therapies, I would say yes, we just have an inability right now to correctly identify and capture who needs those therapies.

I am happy to have a new therapy developed. I think the bar for that therapy is very high because it has to be as safe as phototherapy and either equally effective because more convenient or more effective than phototherapy. So, the bar is very high. I am happy to have it be developed.

The last comment I would make is that I think if you had an opportunity to read the two statements at the back from people who didn't present at the open hearings, but the Joint Commission and the March of Dimes both had an interesting letter there. Perhaps again this is outside the realm of the FDA, but on my desert island, if I were advising the FDA on the issue of prevention of kernicterus, I would recommend that they send--I don't know if they can do this--a

formal letter that would go to NICHD, to the CDC, to the American Academy of Pediatrics urging funding of pilot studies concerning the efficacy of newborn bilirubin screening to prevent bilirubins of--and then you name it, 22, 25, 27, I don't know, I would like to see those pilot studies funded, and that would be my recommendation.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I am still thinking about Norm's suggestion. I think an active control superiority trial with phototherapy head to head with a medication to try and prevent not so much exchange transfusion, but perhaps a bilirubin where most people might contemplate an exchange transfusion, say, 25, so you could get it at 20 and then you hopefully prevent 25, and then you would have to have, if the phototherapy fails, some crossover to the drug, but all those kinds of details could be worked out.

But then I am not sure what the control group would be in an area of underserved, because I would be tempted to want to build up the infrastructure to provide phototherapy, and I am not sure that would, in fact, be doable, and it would worry me if we then take a drug that hasn't

been used a lot, but we have efficacy here, and then decide, well, let's just hand it out to a million kids elsewhere and see what happens in terms of safety.

I will follow you a ways down that road. I am not sure, though, on the details. We would have to work that out.

DR. CHESNEY: Dr. Cummins and Dr. Murphy and Dr. Justice.

DR. JUSTICE: I think I hear a consistent message that the drug should be studied in a population that is at higher risk, and there should be long-term safety, follow-up particularly neurological, hematopoietic, and that the trial design I have heard is a randomized trial of phototherapy versus the drug with perhaps an endpoint of a bilirubin of a certain value or perhaps an exchange transfusion.

That is what I have heard the committee suggest.

DR. CUMMINS: I would add to that, that there needs to be and I have heard very detailed preclinical safety testing because the bar for any new intervention is high because of the safety, known safety of phototherapy.

DR. MURPHY: I would just like to say thank you and I think we ought to let you go because we have got another long day for you tomorrow.

DR. CUMMINS: I could add to that thank you very much. This has been a really productive day and we appreciate your time and input.

DR. CHESNEY: Tomorrow morning we start at 8 o'clock is my understanding. Let me also thank everybody for letting us go so far over, but I think it has been extremely interesting.

[Whereupon, the meeting was recessed at 6:30 p.m., to reconvene the following day, Thursday, June 12, 2003, at 8:00 a.m.]

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