FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE

OF THE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

8:20 a.m.

Monday, April 23, 2001

Food and Drug Administration
ACS Conference Room, Room 1066
5630 Fishers Lane
Rockville, Maryland 20857

ATTENDEES

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ATTENDEES (Continued)

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C O N T E N T S

ISSUE: TREATMENT OF CHRONIC HEPATITIS C IN CHILDREN

P R O C E E D I N G S

(8:20 a.m.)

DR. CHESNEY: Good morning. Just getting last minute instructions here. The microphones that you have in front of you are a little different than we've had before. Be sure please to push the top button to speak, and also introduce yourselves. As you know, this is all being recorded and that makes it easier for the individual recording.

We'll start with introductions and let's start here with Dr. Weiss.

DR. WEISS: Karen Weiss, from the Division of Clinical Trial Design and Analysis, Center for Biologics, at FDA.

MR. FLEISCHER: Russ Fleischer, Division of Antiviral Drug Products in the Center for Drugs, FDA.

DR. RODVOLD: Keith Rodvold, University of Illinois, Chicago.

DR. FUCHS: Susan Fuchs, Children's Memorial Hospital, Chicago.

DR. DANFORD: David Danford, joint section of pediatric cardiology, University of Nebraska Medical Center, Creighton University in Omaha.

DR. EDWARDS: Kathy Edwards, Department of Pediatrics, Vanderbilt University.

DR. SANTANA: Victor Santana, Department of Hematology, Oncology, St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. SZEFLER: Stan Szefler, Department of Pediatrics at the University of Colorado.

DR. NELSON: Robert Nelson, Department of Anesthesiology and Critical Care Medicine at the Children's Hospital, Philadelphia.

DR. HOLLINGER: I'm Blaine Hollinger, from Baylor College of Medicine in Houston, Texas.

DR. O'FALLON: Judith O'Fallon, Cancer Center Statistics, Mayo Clinic, Rochester, Minnesota.

DR. FINK: Bob Fink, pediatric pulmonology, Children's National Medical Center and George Washington University, Washington, D.C.

MS. PETERSON: I'm Jayne Peterson with the FDA. I'm the Executive Secretary of the subcommittee

DR. CHESNEY: Dr. Chesney, the University of Tennessee, Department of Pediatrics and St. Jude Children's Research Hospital.

DR. LUBAN: Naomi Luban, Department of Hematology and Pathology, Children's Hospital, Washington, D.C. and George Washington University.

DR. GORMAN: Rich Gorman, Ambulatory Pediatrics, Ellicott City.

DR. HUDAK: Mark Hudak, neonatology, University of Florida, Jacksonville.

DR. KAUFFMAN: Ralph Kauffman, Children's Mercy Hospital, Kansas City, Missouri, University of Missouri.

DR. SPIELBERG: Steven Spielberg, Pediatric Drug Development, Janssen Research Foundation, representing PhRMA.

DR. JONAS: Maureen Jonas, Children's Hospital and Harvard Medical School, Boston.

DR. SEEFF: Leonard Seeff, NIDDK/NIH.

DR. LINDSAY: Karen Lindsay from the Department of Medicine, Division of Gastroenterology and Liver Disease from the University of Southern California in Los Angeles.

DR. SCHWARZ: Kathy Schwarz, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins, Baltimore, Maryland.

DR. REHERMANN: Barbara Rehermann, NIDDK/NIH.

DR. CHESNEY: And next we'll have the conflict of interest statement from Jayne Peterson.

MS. PETERSON: 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.

Since the issues to be discussed by the

subcommittee at this meeting will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S.C., section 208(b), waivers have been granted to all members and consultants who have reported interests in any pharmaceutical and biological companies.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Ralph Kauffman, M.D., would like to disclose that he has contracts and/or grants from Bristol Myers Squibb, and he is a researcher for Bristol Myers Squibb, Janssen, and Merck. In addition, he has received consulting fees from Johnson & Johnson, McNeil Consumer Products, and Purdue Pharma, and he's a scientific adviser to McNeil Consumer Products and Purdue Pharma.

Steven Spielberg, M.D., would like to disclose that he is a full-time employee of Janssen Research Foundation.

William Balistreri, M.D., is a member of Roche's Safety Review Board.

Maureen Jonas, M.D., is an investigator at Harvard University for a multi-center pediatric Rebetron trial funded by the Schering-Plough Research Institute. Dr. Jonas is also a consultant to Schering-Plough Research Institute. She consults with medical care providers about hepatitis, not necessarily related to treatment or use of Schering products.

Karen Lindsay, M.D., has contracts and/or grants with Schering-Plough Corporation, Glaxo-SmithKline, and Hoffman LaRoche, and receives speaker's fees from Schering-Plough.

Leonard Seeff, M.D., is employed by the Veterans Administration Medical Center in Washington, D.C., and the National Institutes of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health. He's an investigator in the Glaxo-SmithKline-sponsored multi-center trial of lamuvidine for the use in treatment of hepatitis B. As part of his federal duties, he's an investigator in a study of transfusion-associated hepatitis and a study of hepatitis in injection drug users.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the

participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. CHESNEY: Thank you, Jayne.

We have a fascinating day ahead looking at issues of treatment in children with chronic hepatitis C, and I think this has been somewhat precipitated by the introduction of the polyethylene glycol interferon, and the FDA has given us a long list of questions to address.

I see this meeting also as very important, given that as everybody here knows, FDAMA is up for renewal January 1st, and particularly the pediatric exclusivity portion of FDAMA is of concern. Let me put it that way. I think the committee is very interested at this point in knowing what we can do to support the FDA as the hearings, I understand, begin next month in Congress. We look forward to hearing Dr. Murphy's comments at the end of the day as to anything further that we can do, again to support the FDA.

So, Dr. Murphy is going to start us off this morning.

DR. MURPHY: My job is to welcome you, and one of the most important things you can do for children and for the pediatric activities of the FDA is what you're doing, which is take time out of your busy schedules and come here and discuss with us the very important questions that we have about how to approach clinical trials in children in a way that's scientifically grounded and ethically based, because if we make a mistake here, it could have tremendous impact. So, again, thank all of you for taking time to come here.

I wanted to particularly take a moment to address the Pediatric Subcommittee because today is your two-year anniversary. This is your fourth meeting. And I wanted to just remind you of how much you have accomplished in a very short period of time. You have participated in providing some advice and guidance to us in some very important scientific and ethical areas.

As you will see when I do my update later, you've provided guidance to the FDA in whether we should develop products for sleep disorders in children.

You have provided guidance in our approaches to the development of neuropsychiatric oncology products.

And particularly important has been the guidance that you have provided us in the ethical arena, in which you have developed some consensus points, which are

available now on the Web, concerning the conduct of trials involving children who will not derive direct benefit, and recommended at the same meeting that Subpart D be adopted by FDA. I wanted to let you know that that happened last week in the form of an interim rule, and I'll give you a little more follow-up on that later

You provided some important discussion on the use of placebo-controlled trials in children, and I'm going to provide you today, at the end of the day, the draft of the consensus points that we think we have at this point, and provide an opportunity for the committee to continue to provide feedback on that.

As you've heard, today we've asked you to come now and discuss for us both scientific and ethical issues in two very important areas that have long-term implications, as I think is clear to most everybody here. That is, the scientific and ethical issues in the development of products to treat hepatitis C in children. Should we? If so, when and how? And the same for the development of products to treat a need in children who have received neurologic injury and are unable to communicate with us. The areas of concern being both ethical and endpoint assessment.

So, you have a tremendous set of tasks before you over the next two days, and we really do look forward

to your discussion. Thank you.

DR. CHESNEY: Thank you. Our first speaker is Russell Fleischer, who is going to give us a review of the agenda and some background information and overview.

MR. FLEISCHER: Good morning. On behalf of the Division of Clinical Trial Design Analysis in the Center for Biologics and the Division of Antiviral Drug Products in the Center for Drugs, I'd like to welcome you today. I think this is going to be an interesting discussion of a number of issues related to the development of treatments for children with hepatitis C infection.

It really represents a joint effort because both of our divisions are responsible for product development -- us for the antivirals and the Center for Biologics for biologics. As you know, there is a drug combination with biologics available for adults.

So, my job is to try to set the stage for what we're going to talk about today, and so why are we were? We're here to engage in a public discussion and to obtain your guidance and advice on the development of treatments for pediatric patients with chronic hepatitis C infection.

I'd also like to take the opportunity to thank the guests who've come who are going to present and who are here at the table to talk with you, because I believe they will provide a significant amount of background information

that will help this committee's discussions.

So, although the number of pediatric patients with chronic hepatitis C infection is relatively small, we know there's substantial interest in treating them. This interest stems from information suggesting that they exhibit a number of characteristics that seem to be possibly predictive of a good response in adults, which is milder liver inflammation, less frequent cirrhosis, lower viral load levels, and shorter duration of infection.

Also, since chronic hepatitis C virus is currently the primary indication for liver transplantation in the United States, it's been postulated that if we treat children in childhood, we might possibly reduce the risk of progression to end-stage liver disease later in life.

We anticipate that there will be use of both drugs and drug-biologic combinations to treat hepatitis C, even in the absence of labeling. Thus, the labeling of these treatments would likely represent a meaningful therapeutic advance since there are none currently approved for this population.

There are concerns, however, about these therapies, and about treating children with chronic hepatitis C. We know that most of the patients with chronic hepatitis C virus infection are relatively healthy, they typically feel well. The disease is insidious. It

can take as long as 30 years to progress to end stage liver disease. The currently approved therapies are quite toxic, and they also have some specific concerns to children, which is that we don't really know what the long-term impact of these treatments would be, such as on growth and development.

The currently approved treatments yield relatively poor antiviral response, depending on the type of the disease the person has. It can be as much as 50 percent of the patients who are subjected to treatment who will not respond. What we really don't know, though, is, if we treat a child today, or we treat anybody today, will we ultimately translate that into reducing the rates of end-stage liver disease, and potentially hepatocellular carcinoma later on in life.

So, the questions and the issues we're interested in having some discussion on are the need for an optimal timing of studies during drug development. Can we extrapolate that the course of chronic hepatitis C virus infection and the response to treatment are the same or similar between adults and pediatric patients?

If yes, are there some pediatric patients whose disease is somehow different so that extrapolation would not be appropriate?

How can pediatric patients whose HCV infection

might warrant treatment be identified?

What study designs would optimize the collection of safety, pharmacokinetic, and activity data?

Is there a need for additional studies of interferon-based therapies?

And very importantly, what approaches can be used to maximize the collection of long-term follow-up information on pediatric patients?

Then if there's time, hopefully, if you have any specific recommendations for additional research that you believe might help us better understand chronic hepatitis C virus infection in the pediatric population, we would welcome them.

This morning we're going to hear from Dr. Barbara Rehermann from the NIDDK, who will provide an overview of the immune response and some virologic information about hepatitis C.

She'll be followed by Dr. Leonard Seeff and Dr. Maureen Jonas, who will give us, I guess you can consider them, state-of-the-art talks for adults and pediatrics, respectively.

Dr. Karen Weiss will discuss some of the regulatory issues concerning our pediatric initiatives and how they apply to today's discussion.

Then we've got a couple of questions for you to

discuss.

I just want to take this opportunity to thank the other members of the planning committee who put this meeting on. The left column is the Center for Drugs. The right column is the Center for Biologics. And I just want to thank them.

DR. CHESNEY: Thank you. Dr. Rehermann is going to speak to us next on the virology and immunology of hepatitis C.

DR. REHERMANN: Good morning. I was asked to give an overview on the virology and immunology of hepatitis C virus infection. Hepatitis C virus causes clinically inapparent onset of infection in the majority of patients. For this virus infection, it's characteristic that the majority proceeds to chronic infection, with moderate hepatitis, mild hepatitis over the years, but can develop into liver cirrhosis. Hepatitis C virus infection is the leading cause for liver transplantation in the U.S., with more than 4 million people infected, and also hepatocellular carcinoma as an end-stage complication of cirrhosis.

A minority of patients can recover, and it is not known which factors contribute to recovery. It has to be said, to address children's infection, that in contrast to hepatitis B virus infection, where most children are

neonates that are infected proceed to chronic hepatitis, there's a surprisingly high number of children that recover after hepatitis C virus infection. This seemed to be unusual, and to date it's not known whether this is immunologically mediated or whether other factors play a role.

Hepatitis C virus is an RNA virus consisting of 9,000 nucleotides and is translated into a single polyprotein that consists of several structural and nonstructural proteins. The structural proteins form the virus core and envelope, and the nonstructural proteins are important for viral replication and amplification inside the cells.

To this virus, neutralizing antibodies have been reported, and they're mainly targeted against the viral envelope proteins, E1 and E2, that are indicated in red on the left side of the slides. Cellular immune responses recognize all viral proteins, structural and nonstructural, but we believe that an immune response against the nonstructural proteins is especially important because these are expressed early in infected cells, and T cells that might recognize these nonstructural proteins may be able to eliminate virus-infected cells before new viruses are released.

Hepatitis C virus is present in several

genotypes. Up to six have been described worldwide, and also in any individual patient, there is a wide variety of quasispecies present in any patient at any given time point. So, the virus has the ability to mutate and to escape from any protecting immune response.

In the U.S., genotype 1a and 1b are the most predominant, also in northern Europe.

Some determinants for the outcome of the infection are certainly the virus itself, the genotype that infects the patients, the quaispecies distribution, the mutation rate, also the viral inoculate size. Then in terms of the host, the age at the time of infection is important.

The host determines the innate immune response. This is mediated by cells and antibodies that can neutralize the virus immediately, without being induced in the lymph nodes, and then the humoral immune response, the antibodies, and the cellular immune response. The last two points are ones I would like to address in this talk.

This is a graphic description of the immune response to hepatitis C virus. In the left lower side, you'll see the liver, and the liver is the main organ in which the hepatitis C virus replicates. It has its own immune system, natural killer and natural killer T cells are the cells that are most present in the liver. These

cells may mediate an innate immune response.

However, to date, the innate immune response has not been very well defined in the liver, and it's difficult to study because we cannot isolate sufficient cells from liver biopsies, for example. So, this will probably remain an unknown for the next years.

Hepatitis C virus then induces specific T cells in the lymph nodes, probably also in the bone marrow, and these are CD4 and CD8 T cells on the right-hand of the slide, that can proliferate in response to viral antigens, expand, and then migrate to the liver, recognize infected cells there, and eliminate them.

B cells are also induced, and B cells receive help by CD4 positive T helper cells that produce certain cytokines, Th2 cytokines, such as IL-4, IL-5, IL-6, IL-10.

However, in the infected cells and for the outcome of viral infection, another cytokine profile has been described to be important, and this is the Th1 cytokine profile. It's also indicated on slides on the right-hand in yellow. This is interferon gamma and TNF-alpha. So far, every patient who had recovered and had been studied had a strong T cell response, and those T cells produced interferon gamma, TNF-alpha in response to viral proteins.

There is certainly evidence for the role of

both the humoral immune response and the cellular immune response. This will be reviewed in the next two slides.

For the humoral immune response, there are clinical studies that indicate that certain antibodies have been associated with resolution of acute hepatitis C virus infection. These are antibodies against a hyper-variable region, a region within the envelope protein of the virus that has been analyzed and studied by Ziebert, et al. on a single-source outbreak of hepatitis C virus infection in Germany 20 years ago by contaminated anti-D immune globulin.

Also resolution of chronic hepatitis C has been associated with antibody titers that can be measured in neutralization of binding assay. This is the best antibody test that we have so far to determine neutralization of antibodies. However, what is not known is whether the virus is neutralized prior to infecting responsible cells because there is no infectivity assay established yet. So, in tissue culture we cannot determine whether the virus infects it or not. All we can measure is whether there are antibodies that can neutralize the envelope proteins of the virus.

In the chimpanzee model, neutralization studies and also vaccine studies have been performed with the envelope proteins. Short-term neutralization has been

reported, but long-term neutralization is not possible because the virus then changes its sequence and escapes from this antibody response.

In terms of the cellular immune response, resolution of infection in the absence of antibodies has been reported, for example, in hypogammaglobulinemic patients, patients that cannot synthesize antibodies against hepatitis C virus, and also in chimpanzee studies. In these chimpanzee studies, recovery has been associated with a cellular immune response and the absence of antibodies.

In summary, to summarize several clinical studies, it has become evident that in chronic viral infection a cellular immune response is detectable but weak, and antibodies against all different viral proteins have been described. In contrast, in recovered patients, the cellular immune response is much stronger than in the chronic ones, and the antibody response is weak and can even disappear.

The study on the single-source outbreak of HCV in Germany that I mentioned before describes that antibodies may disappear in recovered patients between 10 and 18 years after infection. This has been shown in up to 40 percent of the recovered patients. So, these patients cannot be diagnosed as recovered anymore because the

antibody test is the current diagnostic assay.

In contrast, T cell responses, cellular immune responses in these patients persist in the peripheral blood. In recovered patients, they are targeted against all viral proteins. They're indicated there as core, NS3, NS4, and the two NS5 proteins of the virus. In chronic patients, these responses are much weaker.

This is the same as an acute hepatitis C virus infection.

Just one example for several clinical studies that describes that patients who can normalize their liver enzyme values and can recover from hepatitis C virus infection indicated by the green bars have a much stronger cellular immune response than those who develop persistently elevated liver enzymes, indicated by the orange bars. And again, the immune response is targeted against all viral proteins.

Which assays are available to study cellular immune responses? I just would like to review that because it may be important for studies in children.

There are a large variety of assays available right now. None is used for clinically diagnostic assays, so all of these assays are based in research labs and used for research studies. There are qualitative assays which measure the function of specific T cells such as

proliferation, cytotoxicity, or cytokine release. And then there are new quantitative assays such as MHC Tetramer, on the left side of the slide. And then there are several that are in the middle, like ELISPOT, or Intracell, a cytokine analysis.

I'm just going to show you two examples for the Tetramer analysis and also for the ELISPOT analysis because these are the most frequently discussed assays at this time. Also, all of the functional assays on the right-hand slide are really not feasible in children because they require a large amount of blood to isolate lymphocytes and to study their function in vitro.

So, the Tetramer analysis is a specific complex of four HLA molecules, that are indicated on the left of the slide. These are depicted in the violet color. Each of these HLA molecules presents a specific HCV peptide that we know that is recognized by T cells to those T cells. This whole complex is stained with a fluorochrome, and therefore it is possible to use the complex to stain T cells that recognize the HCV peptide and then to quantitate the number by FACS analysis.

Importantly, for any given HCV peptide, the number of T cells that recognizes this peptide is very low. It has been described as .01 to .5 percent of all CD8 positive T cells in the blood. So, this is another reason

that makes this assay very difficult to use in patients, especially in infants because you need a lot of lymphocytes, a lot of blood to obtain the number of T cells suitable for analysis.

The T cells that are HCV-specific are present at a much lower frequency than, for example, T cells against other viruses. In EBV infections, this can be up to 40 percent of virus-specific T cells in the blood. Even in HIV infection, up to 20 percent. In HBV infections, it's also much more. So, in general, HCV seems to avoid to induce a good cellular immune response in most cases.

However, these T cells are present in the liver. We have detected them at a 30 times higher frequency, and all of these T cells in the liver express activation markers, meaning that they are probably activated by virus-infected cells, that they can recognize these cells, lyse them, and cause liver damage, contribute to liver damage in the liver.

So, the second assay that I would like to discuss is the ELISPOT. This is a graphic description of the ELISPOT assay. For this assay, only a few lymphocytes from the blood are required. I would estimate that analysis of the T cell response against all viral proteins could be performed with 5 to 10 mls of blood so that it may be possible to do it in adults or even in children.

In the ELISPOT assay, cells are stimulated in multi-well culture plates with individual HCV proteins, and then these plates are coated with specific antibodies to T cell-derived cytokines such as interferon gamma. If a T cell is stimulated by the specific HCV antigen, it will produce interferon gamma or other cytokines. The cytokine will bind to the plate. You can then wash away the cells, and for each cytokine secreting cell you can visualize one dot in the ELISPOT culture. So, on this slide, each dot represents one cell that produces interferon gamma in that case to HCV proteins.

In the middle, we have an HCV peptide that is frequently recognized, and on the right-hand side we have a positive control, which is the cytomegalovirus peptide. So, you can see in this case there is a strong immune response against this particular HCV peptide, and it's equally as strong as the one to the CMV peptide, and much stronger than the medium control on the left-hand side of the slide. So, this is a way to quantitate the number of T cells that produce specific cytokine in response to HCV proteins.

Which studies have been performed during interferon gamma ribavirin treatment or other viral treatments? This is a study just recently published in Gastroenterology. Two groups of patients have been

studied, responders to interferon ribavirin treatment and nonresponders, depicted as the strength of the T cell response, the percentage of patients with T cell reactivity against all HCV proteins.

As you can see on the left side, indicated by the green bars, the response of treatment responders increases with time of treatment. Only approximately 10 percent of the patients have HCV-specific T cell reactivity prior to treatment in chronic infection, and then this percentage increases to up to 60 percent at the end of treatment.

In contrast, in nonresponders the percentage of responses decreases. At the end of treatment, it's only 20 percent and, in the year of follow-up, decreases to zero percent.

So, it is possible by antiviral treatment not only to decrease viral load but also to increase the immune response.

In summary, I've written what is known about the cellular immune response in acute self-limited hepatitis C. We know that a vigorous, multi-specific, and sustained CD4 and CD8 T cell response is associated with recovery from hepatitis C, all studies performed in adults so far, and it needs to be maintained to ensure that viral clearance. In individual cases, it has been shown that the

T cell response may decrease up to 6 months after the first negative PCR for the virus in the blood. Then the virus may reappear and the patient may still become chronic. So, this T cell response seems to be necessary to maintain for a long time after viral clearance.

After recovery from HC infections, circulating HCV-specific antibodies may decrease. I say "may" because this is not the case in every patient, and only after long-term recovery while Th1 and Tc1 cells remain detectable in the blood for decades, and Th1, Tc1 cells are the cells that produce interferon gamma as the predominant cytokine.

So, why is recovery not present in a rare percentage of patients? What may be the factors that determine viral persistence? There are a lot of possibilities right now that are being studied and discussed. The next slide may describe a few of them.

So, for example, lack or loss of neutralizing antibodies has been discussed.

The frequency of HCV specific T cells, as I mentioned, is very low and may not be high enough to clear HCV in most patients.

HCV sequence variation, quasispecies may play a role, especially because this is an RNA virus that introduces mutations in the viral genome during replication.

HCV may interfere with antigen processing. It may not be susceptible to most T cell cytokines.

Then certain HCV proteins, such as the viral core, may alter T cell-induced cell death, may change the T cell response in general.

And certain viral sequences within the viral envelope and NS5 proteins have been shown to interfere with activation with interferon-induced enzymes that then inhibit viral replication.

So, the virus has found a way to escape from a productive T cell response, even from antiviral treatment, because it may interfere with the intracellular response of host cells that respond to cytokines coming from the outside. So, by developing mutations, HCV may have developed certain ways to escape from a strong cellular immune response.

Thank you very much.

DR. CHESNEY: Thank you very much. We'll save questions until a little bit later.

Jayne tells me that Dr. Rehermann sent copies of her slides by Fed Ex and hopefully they will arrive and we'll be able to have copies before too long.

Thank you. That was very informative.

Our next speaker is Dr. Leonard Seeff, who is going to talk about the natural history of hepatitis C in

the adult population.

DR. SEEFF: Good morning, everybody. Yes, indeed, I was asked to talk about the natural history, and if I have a little time, a brief summary of treatment with pegylated interferon. I may not have that time, but I'll do the best I can.

As you know, one of the most difficult issues that we face in the study of hepatitis C is trying to define its natural history, and the reasons for this are obvious to everybody. This is a disease, as you know, that when it begins, is usually silent. Upwards of 80 to 90 percent of people have no symptoms. As you've heard and as we know, there is a very high rate of progression to chronic hepatitis, and even when chronic hepatitis evolves in the first 15 to 20 years, it is by and large silent and people are identified later in the course of the disease. And if it evolves into end-stage liver disease, it takes many, many years, longer than the life of most investigators, so it's become very difficult to, in fact, identify the long-term natural history.

So, the controversy that has plagued us is as follows. Is fibrosis progression linear, and therefore advancement to end-stage liver disease and ultimately death from liver disease inevitable as long as people don't die of something else first? Or is fibrosis progression not

inevitable, but may be affected by virologic, host, environmental, dietary, other extraneous factors which may limit and modify outcome. This is a struggle I guess we've had and we still don't really have the answer to that.

The sequence of events, as I think everybody knows, is as follows. If you look at the very top here, the disease begins usually silently as the initial infection. It then progresses to chronic hepatitis, which is initially presumably first minimal and then moderate. And then eventually it progresses to much more severe chronic hepatitis, namely the development of cirrhosis and/or hepatocellular carcinoma. So, this whole process may take 20 to 40, even 50 years.

So, how do you study that?

Well, as you know there have been three approaches, and the first approach, and the approach that gave us great concern were the retrospective studies, in which people began looking at individuals with severe end-stage disease, tracked them back to the beginning of their disease to determine how long it took and, of course, beginning then with fairly severe disease, identified the fact that this was an infection that evolved into serious liver disease.

More appropriately would have been to do prospective studies, and the prospective studies would have

permitted us to start from the beginning of the infection and to follow through to its end. The trouble is, we can't define the beginning of the infection in most instances, and the end takes forever, so that's a problem.

More recently there have been a series of studies, so-called retrospective-prospective so-called, or nonconcurrent cohort studies -- and I'll summarize these -- which have given us a little different perspective on this infection, a little different from our initial studies, which were those data derived from the retrospective studies. I'm going to quickly summarize these as quickly as I can.

So, a quick summary of the retrospective studies, and I've listed just a few at the bottom here, a couple from Japan, from the United States, from Germany, and another one from the United States. Putting all these studies together, the number of patients that were studied was somewhere between 70 and 840. The intervals from exposure in the retrospective studies were listed as 9 to 29 years.

As you can see, there was a very high rate of development of cirrhosis; 17 to 55 percent of these studies were reported to have developed cirrhosis over a period of 20 years. I forgot to mention that in that initial slide the usual view that is held is that cirrhosis develops in

about 20 percent of people at the end of about 20 years, approximately. So, here we see much higher rates of cirrhosis.

There was a high rate of development of cancer and liver-related death.

So, these studies, which were extremely important in defining the potential severity of this disease, were somewhat concerning, indicating that there was a very high rate of evolution to cirrhosis and to cancer.

As I've said many times, one of the problems with these studies is that we began with individuals who are, in many instances, were already ill, and what we missed out were those who never got to the tertiary care centers where these studies were done.

Well, what about the prospective studies? Well, I list the prospective studies here: DiBisceglie, Koretz, Mattson, Tremolada.

One of the problems with these studies is they were relatively short. They did not exceed 15 to 16 years. The number of patients studied were 61 to 135. Intervals from exposure, as you can see, was 8 to 16 years. In these studies the evolution to cirrhosis appeared to be much less; 16 percent was the top number. And the development of cancer was lower. Liver-related death was lower, but of

course the problem with these studies was that they were short, and indeed, we believe that it takes 20-30 years before you end up with liver cancer.

How do you then get the information that you need in order to track the outcome?

Here are the so-called retrospective-prospective studies, and I'm going to go through each of these in turn. I think if you look at the right-hand side over here you'll see that, by and large, the development of cirrhosis in these studies, for a variety of reasons we'll talk about, seem to be lower than some of the earlier studies. Liver cancer is somewhat lower, and liver death is somewhat lower.

Let's start going through. I thought what I would do is to break them down into various types of studies that have been done.

There have been two studies involving young women. Both of these are immune globulin contaminated follow-up studies. Dr. Rehermann has mentioned the study from Germany, Dr. Wiese. I'm just going to show you one slide from each of these, reminding you that we anticipate a 20 percent rate of cirrhosis at the end of 20 years.

So, the first study from Dr. Kenny-Walsh and her group in Ireland, in which some 363 women were tracked who had, 17 years earlier, received contaminated anti-D

immune globulin, came out with somewhat surprising data. This was really quite a surprise when it first came out. It showed that, indeed, 20 percent of this particular cohort had not developed cirrhosis. 2 percent showed cirrhosis. There was 10 percent with bridging, which is a serious problem, and could well evolve into cirrhosis over time. But here we have a 20-year follow-up with a lower rate of cirrhosis, and that was somewhat of a revelation.

Well, it was followed by a study from Germany, Dr. Wiese, et al. Again, this was a large number of women, 264 livery biopsies in women who, 20 years earlier, had been exposed to hepatitis C.

Here we use the Ishak Fibrosis Score, 0 to 6. 5 and 6 represent cirrhosis, 3 and 4 represents fibrosis, and less than that is very little fibrosis.

So, here again we see that almost none of them had developed cirrhosis. The numbers show a very low rate again, quite similar to the data that we saw from the Irish study. So, certainly it appeared that in young women, at least, evolution to cirrhosis at the end of 20 years was a little lower than had been anticipated.

What about studies in children, which is important over here? I don't know too many. Perhaps Dr. Jonas will tell us more about the natural history in children.

This is the one well-known report that appeared in the New England Journal from Vogt, et al. This was a study of young children who had undergone cardiac bypass surgery in the first three years of life, had been transfused, and they followed them up some 20 years later. They started off with 458 patients, and 20 years later they went back to the original samples. 14.6 percent were anti-HCV position.

What was interesting, and it's a point that again Dr. Rehermann has made, and I'll come back to that later, is that when they followed them up 20 years later, 45 percent of these youngsters were now RNA negative. They had spontaneously lost virus. That was a much higher rate of spontaneous loss than we had usually thought to be the case, which was about 15 percent.

Well, increased ALT was found in one, with congestive heart failure. Liver biopsy was done in 17. Fibrosis, 2. Both happened to have congestive heart failure. Cirrhosis in one, and this was a child with HBV, so again, there was a very low rate.

I also happen to have some data here that you might be interested in that I got from Jay Hoofnagle on Friday about a split database on pediatric liver transplantation from June 2000. This is a study that's being supported by the NIH. This is a study that covers

transplant centers, 29 participating centers since 1995.

So, far they have data on 1,144 children who were listed for transplants. 12 had cirrhosis due to hepatitis C, 1 percent, and 1 had subacute hepatitis C. Of these 1,144, 706 children underwent transplant, of whom 6 had hepatitis C, or 0.8 percent, 5 with cirrhosis, and 1 with subacute hepatitis. So, transplantation in children is not very common for hepatitis C. That doesn't mean to say that 20 years later that this becomes a problem once they become adults, and that's the big issue that we face.

So, now let's go quickly to a series of studies in transfusion recipients. These are studies that I was involved with. Blaine Hollinger here has been involved helping me out with these studies, Harvey Alter, and so on. These are long-term studies. We reported the first time in 1992, and then we actually have a paper, which I say in preparation here, that was reported in Hepatology a couple of months ago.

Just a quick summary. This was a study in which we went back to five prospective studies that had been done in the 1970s in which patients were diagnosed as having hepatitis C on the basis of evolution of abnormal enzymes after transfusion. We put all the studies together. They all used, more or less, the same criteria. We have been following the individuals who developed

transfusion-associated hepatitis C for the last 25 years, matching them 2 to 1 with individuals who are very carefully matched, transfusion recipients, and didn't get hepatitis C.

What's happened to them?

Well, in our first report at 18 years, all-cause mortality was no different. All-cause mortality, 41 percent versus 42 percent, and 23 years later, all-cause mortality is no different. Now that doesn't mean to say that that makes hepatitis C a benign problem because these were, after all, adults who were in their late 40s who were transfused for a reason. What this really tells you is that people who are transfused have a high risk of dying, not necessarily of viral hepatitis.

If you look at viral hepatitis on the right-hand side, it was 2 percent among the cases versus 1.3 percent among the controls, and then 23 years later it had gone from 2 to 3.1 percent, whereas the controls stayed the same. So, there is a slight increase in mortality from liver disease. These are 23 years. We have 25 years' data. It's about the same, about 3.4 percent at 25 years. It does indicate, then, that transfusions are a serous thing to receive because that's what often kills you. Many of these people have undergone cardiac bypass surgery.

What I think was interesting -- and also it

speaks to the issue that Dr. Rehermann has spoken about -- is what happened to those individuals who had transfusion-associated hepatitis C, were positive, and did not in fact die? What happened to them some 25 years later?

Well, we find that 25 years later 77 percent remained viremic, antibody and viremic. But 17 percent are nonviremic, and this has been tested many times, including in Blaine Hollinger's laboratory. They are anti-HCV positive, but also in keeping with what she told us, 7 percent have lost all markers. These were people whom we saw develop hepatitis C and yet 25 years later are negative for virus and are negative for the antibody. No evidence that they'd been infected.

What this tells me is that the total number of people in this country who have been infected are, in fact, higher than the number that we have accepted now, which has come from NHANES of about 4 million people. There may be more people who have been infected and who lose all evidence of virus. Here we see 24 percent of people have lost virus and not the 15 percent that we used to think about.

In this next very complicated slide, which I won't go through in detail, what we did was we tracked each of these groups to see how many of them ended up with cirrhosis. Not all of these people were biopsied for a

variety of reasons, but based on the biopsies we did do, we calculated somewhere between 15 and 17 percent of people did develop cirrhosis. So, here we are closer to the 20 percent that we had anticipated to be the case.

There's another series of studies in injection drug users. There's well-known study that comes out of Hopkins. Dave Thomas and his group have been looking at a large number of drug users. Dr. Schwarz, who has been involved in that, is doing some studies herself looking at this particular group. Let's see the data.

This is 1,667 anti-HCV-positive drug users who have been followed for a median period of 8.8 years. It turns out that 2.4 percent of them ended up with end-stage liver disease. That's not small. On the other hand, 10 times as many, 22.4 percent, died of non-liver disease. That means drug overdose, trauma, HIV, and so that more people were dying as a result of other causes than of liver disease, so that doesn't detract from the fact that liver disease is important.

I might just mention -- I don't have a slide -- I am doing a 25-year follow-up study now in a VA cooperative study that we did 25 years ago in which we studied 600 drug addicts, and we followed them now 25 years later, wanting to see what happens to hepatitis C. Well, it turns out that when we studied them initially, they were

all HIV negative. Now it turns out that 60 percent have died. These were young men 25 years ago. 60 percent have died. Our control group is 6 percent, so there's a 10 times higher mortality.

And what's the cause of death? In about 80 percent it's HIV. The the original samples were negative. They came in just as HIV was evolving. Unfortunately, they lived through the period of time where treatment had not yet become effective, and they died of HIV. We're struggling, in fact, to determine what happened with hepatitis C because it's a big problem.

There's one more slide from Dave Thomas' study. When he did liver biopsies in 210 patients, 2 of them had cirrhosis.

Well, there have been a couple of interesting so-called community-acquired hepatitis C. I've learnt a little bit more now. This is a study that we did that I will quickly report on, and I didn't bring slides on this one.

We happened to come across, and people may know this, almost 9,000 blood samples that had been drawn between 1948 and 1952 at an Air Force Base in Wyoming. Dr. Ramelkamp was at this place at the time. He was an expert in strep. There was an outbreak of streptococcal infection. He drew blood from all these people, tested it

for strep, sequestered the samples, sent them back to this hospital in Cleveland, and it sat there for 45 years. And we learned about it about five or six years ago and decided here was a wonderful opportunity. In fact, it's giving us an opportunity to do a number of studies which we are in the process of doing now.

But one of them was to go back and test for hepatitis C. To my knowledge, I don't know of any data that take us back to 1948 with respect to hepatitis C. But we did test, and we found using the third generation test that 34 people were positive. Now, that's not a heck of a lot. But remember, these were so-called young, healthy individuals who entered the Air Force, and you assume that they are low-risk and this is what you would expect in a blood bank.

Well, we then did the RIBA test on them, the third generation test, and it turns out that 50 percent were positive. The others were either indeterminate or negative. So, we decided to focus our attention on these 17 people. A small number, but this is the earliest, as far as I know, reported evidence that hepatitis C has been around, and I believe that hepatitis C was around since the Second World War, probably in low level. Then when the drug culture began to flourish, it probably increased, and that's why we're dealing with a big problem now.

So, what's happened to these 17 people 50 years later?

First of all, we did RNAs on them, and to our surprise -- remember, these bloods were drawn in the field, they were sitting around for a while, they were then put into a freezer. We thought we would never find anything. Well, 11 of these 17 turned out to be HCV RNA positive, 65 percent. We were able to genotype all but one, and they're all genotype 1b. So, that's a little different from what we see today.

What's happened to these 17 people? 7 have died and 10 are alive. Of the 7 who have died, 1 has died of liver disease, and I'll show you what's happened to the 10.

Here are the causes of death in 6 of the 7. We could not find the data on the seventh person. One died of alcohol abuse, one of trauma, one of heart failure, another of heart disease, multiple myeloma, and one patient died of viral hepatitis and chronic liver disease 42 years from the time of the original phlebotomy.

Now what about the people who are living? This is not an updated slide. But what we have managed, of the 10 people that we know to have been infected and alive, 2 of them we cannot find. That leaves 8. One of those 8 has had a stroke and the family will not permit us to see that

person. The other 7, we have seen all of them. This shows you 6 of them, and I don't have the seventh one in, but I'll quickly summarize by telling you that every one of them are still anti-HCV positive. All but 2 are RNA positive, and 1 has the highest level of RNA I have, frankly, ever seen. Almost all of them have still got abnormal enzymes. We didn't do biopsies for a variety of reasons, it was ethically not possible. So, I would love to see those but we can't do them. So, we used surrogate markers, albumin and platelets.

The only one who had low platelets was this one, of 110,000, 3.5 albumin. This happened to be a very heavy alcoholic, and so he had a huge, long history of alcohol, as well as hepatitis C. I didn't know what caused this. We have now spoken to these people, and in fact 3 of them admitted to using drugs prior to entering the Air Force in 1948. So, I think they've actually been infected for more than 50 years.

Now, this is a vignette. This hardly speaks to the whole issue of what the natural history of hepatitis C is. These were young, healthy men. It's a different story and we don't really say that this is what normally happens. But here is evidence that you can certainly live with this disease for 50 years. None of them were treated. Frankly, when I spoke to all of them, none of them have actually

clinical evidence. Two of them have mild hepatomegaly. The alcoholic has splenomegaly and I think probably has cirrhosis. But this is 50 years.

So, the natural history of hepatitis C. Do all persons with HCV infection have the same long-term outcome?

I think the answer is that it is not true that everyone has the same outcome.

We've heard that age is a very important determinant.

Gender may be possible, although now some evidence suggests that that may not be the case, but I think it may play a role.

There's a very interesting story developing about African-Americans, yet to be determined. We have a big study that's coming up at the NIH to look at this whole issue about the treatment and natural history of the disease in African-Americans.

Obviously we've heard about genetics.

I believe that there's a difference in the outcome depending on how you get the disease. If you have transfusion as the basis, you have to worry about the reason for having been transfused in the first place. If you're an IV drug abuser, you have to worry about the fact that you co-infected with HCV.

Viral genotype clearly is extremely important,

as we know, as far as treatment is concerned, and may play a role in outcome.

And then there are certain co-factors that I believe we still need to spend more time looking at. We know that alcohol is an important issue. Smoking may play a role, diet may play a role. Environmental factors may play a role.

I am personally intrigued by the fact that the death from hepatitis C in Japan is so much more commonly a result of liver cancer than it is in this country. I've just reviewed another paper in which there was a long-term follow-up of hepatitis C in Japan, and of those people with hepatitis C who died, 68 percent died of liver cancer. Now, that's not what we're seeing in this country, regardless of what we think. It's much higher there. The question is why.

I happen to believe that there may be environmental or dietary factors that may play a role. I don't know this, but I believe that that's an area that we may need to look at in more detail.

So, let me show you what we've done over here. Harvey Alter from the NIH and I happened to write a review article, and we tried to project a lifetime outcome based on our review of the literature. Now, this is obviously pure fantasy, but it's not pure. Nothing that we do is

pure, certainly not Harvey.

So, we started off with 100 patients with acute HCV infection, and we're making the assumption that about 20 percent recover. As I'll show you and as we've already heard, it may be higher than that in some populations, leaving 80 patients with persistent infection.

We think that if you follow these people out, 30 percent will have stable chronic hepatitis, and by this we are now talking about histology. That is, if you do liver biopsies, you're going to see less than 3 out of 6 Ishak fibrosis. 40 percent, variable progression. That means individuals with bridging fibrosis, and 30 percent of this group, which is 20 percent of that, with cirrhosis. Then you treat those people, as we are now doing, and this was before we have the pegylated interferon, and this may get better. We say there's a sustained response rate of about 35 percent, or 20 patients, leading to treatment failure in 65 percent.

So, what we estimated is that there's a favorable outcome in some two-thirds of individuals, and a potentially unfavorable outcome in about a third.

Now, how do we choose these, and how do we find out who falls into which category? That's our big problem. Remember, that if we do have 4 million people, and a third of those have a potential for severe outcome, that's a lot

of people, and that's why we're seeing so many people ending up in the liver transplantation, and that's the reason for our panic and concern about trying to treat these patients.

So, let me just quickly summarize the data demonstrating a higher than expected rate of spontaneous recovery. In our study, 24 percent of individuals who are transfusion-associated have spontaneously recovered. If you look at the NHANES data from Miriam Alter, 26 percent have recovered. Here are the data from leukemic children; 29 percent of her people have recovered. The Kenny-Walsh and Wiese study, the contaminated Rh immunoglobulin, 45 percent have recovered. The study from Germany, 45 percent have recovered. And in the paper that I didn't report to you from Australia, 46 percent have recovered spontaneously. The question is when and why, and that's why we pay Barbara to help us find out why they recover.

So, that finishes my talk on the natural history, and if you want me to proceed, I've got about four or five slides on treatment. If that's too late, I can come back to that.

DR. CHESNEY: You go ahead, please.

DR. SEEFF: All I'm going to tell you about are the pegylated interferon studies. I think we're all aware of the fact that we're moving into a new era, and the era

is going to be pegylated for the immediate future. These slides, by the way, were made by Jay Hoofnagle for a presentation he was giving, and when I told him I was coming here, he lent them to me. They're just very brief.

The first study was reported in the New England Journal in the year 2000, an international trial using PEG-interferon alpha-2a. This was 531 patients randomly assigned to receive 180 microgram PEG-interferon weekly versus 3 to 6 million units of standard interferon three times a week for 48 weeks. The endpoint of virologic response was to reach HCV RNA negativity 24 weeks after stopping.

Here you see the striking difference between standard interferon and pegylated interferon. The top bars show you the end-of-treatment response. The lower bar shows you the sustained response. So, it was 39 percent versus 19 percent in individuals who received the PEG-interferon versus the standard interferon.

The next slide is the study which focused now its attention on individuals with cirrhosis or bridging fibrosis, and this was again an international trial, 271 patients who were assigned to receive either 90 or 180 micrograms of pegylated interferon weekly versus the 3 million units standard interferon, and again, the endpoint was loss of virus at the end of 24 weeks after stopping

treatment.

Here we see that in the standard interferon, the end-of-treatment response was 14 percent. When we got to the pegylated interferon, there was no difference in the end-of-treatment response between those who received 90 and those who received 180, but there was a significantly higher rate of sustained response, 30 percent versus 15 percent versus 8 percent. So, those were the two reported studies.

There is also a large ongoing study that was reported at the AASLD meeting by Dr. Michael Manns, and I don't have the data other than in abstract form, but we took some information at the meeting and this is a summary. This is 1,530 treatment-naive patients with compensated chronic hepatitis C, with RNA in the serum and raised ALT, stratified by genotype and cirrhosis. Three arms, 48 weeks of therapy. They received either interferon alpha and ribavirin, 1 to 1.2 grams per day, PEG-interferon, 0.5 micrograms, plus ribavirin. As you can see, the dose over here, and then PEG-interferon 1.5 plus ribavirin.

Here you see the standard versus the PEG-interferon. This is the PEG-interferon 0.5 versus the PEG-interferon 1.5. There's 47 percent sustained response, 47 percent sustained response, 54 percent sustained response. It was significant at the p .01 level.

The next slide shows you what happened over here. Here is the end-of-treatment response. The end-of-treatment response appeared not to be different, but the sustained response was different. The relapse rate was much less. So, there was a significantly higher response rate among those who received the PEG-interferon 1.5.

There was obviously a dramatic difference between those with genotype 1a and 1b versus genotypes 2 and 3. As you can see, the standard went from 33 to 34 to 42 percent in the genotypes 1b, a dramatic response in genotypes 2 and 3, 80 percent plus. I think now we're reaching the point where this is virtually a curable form of hepatitis C if you have genotypes 2 and 3, and I hope that that will get better as time goes on and reach 100 percent. In fact, it may have reached that already.

What was very interesting was that body weight played a role. The higher the body weight, the less the response. As you can see, there were people who were more than 85 kilograms who had a much lower response rate. So, body weight is now important with respect to the likelihood of response to treatment, and it requires us then to consider the amount of interferon that needs to be given.

What was also interesting was an effort to look at the ribavirin dose, and they cut it, I guess at 10.6 micrograms per kilogram. Is that about 800, Karen? 800,

right, okay. So, here we see that the difference between those who received lower doses, the risk of those who received slightly higher doses.

Now, what about the adverse effects? Well, here we see early discontinuation. About 14 percent of all groups had to discontinue, and there was a somewhat higher rate of dose modification in people who received the higher dose modification. So, it's obviously more effective but it does come with obvious side effects, which you will be discussing in more detail.

Let's skip this slide and just go to the final slide to show you the changes that really have taken place and are pretty remarkable, I think. We began with interferon for 6 months, 6 percent. Interferon for 12 months, 16 percent. Interferon plus ribavirin for 6 months, 34 percent. Interferon plus ribavirin for 12 months, up to 42 percent. PEG-interferon about the same, 39 percent. And PEG-interferon with ribavirin, up to 54 percent. So, clearly over the years there has been a remarkable improvement in the response rate to treatment. I guess that's where we are likely to be in the very immediate future as far as treatment is concerned.

Now, your problem is to decide what happens to children who are infected once they reach 20 and move on to 30 and 40 and 50 and 60. There's no answer to that. I

guess the question is, I think we all do believe that the older you are when you're infected, the more likely the disease is to progress.

Now, what happens if you're infected at age 5 and you get to 50? Do you then assume the circumstances that occur if you're infected for the first time at 50 and progress thereon, or does this remain as a flat curve rather than one that goes up? I don't know how to answer that question, and that's a quandary that I guess this committee has to face.

Thank you.

DR. CHESNEY: Thank you very much. Very informative.

Dr. Jonas, from the Division of Gastroenterology at Children's Hospital in Boston, is going to give us all the answers about hepatitis C in children. Thank you all in advance.

DR. JONAS: Thank you all for this opportunity to share this important issue with you. I know for all of us pediatricians around the table, it's rather gratifying to hear our adult colleagues talk about weight-based dosing in medication, and maybe it's important. But eventually they caught up.

(Laughter.)

DR. JONAS: What I'm going to do in these next

20 minutes is sort of touch on some of the issues you've heard discussed on hepatitis C in children. Our data are nowhere near as mature as things you've heard from Dr. Seeff this morning, unfortunately, but maybe with this committee's help we can get some direction about how to pursue your learning what the important topics are at least.

These data I actually extracted from Dr. Alter's paper and from the NHANES data that you've heard alluded to earlier, and this is just looking at prevalence of antibody to hepatitis C by age in the United States. You can see that most cases are certainly not childhood cases. The two pediatric age groups are described here, and the prevalence of this antibody is quite low, less than .5 percent of the population have been infected or are infected with hepatitis C.

If you look at it a different way, the same data, just shown a different way, but the proportion of infected people that are in the pediatric age groups is quite small, so we're not talking about huge numbers of patients. When I tried to do the math to extrapolate this out, it came out to about 250,000 children in the United States infected with hepatitis C in this one survey alone.

Dr. Alter is quick to point out that the incidence of new cases is rapidly decreasing, and the

reasons for this are not totally known. I start to think about that, and probably the incidence of new cases in children is not rapidly decreasing in parallel because I think that, as you'll hear, the most common way children will be infected now will be perinatally, and there's no reason to think that all of a sudden infected women of childbearing age will stop having children. So, I'm not sure that the general gist of decreasing incidence is pertinent to children.

So, which children are at risk? Well, these I think have been defined. Certainly children who've had recurrent blood or blood product transfusions over their lifetime, and the risks there are obviously in the pre-donor screening era, but children with hemophilia and thalassemia have prevalence rates that you see listed there: 80 percent of hemophiliacs in the pre-recombinant factor era; thalassemic children have a very high incidence.

Obviously, blood or blood product transfusion, even 1 prior to 1992, and we all have many of these children in our practices who had one blood transfusion. But certainly those who were exposed to a large amount of blood, either treatment for acute lymphoblastic leukemia, cardiac surgery, these prevalence rates are about what are quoted in the literature in more than one study, somewhere

in the 4 to 10 percent range. Children who have had orthopedic surgery, care in the neonatal intensive care unit with a lot of blood exposure prior to 1992. So, obviously these children are at least 9 years of age now.

Adolescents with the high risk behaviors that allow adults to contract hepatitis C are certainly at risk.

And then I think what is the most common and important category for us to spend some time on is children born to HCV-infected women.

This is a study we actually did some number of years ago in Boston to try to get a sense of are there a bunch of kids out there infected with hepatitis C and we don't know about it, and they have no risk factors that we know about. This was at the time when we talked about a lot of adults with no risk factors, and we know now that's sort of a myth as well.

What we did is we were doing a hepatitis B vaccination study, so we had a lot of kids involved with questionnaires and blood. And they were in our adolescent clinic at Children's Hospital and they were in a local high school-based clinic. We did some serologic testing. We looked at them across the board for socioeconomic group. They were very scattered, whether they had insurance or not, and so forth.

But basically this is what we found, that

although hepatitis B continues to remain an issue in adolescents -- so this is 3.2 percent of these kids that were repeatedly core positive for hepatitis B in more than one specimen -- hepatitis C was not a big deal. Only one subject was antibody positive.

So, I don't think in pediatrics this is a disease of kids with no risk factors and they're out there in the community and there's this big pot of them out there. But I think, on the other hand, pediatricians need to know what the risk factors are and who to test.

I want to spend a few moments on perinatal transmission because I think, as far as pediatricians in general, this is where we have to concentrate a lot of our thinking and our efforts.

I've extracted data from these papers only to include women who were HCV viremic, not just antibody positive, because people who are antibody positive but not viremic do not transmit hepatitis C to their neonates, and HIV negative for the purposes of this slide.

If you look at the early studies, it seemed a little bit high as far as percentage of transmission, but if you look at the later studies with larger numbers of women, hepatitis C-infected, HIV negative, the perinatal transmission rate seems to circle somewhere around 4 to 5 percent. I think that's probably fair.

I wanted to bring to your attention this study, however, and the next couple of papers, about about the dynamics of perinatal hepatitis C transmission because I think they're important.

This is a study reported last year also in Hepatology. In this study, 266 infants were born to hepatitis C viremic women. I will point out to you obviously all infants are antibody positive at birth because there is passive transfer of antibody. This is an IgG antibody, so testing for antibody in the infants, at least in the first year, 15 months, is not very helpful in understanding this issue.

What these investigators did was look for hepatitis C RNA at birth by sampling cord blood. 18 of the 266 were positive, indicating that there was already maybe some viremia at the time of birth, and most were negative. But if you look at 4 months of age, the vast majority of these infants had cleared hepatitis C RNA. Were they truly infected? Qas it a transient viremia? It's not really analogous, for example, to HIV, I think. But 2 remained positive.

But look here. Of all of these infants who were negative in cord blood, 6 more were positive at the age of 4 months. That gave a total of about 8 perinatally infected infants. It gives you somewhere around that 5

percent, so it makes sense. And of the 8 that were followed, all of them remained infected at 18 months.

So, the transmission may occur a little bit in utero, but probably is somewhere between birth and 4 months when this happens, or at least can be detected in the newborn. I think that's important for understanding when you talk about intervention, or when to make this diagnosis.

If you look at risk factors, which mothers transmit hepatitis C to their infants, it's been recognized a long time that co-infected mothers, HIV positive mothers, have a much higher increased incidence of transmission of hepatitis C. And importantly, it's not necessarily associated with HIV co-transmission, so their infants will get hep C infected but not HIV infected.

Looking at other sort of risk factors that might increase this, there is some data that were presented here from CDC where prolonged rupture of membranes was a risk factor increasing the likelihood, and they chose a 6-hour cutoff to make that designation. The use of internal fetal scalp monitoring makes sort of sense. Pricking the skin of the neonate with maternal blood increased the likelihood. In most studies, mode of delivery -- i.e., vaginal versus C-section -- has not been a demonstrable risk factor.

Just a word on HIV co-infected women. Perinatal hepatitis C transmission, you can see the significant increase in the likelihood of hepatitis C transmission from HIV co-infected women.

On the other hand, the Italian study that I showed you, if the HIV is very well and aggressively treated and the HIV viral load is low in these women prior to delivery, this transmission rate actually goes back down towards the 5 percent again. So, aggressive treatment of the HIV in the mothers can decrease the likelihood of perinatal hepatitis C transmission.

This is a rather intriguing study that came out last year. And I think it might give us a little bit more insight, once again, looking at perinatal hepatitis C transmission and the fact that it probably occurs around the time of birth and not before birth. They examined a large number of mother-child pairs, 441, and once again, the overall rate, 6.7 percent, pretty consistent with what I've told you from other studies. Once again, a much higher transmission rate from HIV co-infected women without concurrent HIV transmission.

Most of the newborns that were eventually proven to be infected with hepatitis C were negative by PCR testing at birth. Once again, if you examine infants at birth, this is not the way to make that diagnosis.

They looked at mode of delivery and they separated them out a little bit. Looking at vaginal delivery versus C-section, in general there was really no difference. But if you took emergency C-section and elective C-section, this is the intriguing part. There may be a difference here. You can see the odds ratio.

And the postulate was that these women, because an emergency C-section had earlier rupture of membranes, here in elective C-section the membranes are ruptured right at delivery, so maybe once again saying that there's something around after rupture of the membrane when this transmission occurs, and something for us to think about as far as prevention.

So, these are current recommendations regarding perinatal hepatitis C transmission. These may change as our knowledge increases, but right now it is not recommended that all pregnant women be tested, as they are for hepatitis B. On the other hand, targeting testing, which means that obstetricians need to know who should be tested, women obviously with a history of IV drug abuse, women with a history of blood transfusion prior to 1992, women with an unexplained ALT elevation and so forth, or as I say, any woman who requests to be tested typically should be tested.

At this point elective cesarean section to

prevent hepatitis C transmission is not recommended. I think more data needs to be accumulated regarding that, but certainly there is the hint that maybe we should consider avoiding internal fetal monitoring or prolonged rupture of membranes in that setting.

A word about breast-feeding. It's very difficult to tease out the additional contribution of breast-feeding to perinatal hepatitis C transmission in most of the studies. There always are a number of women who breast-feed and some of the infants do or do not become infected. But if you look in breast milk of infected women, it's very difficult to find hepatitis C. Most studies show that it's either not there or there in very, very trivial amounts. So, at this point there are no hard data to indicate contraindication of breast-feeding that setting.

What's recommended now is that infants of hepatitis C infected women be tested after 15 months of age for the antibody because at this point maternal antibodies should be gone and an antibody is probably helpful at that time and can be pursued with further testing if positive.

Now, clinical features. How do these children look? Well, you all know that really you cannot pick them out in a crowd. Acute infection is rarely symptomatic in children, and chronic infection is even less symptomatic, I

believe, than in adults. First of all, chronic fatigue, which is considered the major symptom in adults, is very difficult to assess, I think, in children. And extrahepatic manifestations, immune complex disease, kidney disease, vasculitis, dermatologic manifestations are also much less common in children than adults. So, this is an illness or a condition, if you want to say, without any symptoms. I think targeted testing and recognition is very important for those of us who want to identify and take care of these children.

Natural history. This is the hardest part, I think, as Dr. Seeff alluded to. He has some of the same questions, I think. Does fibrosis progress linearly? That's what we all worry about as hepatologists, is how much scar tissue is in their liver, because when you have fibrosis and you get cirrhosis, you start having all of the bad complications. Actually that may be a topic for discussion of the committee: Is that the only thing we care about with hepatitis C in children? But certainly from a medical point of view does fibrosis progress linearly?

What are the risk factors during childhood that may contribute to progression of disease? I think as you heard earlier, some of the risk factors in adults have been identified.

What is the role of underlying disease? Remember, these children were either transfused for an underlying condition, or what is the role of mode of acquisition? In other words, is the natural history of perinatally acquired hepatitis C different than transfusion-acquired in children?

Natural history studies we have thus far are basically cross-sectional cohort studies. People are trying to do prospective studies, but they go out a few years. As you've just heard, a few years is nothing in this disease, and we really need to do them over decades.

Looking at just a few studies of natural history transfusion acquired hepatitis C in children, I've just summarized a few of them here and I'll walk you through this slide. This is the study that Dr. Seeff alluded to that was presented in the New England Journal, cardiac surgery. But there are a few others here.

You can see that children acquired hepatitis C from transfusion in this percentage. So, here almost 50 percent of these leukemic children became infected with hep C; 15 percent after heart surgery in this German study.

But if you look at follow-up, and again look at the duration of follow-up, look at the length of time for follow-up, there is a drop-off. So, sometimes as many as a third to a half of the children are no longer infected when

looked at 10 to 20 years later. What does this mean? It's very difficult to know.

I notice there are several panel members from St. Jude's. This is actually a study that was published last year from St. Jude's, and they tried to look at the importance of hepatitis C infection in their population. They looked, first of all, at children who were transfused and had died, and they were able to study 346 of them. 3.5 percent had evidence for hepatitis C infection. Then they went to look at the cause of death in these 12 children. Interestingly, one died from liver failure 9 years after his original cancer treatment, and there were two deaths from hepatocellular carcinoma, which was not their primary malignancy, 25 and 27 years later. So, of the 12 deaths in the hepatitis C group, 3 of them may have been related.

Obviously that's retrospective. It's difficult to take that information and go forward.

They looked at their transfused survivors of the 6.6 percent who were infected with hepatitis C. Of those, roughly half had undergone a liver biopsy at some point. These were all different time points after their transfusion and their cancer therapy. But all of them were abnormal. 9 percent, which is only 3 patients, had cirrhosis, and you can see 10, 20 and 30 years after treatment. So, some children who get transfusion-

associated hepatitis C have a bad outcome. It's the minority, but there it is.

This is a complicated, messy slide but there's really no data on it of any importance, so it doesn't matter. But this is what there is regarding the natural history of perinatally acquired hepatitis C. There are very small studies with pretty much short duration follow-up. These things are hard to get your hands on, but you can see most children who become infected, followed for 1 to 2 to maybe 7 years, remain infected with hepatitis C. That's really all you can say from these prospective studies that have been done because we only have a few years of data.

I put on here a couple of anecdotes because they are striking anecdotes, and these are the patients I think that are going to concern all of us, that we have to deal with. They are anecdotes, but that's what I have.

These are in my practice. Two children who were perinatally infected developed cirrhosis by age 11 and 13. One has had a liver transplant. She had membranal proliferative glomerulonephritis as well. The other is now awaiting a liver transplant. She has decompensated cirrhosis. She's several years older, though. I should say she's almost 18. These children are reported in a response to an editorial describing the "benign" natural

history of hepatitis C, where three perinatally infected children had decompensated cirrhosis very early in life.

I know about another anecdote -- I'm sorry to share only anecdotes with you, but that's what I have -- about an 18-year-old girl who developed this perinatally who now has hepatocellular carcinoma and cirrhosis. So, there are a few that become sick with this disease.

Just to show you that it probably is the same disease as in adults, just looking at histopathology. I didn't bring slides to show you liver biopsies, you'll be happy to know. But I will show you that if you look at the major histologic features that have been recognized in hepatitis C -- sinusoidal, lymphocytes, lymphoid aggregates, steatosis, bile duct damage, and so forth -- you'll see that if you put a few studies together, the percentages of these findings are not all that different in adult and pediatric studies.

Bridging fibrosis is only described in one of the adult studies I reported here, but is seen in children.

Then interestingly, the rate of cirrhosis. Now in adults, depending on which study you look at and where you start in the natural history, as you've heard today, it can be very uncommon if you start early, or it can be very common if you start late natural history studies. There are children in some studies with cirrhosis from hepatitis

C during their pediatric years.

So, how do you interpret this? Well, I think that by saying the features are generally the same as those seen in adults, it probably is the same disease and has a very similar pathogenesis in children, if I can make that inference. And interestingly, in two of the major studies, our own included, looking at these histopathologic features, where a mathematical equation was tried to be generated, there was an association between extent of fibrosis and age and duration of infection. I don't want to say that it's linear, but there's definitely some sort of association. So, there is progression over time.

So, hepatitis C in children. Tthe natural history may be different in children infected by transfusion versus those infected perinatally, and we may need to keep that in mind if we're designing trials. It may be different according to the underlying disease by which the transfusion was indicated. I think at this point it's fair to say that the natural history of hepatitis C is benign in the first two to three decades in most instances. But a few children have very aggressive disease and we do not know the associated factors for that, and we certainly don't know anything about the third decade and beyond in children.

Now what about treatment? What do we want to

do with hepatitis C therapy? Well, sustained normalization of ALT sounds good, but I think many of these children that we detect after perinatal transmission or after transfusion associated disease, 10 years later, have normal ALT already. So, that is not always an important outcome variable, I think.

I think sustained virologic response, as you've heard alluded to before, not having hepatitis C in the serum 6 months after any kind of therapy is probably the gold standard that I think is used in most studies.

Improvement in hepatohistology. We need to think about that a little bit. I've showed you that children do have fibrosis and inflammation. The scores in general are lower. We talk about histologic activity scores as numerical sort of variables, and in children they're lower. So, I think it's going to be very difficult to show changes in low numbers, in small numbers of children. Obviously, it makes medical sense to look at that as an outcome variable, making inflammation less. Obviously, we do want to decrease the long-term risk of cirrhosis and hepatocellular carcinoma, which are life-threatening to these children later in life.

What do we know about interferon monotherapy? Well, because there was no group such as this, and no laws, such as the one you're discussing, five or seven years ago,

we really have no large randomized controlled trials. So, when we start talking today about newer therapies and what to compare them to, I'm going to show you a little bit of information about what we know about plain old interferon monotherapy. We have nothing of any substance that you can dig your teeth into.

The trials that have been reported that I'm going to show you have very heterogeneous patient groups. Different dosages of interferon were used, different types of interferon, and different lengths of treatment. So, it's very difficult to make definite implications from this.

Here's a potpourri of interferon monotherapy trials in children, and I'll briefly walk you through this. I didn't put all the data because, again, different doses of interferon, different lengths of therapy. You can see the kinds of patients: only transfused patients, mixed patients, leukemia patients, only thalassemia patients, not all of them were pediatric. Some of them repeated some are the same patients. It's very difficult to make a lot of sense out of the details. There's only one randomized, one control trial in all of these trials.

But I did want to point out the bottom line here, which even though the trials are all done in very different ways and the patients are all different kinds of

patients, if you look at this one outcome variable, sustained virologic response, i.e., no virus in serum, 6 months after the end of therapy, you seem to get a number that's significantly higher than what is reported in adults with interferon monotherapy. This is plain old interferon, not long-acting interferon.

Again, these numbers are small and I don't want to put a lot of stock in the absolute numbers, but they are fairly consistent and probably a little bit higher than what's been seen in adults.

These authors tried to do a meta-analysis of a bunch of interferon monotherapy trials. They looked at 11 manuscripts and abstracts that included 270 treated children and 37 controls. One of the controls lost RNA over the time period of the study. They had a sustained virologic response in treated subjects overall of 35 percent, not inconsistent with what I just showed you. And just as you see in adults, a very striking difference, whether the virus was genotype 1 or non-1. Once again, though, this meta-analysis includes very few controls, very heterogeneous therapy, and they did discuss the possibility of publication bias towards success.

So, does interferon monotherapy have greater efficacy in children than in adults? I think we need to think about this as we talk about study design later on.

There are reasons that it could. These children are younger at the time of therapy. They certainly may have an earlier stage of liver disease compared to adults that were originally included in the monotherapy trials. They have different modes of acquisition. Again, we talked briefly about weight and dose. We don't use a standard dose. We use a weight-based dose, or that had been used in all of these trials. So, it actually turns out to be higher for body weight than what an adult would get.

There may be lack of important co-factors that would allow interferon to be more efficacious, or it may simply be artifactual and it's not more efficacious at all because these studies were not the way we like them.

Interferon has significant side effects in children, and I'm sure we'll talk about those a little bit more.

Virtually all the children get the flu-like illness, but it's not, I would say, rate-limiting or lifestyle changing.

Neutropenia is very common but serious infection is very rare and usually well tolerated.

Weight loss and failure to gain weight is, I would say, almost universal, especially in the young school age children. We talk a lot about nutritional supplementation and very close follow-up of this.

Virtually all the children regain the weight after the interferon is stopped. They actually quite rapidly in the first few months regain the weight.

I haven't talked a lot about linear growth here. There are very few data about that, and it's one of our concerns. But it really hasn't been well documented except for one or two of the studies that you have in your handout. Neuropsychiatric symptoms. Certainly, as you know, in adults interferon and depression and other psychiatric problems -- they're reported in children on interferon, but the severity and the frequency have been very difficult to characterize from the study reported to date, but certainly a concern.

Likelihood of seizures or lowering the seizure threshold in children who may have a seizure disorder already.

The treatment of very young infants I think needs to be looked at very critically and separated out. In our own institution, children were treated with alpha interferon for hemangiomas early in life. So, these are life-threatening hemangiomas. They were treated with the same kinds of doses that we talk about for hepatitis C. There was an incidence of spastic diplegia, when they were looked at after a year, year and a half of age. So, I really don't consider using this for this disease at this

point early in life until we understand that a little bit better, at least.

Then, of course, we have no knowledge of very long-term side effects.

ribavirin we're going to talk a little bit about. What is the toxicity? Well, we know that in almost everyone who gets it there is some anemia, hemolytic anemia. It is most common in the first weeks of therapy, and then usually stabilizes. Most commonly the drop is less than 2 grams of hemoglobin, although very striking and dramatic drops can be seen and have been seen. It is reversible and dose-dependent. So, usually if you understand it and look for it and monitor it, it can be, I think, safely handled.

On the other hand, we know that certainly this is a teratogenic/mutagenic drug. There are issues regarding contraception that need to be discussed, and not fertility, but really pregnancy that may need to be handled.

Then obviously, what about this drug in growing children. I think not much is known about that.

Let me tell you a little bit about the trials that are ongoing for Rebetron, which is standard interferon with ribavirin in children. There are basically two studies.

The first study is a phase one dose-finding study, which has been completed, which included children, 48 weeks of therapy with both drugs and 24 weeks of follow-up. The interferon dose was 3 million units per meter squared. So, remember, some of these children will be getting more than an adult would get, if they're more than adult size. Three different doses of rhe ribavirin were used: 8, 12, and 15 milligrams per kilogram per day. Eventually the 15 milligram per kilogram dose was selected for the later study based on pharmacokinetics that were done in the fourth week, and some safety data.

The first study included 61 children, school age and early adolescent children, and there they are: 57 treatment-naive and 4 who had relapsed.

The ongoing study now is the phase III study. It's open-label. There is no control group. 48 weeks of therapy, again. 24 weeks of follow-up. All getting the same treatment: interferon, 3 million units per meter squared, three times a week, and the ribavirin. This study includes 105 children. We went down a little bit lower to age 3, and they're all treatment-naive.

Safety data from the first study. Basically the types of adverse events were similar to those seen in adults. Neutropenia has been seen. There were two of the children with depression, is my understanding. There were

serious adverse events that included the depression and non-related kinds of illnesses. Most dose modification was required in 11 percent, and 3 percent discontinued the medication. I think the agency has more of this data. I think they're looking at it right now, more than I have.

If you look at response in the phase I, this is only 60 children. This was the dose-finding study, so they're getting three different doses of ribavirin, but this is what we have. Remember, again, all the kids got interferon alpha, 3 million units, three times weekly, plus one of these doses of ribavirin daily. If you look right across the board at all patients, this is the sustained virologic response rate: virus negative 6 months after therapy, overall about 38 percent. Very similar to what's been seen in adults.

Broken down by genotype, again, a significant difference between non-1 genotype, genotype 1, 31 percent, non-1. These numbers are pretty small.

There wasn't a huge amount of difference in the different doses of ribavirin, but this dose actually gave pharmacokinetic properties very similar to the standard adult dose, and had no really more significance to safety issues than the lower doses, and that's why this was chosen.

So, what are the therapy considerations for

hepatitis C in childhood? Well, we really don't know the long-term natural history completely. It seems that in the first couple of decades this a benign disease, but in some children it's quite aggressive.

Which children should we treat? Well, should we use the criteria that people are now recommending for adults: moderately severe hepatitis, some fibrosis, not normal liver biopsies, or very minimal liver biopsies?

Should we treat no children because we have no randomized, double-blind, placebo-controlled trials on which to base these recommendations?

Or should we really treat all children because we think, number one, they have less severe disease, they're earlier in their infections, they may be more likely to respond to therapy, and there may be other therapeutic considerations, like getting rid of an infection which we didn't really talk about? But as far as the emotional and social issues regarding hepatitis C throughout your life, is there any value to trying to eradicate this infection, even though it hasn't caused serious chronic liver disease yet?

Thank you.

DR. CHESNEY: Thank you very much. That was superb for filling us all in.

Dr. Weis from the FDA is going to speak to us

now regarding an overview of the FDA initiatives.

DR. WEISS: Good morning. I also want to extend my welcome and appreciation to all of our additional guests who have agreed to come and share their knowledge with us.

My job is to just go over some of the initiatives the FDA has taken over the years with regard to pediatric drug development. I know for the existing standing members of this pediatric subcommittee, you've heard these types of presentations over the past few years, but hopefully this will be just a brief summary and will provide some information to our guests, who may not be as familiar with all these initiatives, which will hopefully help in addressing the questions that we have for you later on.

This is just a chronology of the various initiatives the FDA has undertaken over the years, and I'm going to go over each one of these in just a very brief type of discussion.

I might add, though, that this actually started even before FDA's involvement with the American Academy of Pediatrics, who had a significant role in, I think, shaping these initiatives. Before the mid- to late 1970s or so, the attitude for a number of different types of populations, including children, including women of

childbearing potential, other types of "vulnerable" populations, was that they should not be enrolled in studies because of the concern about the risks of investigational products in these populations. There started to be a change in thinking over the years, somewhere in the 1970s, that the problem is not not putting them in trials. The problem was not putting them in trials and not understanding enough about the treatment and the response to treatment so that when products were ultimately marketed, they started to be used in certain populations without really good data to understand how to use them. That was felt to be really more of an ethical issue. Again, this started I think in 1977 with the statement from the American Academy of Pediatrics to that effect.

In 1979 the agency published a regulation that established for the first time a pediatric use subsection of the labeling. The idea of this regulation was to encourage information that would regularly contain data regarding prescription drugs in pediatric populations. The regulation specifically said that the basis for including pediatric data would include substantial evidence from adequate and well-controlled studies in the pediatric population unless that requirement was waived. The substantial evidence from adequate and well-controlled studies is our standard efficacy requirement.

Now, the problem with this 1979 regulation was that there was a waiver, and that was intended to be able to be used when other data, other than adequate and well-controlled investigations, would suffice. However, the basis for requesting or granting such waivers was unclear I think, both to the outside as well as to people within the agency, and the bottom line was that most prescription drugs continued to lack information on pediatric use. In fact, the standard default, which every pediatrician was very familiar with if you looked at labeling, was safety and efficacy below the age of 12 or 16 or whatever have not been established, despite the fact that most pediatricians developed some type of expertise and comfort level with using medications despite the lack of information in labels. Obviously, the 1979 regulations really didn't have the intended effect.

In 1992 the agency proposed new regulations, or revised regulations. These were finalized in December of 1994, and we refer to this as the 1994 rule. The citations for all of these things that I'm going to be speaking about are the last two slides in your handout. The intent of the 1994 rule was to allow a broader basis for inclusion, or to clarify a broader basis for inclusion of pediatric data in the label. It specifically said that evidence to support pediatric claims can include effectiveness data in adults

and additional data such as perhaps some PK or safety data in pediatric patients, when the agency concludes that the course of the disease and the drug's effects are sufficiently similar to permit extrapolation.

That was very much a landmark kind of regulation, and it really clarified that recognizing that certain diseases were very similar and some of the difficulties of actually doing large randomized trials in pediatric populations, this would be a basis for actually including information about pediatric use in the label.

The 1994 rule called specifically for our sponsors or manufacturers of marketed drugs and biologics to review their existing data because at that time clearly there was a lot of what we call off-label use of these approved products for pediatric patients. And it called for our manufacturers to review their existing data, with the idea that perhaps there would already be a large amount of experience already out there in the community about the pediatric use of these products, and called for these manufacturers then to survey their data, to put it all together, and to submit it to the agency so that we can use that information to update labeling.

It specifically said that there would be no need to submit pediatric data if there was a belief that the disease or drug effects were not similar and if

pediatric use was not otherwise adequately supported. That was somewhat vague. It specifically did not actually require the conduct of new pediatric studies for new products, or already marketed products.

So, what was the impact of the 1994 rule? The problem was that it really didn't result in more pediatric labeling, and there were some surveys that were done, as we started to format the new rule, that came out regarding the impact of the 1994 rule. There were some pediatric data that were submitted on a fraction of the approved drugs and biologicals, but not that many of them resulted in actual useful information on the labeling for pediatric use. Of the new products that were coming to market where there could be a potential use in pediatric patients, only about one-third of those products actually provided data on pediatric use. So, this rule took some steps but really didn't quite go far enough.

So, in 1997 the agency proposed again new regulations. These were finalized in December of 1998. We refer to this now as the 1998 rule. This basically required for the first time -- it was a requirement -- that new drugs and biologicals that were being studied in adult patients would then be studied also in pediatric patients for the indication being studied in adults, unless that requirement was waived. The waiver would be if it was not

likely to be used in substantial numbers of pediatric patients or did not represent a meaningful advance in pediatric patients.

The rule went on to discuss some aspects of timing in pediatric studies. If studies were going to be done, when should they be done? Should they be done concurrently with the adult data? Should they lag behind? And if so, should it be during phase III of the adult studies. Should it be after post-marketing?

And that's not really a very easy question to answer. For many indications, the pediatric studies will just by necessity and practicality lag behind the adult studies. Oftentimes there is at least some phase I data generated in adults before pediatric patients are exposed to certain types of products.

But many other factors will influence the timing of the pediatric studies. The seriousness of the disease, the safety and activity profile that's been determined from adult studies, availability of the therapies, ability to develop a pediatric formulation are just some of the issues that will impact upon the timing of the pediatric studies.

What kinds of studies would be required in pediatric patients? Well, the rule did not mandate any particular type of study, and it specifically retained the

language of the 1994 rule, that being, where appropriate, pediatric use can be based on extrapolation of adult efficacy data plus other types of data.

The impact of the 1998 rule. We don't have really hard numbers right now because this is just coming into play as we're reviewing all of our drug development programs with our manufacturers and reviewing licensing applications. There's clearly a greater emphasis on the need for and the timing of pediatric studies, and pediatric drug development considerations are included in the overall drug development schemes for every new product, every new indication, every new formulation, whenever that's coming before the agency. So, for every product for which there is a potential use for pediatrics, there are discussions with the manufacturers regarding when the studies are going to be done and what kinds of studies should be done.

So, that is the evolution of the regulations regarding pediatric use information for labeling.

There are a couple of other very important provisions, some of them very recent, that I just want to mention briefly.

The first, and I know the existing committee members are very familiar with FDAMA, which is the exclusivity provisions in the FDA Modernization Act. FDAMA exclusivity is available to certain drugs that are approved

under section 505 of the FD&C Act. It specifically -- and it's somewhat important for some of the discussions that we have -- excludes biologics, which are approved under a different authority, and it excludes certain classes of antibiotics known as the old antibiotics.

The way exclusivity works is the manufacturer voluntarily conducts pediatric studies that are responsive to an FDA's written request. The written request would include detailed information about the kinds of studies to do, the numbers of studies to do, the types of patients to enroll, the age range of the patients, et cetera. If the manufacturer conducts studies that meet the terms of the written requests, they would be eligible to receive six months of additional marketing exclusivity or patent protection attached to whatever existing exclusivity they already have.

That's a slide that just shows the comparisons between FDAMA and the rule. Under FDAMA, they're voluntary; under the rule, it's required. Under FDAMA, the exclusivity covers the entire moiety; in the rule, the studies are only on the drug product and the indication that's being sought. FDAMA has an incentive; the rule is not an incentive in terms of a financial incentive. And FDAMA excludes old antibiotics and biologics, and under the rule, the only thing that's exempted are orphan drugs.

Impact of FDAMA. These numbers are constantly being updated in the Center for Drugs. But as of April 1, 2001, the FDA has issued 188 written requests, which cover 411 studies because each written request, of course, may include more than one study. The agency has given 28 grants of exclusivity, and 18 products have come along now with new labeling for pediatric use. The manufacturer will be able to receive exclusivity for conducting the studies, even if the studies do not result in changes to labeling, but that's part of the agreements under FDAMA.

ICH E-11 is a guidance document that was developed under the auspices of the International Conference on Harmonization, ICH. ICH is a process whereby regulatory authorities and representatives from industry from the U.S., Europe, and Japan get together to come to agreements, harmonize, on the technical requirements for drug development. ICH covers various types of manufacturing aspects, preclinical requirements, as well as clinical types of data that would be necessary for certain types of settings.

ICH E-11 was the pediatric guidance document. It was a document that has now been finalized. It's available on Web. Towards the end, I have the Web address. But it has a number of issues with respect to guidance on pediatric studies. It talks about considerations in

determining the need for a program, issues to consider in pediatric formulations, in terms of timing of studies, types of studies that might be done.

Steve Spielberg, who is here at the table, was a major leader in the development of the ICH document. There are a few people as well, like Dianne Murphy, Rosemary Roberts, who couldn't be here, and I who represented the FDA, and this was a very interesting and informative process.

The Subpart D regulations. Dianne Murphy just briefly mentioned this. I think there's going to be more of an update on this, but this is our newest initiative and it was just actually available this past week, so it's extremely new.

Subpart D is our abbreviation for this regulation, but it has to do with the fact that in October of 2000 then-President Clinton signed into law the Children's Health Act. Among the things that were in that act was a directive to the Secretary of HHS to require all research involving children that was conducted, supported or regulated -- and I added that emphasis on "regulated" -- by HHS to be in compliance with Subpart D of the common rule within six months of enactment. And that meant that it had to be in place by April 17th, which is just last Tuesday.

This committee I'm sure is very familiar because some of these discussions occurred with issues regarding placebo controlled trials, but IRBs are extremely familiar with provisions for children involved in clinical research over the years. They've been following Subpart D of the common rule for quite some time now, and that has to do with issues such as level of risk and whether or not the research involves minimal risk or more than minimal risk, and the chances of direct benefit, issues that the IRB needs to consider when determining whether or not that type of research will be accrued at the institution.

That rule has been in place for HHS-conducted or supported research, but it has not actually been specifically stated for FDA-regulated research. So, the impact of this Children's Health Act and this rule was now the FDA is in compliance with these aspects of protection of human subjects for FDA-regulated research as well.

I think that's my last slide for here. The next two slides are just the different citations for the documents that I mentioned, so you can have those and refer to them if you're interested in looking at any of the websites for the documents.

Thank you very much.

DR. CHESNEY: Thank you, Dr. Weiss. If the other committee members have as many questions as I do

about the presentations, we won't finish in 10 minutes, because I'm going to take 20. I would like to propose that we take a break first, and we're allowed 15 minutes for the break. So, if we could be back here at 10:30, is that acceptable to everybody?

Thank you.

(Recess.)

DR. CHESNEY: Before we start the questions, I wanted to introduce everybody to Dr. Bill Balistreri, who is sitting over here next to the famous Dr. Spielberg. Dr. Balistreri is head of Pediatric Gastroenterology, Hepatology and Nutrition at the University of Cincinnati, and recently spoke at our own grand rounds on this issue. So, we look forward to his input during the questions and discussion.

We are scheduled now to have the open public hearing. Nobody has signed up for it. Is there anybody who hasn't signed up who would like to speak at this time?

(No response.)

DR. CHESNEY: I don't see anyone. So, we will go ahead and ask members of the committee and the people who actually spoke to us, if you have questions also, to please feel free to address them to our morning speakers. Yes, Dr. Nelson.

DR. NELSON: To some extent my questions

started being answered as I talked with people over the break, but let me ask it anyway to reinforce it. My question relates to how one is excluding patients with hepatitis C who would have the potential for a spontaneous recovery given, I gather, the anywhere from 25 to 46 percent chance after an acute infection to sort of have a virological clearing and loss of antibody, when one is designing an intervention study. It came up in listening to Dr. Rehermann's remarks and also, since I don't recall the inclusion and exclusion criteria for the Rebetron study, how is one being sure that you're not intervening in a situation where they would get better anyway?

DR. CHESNEY: Did you want to address that to anybody in particular?

DR. NELSON: It came up in thinking about the response on the initial question. If the cellular response predicts who not only recovers and who responds, how can you be sure you're not giving a drug and then finding that you're measuring both just those that are going to recover anyway, and it came up in thinking about the Rebetron study how one excludes children, for example, who might have a spontaneous recovery. Does that make sense?

DR. REHERMANN: Well, I think the data I showed on the interferon/ribavirin study was the treatment of chronically infected patients, and those patients who

responded to treatment would have not recovered without treatment. So, the T cell response was somehow induced by the antiviral treatment or enhanced by the antiviral treatment, as we would interpret it. But without the treatment itself, the people would not have recovered.

DR. NELSON: Just given the 7 percent in one of the other talks of recovery, at what time do you decide it goes from acute to chronic?

DR. SEEFF: Well, traditionally we've said that if you could identify acute hepatitis, if they persist in it, being abnormal for 6 months, by definition we call that chronic hepatitis.

But I think you're asking a question for which there is, at this moment, no answer. I think once you develop chronic hepatitis C with HCV RNA, the likelihood of losing it is remote. I don't know when it occurs. We don't know when the 7 percent that you referred to occurred. We have the original samples from these patients. We had follow-up samples some years later, and we didn't have sequential samples to know when it occurred. My own guess is that it is going to be a spontaneous loss that's going to probably take place during the first year or fairly early on. I don't think it's going to be late, but I don't know that we have the data to support that unless Barbara has additional sequential data. I think

that most of us, once we see a patient who comes in with chronic hepatitis C, the likelihood of their losing virus is pretty remote.

DR. CHESNEY: Yes.

DR. SCHWARZ: I think implicit in your question -- and it's an excellent one -- is at what age should pediatric trials begin. So, from the excellent presentation that Maureen Jonas gave, I think it is clear that infants who are PCR positive -- at least if they're PCR positive in the newborn period, according to the study of Conte, et al. -- may clear the virus within a few months.

So, for two reasons, spontaneous viral clearance being one of them and adverse effects of alpha interferon on the neonatal brain, spastic diplegia, when we've talked about designing trials, we began at age 2 just to avoid serious toxicity and also to allow for spontaneous viral clearing.

DR. CHESNEY: Yes.

DR. LINDSAY: Unfortunately, I think that we confuse people because we use the term chronic hepatitis to mean all three, chronic elevation of aminotransferases, chronic detectability of HCV RNA in the serum, and histologic features on liver biopsy.

So, in the adult studies, what we've done in

the screening period of patients for the Rebetron trial and so forth was to test for HCV RNA in the 3 months prior to initiation of treatment and do a liver biopsy confirming the presence of histologic chronic hepatitis. When we look at the patients who then enter the study and the baseline samples, I don't know of a case where HCV RNA has become negative, undetectable, in the modern HCV RNA testing era. I don't know if that clarifies it.

DR. CHESNEY: Dr. Jonas.

DR. JONAS: I'm interpreting your question a little bit differently. I think you're asking about a placebo effect or the natural history, how many people are just going to lose viremia and we're going to attribute it to a therapeutic effect.

I want to point out I think it's a time difference that's very important. In other words, the studies that show this loss of viremia are over decades, and I don't know at what point it happens. It's true. But the therapy is 1 year with a 6-month follow-up, and at least in adult studies where there have been control patients, there's a trivial, if any, rate of control patients losing viremia in a 1-year period of time.

So, your argument could be how are you going to pick out the kids that would have lost viremia in the next decade, not necessarily your treatment versus control is

what I think. I don't really know how to select for those patients other than maybe we would accelerate that natural history and is there any benefit to that with therapy. That would be another way to look at it.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I'd like to try that question in a slightly different direction. Is there a consensus among the pediatric community about when you diagnosis chronic viremia with this virus? Assuming most infections in the year 2001 will be vertical so you have an idea of when they occurred, when do you diagnosis them as chronic viremic?

DR. JONAS: Again, you're separating out the perinatals. I think there's not yet a consensus, but I think there are some studies coming out now that are going to suggest to us a consensus. There are several studies now that show not just at birth is not the best time, but there are children in the first 2 to 3 years who will lose this virus, or an appreciable percent. I can't give you the exact number yet, but 20-30 percent, something like that. So, it may be that we do need to establish a time when we will allow the natural history to take its course before we jump in.

Some of these younger children -- again, it's anecdotes -- have had liver biopsies that show significant chronic hepatitis, they have transaminases of several

hundred. You don't know if they're going to just sort of burn out and lose the virus, their immune systems will mature and kick in, or what. It's just hard when you're looking at an individual child to know which course it's going to take.

But I think there will be a time when this is going to stay, age 3 or something like that, age 2.

DR. CHESNEY: Dr. Edwards.

DR. EDWARDS: The genotyping information is really quite fascinating. Is there data to suggest that the progression of the type 1a versus 2 or 3 is any different if it's untreated?

I guess one of the questions that I was wondering, since we're so interested in a risk-benefit ratio in the use of these drugs, would it make sense to study the type 2 or 3 infections in children preferentially that might have a better benefit of these antivirals than a type 1a or 1b, or is that naive?

DR. SEEFF: There are conflicting data about the value of genotyping in defining outcome. Clearly there is a distinct difference with respect to treatment. There were some studies that suggested that people with genotype 1 were more likely to progress and others that did not indicate the case. My sense at the moment is that genotype is not a terribly good indicator of what's going to happen

to the person, other than the effect of treatment.

With respect to genotype 2 or 3, the response rate has been so dramatic, that I do think that these need to be separated out. I really do.

Let me just also come back to this issue of chronic hepatitis. Karen is absolutely right. When you define chronic hepatitis, you define it as enzyme elevation, as virus, and as histology, but all of that is needed for the treatment purpose. The question is how do you define chronic hepatitis C.

I think there's a difference between the adult and children. In adults, I think that at this point in time, so rare is it to see HCV RNA as an acute disease, that if I see somebody who has HCV RNA, in my view that patient has chronic hepatitis C. We used to feel that we needed 6 months. Then we said 3 months. But it's so rare that you see the incidence of the patient with acute hepatitis C who has HCV RNA and then loses it, that the identification of HCV RNA defines, in my view, chronic hepatitis.

Now, that does not necessarily mean chronic hepatitis that is serious or potentially serious or should be treated because there still is a controversy about who should be treated. There are some people who believe that everybody should be treated. There are others who still

believe that until treatment is more effective and perhaps less harmful, that we would like to select people a little bit more carefully.

So, I think that there's a difference between defining chronic hepatitis in the adult population from the pediatric population, particularly since I think they all have antibody and then some of them have HCV RNA, and it changes at different times.

DR. CHESNEY: Could I follow up on Dr. Edwards' question? What do we know about genotyping in infants, and specifically, are there any differences in transmission rates, a mother who is one type as opposed to another? Do we know very much about the genotyping in infants and transmission?

DR. JONAS: I don't know any data actually from this country. There are European studies, Italy I think primarily, where they look at that.

It's difficult to separate out genotype and viremia. Genotype 1 individuals I think, by and large, have higher virus levels when you look at them, although it's not 100 percent, but it's difficult to sort out, is it the viremia level or is it the actual genotype.

But I think that there's not a huge difference in likelihood of transmission just by the genotype alone. It's hard to take it out as an isolated factor, but I think

that it's never been shown to be this is a factor that increases the likelihood of transmission.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: Yes. I have a question about some of the treatment data and that is I noticed that no one talked about cure. We talked about response rates. I was very impressed with the fact that different therapies and evolutions in therapies produced a greater response rate with I guess the 48-week treatment course. But there was this end response and then there was the sustained response, and there was attrition in that response. I was wondering if there were any longer-term data that looked at that curve to get some extrapolation as to whether or not one would expect that sustained response at 24 weeks to actually be permanent clearance of viremia, or whatever marker one was using.

DR. SEEFF: The data are very compelling that it does represent cure. There have been at least two long-term studies, one out of the NIH and one out of the French group who followed up as much as 10 years later. Those people who are nonviremic 24 weeks after treatment remain nonviremic. Their liver biopsies show improvement and certainly regression of inflammation. So, I think there is the potential for cure.

DR. CHESNEY: Yes.

DR. LINDSAY: I think the other aspects of clinical benefit from a sustained virologic response are also things that we should talk about. In Japan, there has been a national registry of patients treated with interferon with hepatitis C, and several of the studies appeared to demonstrate a reduction in the subsequent rate of hepatocellular carcinoma over a relatively short period of follow-up that varies differentially among individuals who had a sustained virologic response, those who normalized ALT, and those who did not.

The other very important aspect is the aspect of effect on quality of life. I think we have a lot of difficulty in the instruments that we use to measure how patients feel and function with this disease during treatment and following treatment because they really don't necessarily capture how patients feel and function very well.

But we've used a pretty standard instrument throughout the treatment trials, the SF-36, and when that instrument is applied to patients before, during, and after treatment, those who have a sustained virologic response clearly have improvement using that instrument scale. In retrospect what they say is they didn't realize how poorly they felt before they took treatment.

DR. FINK: This is a question about infants.

Before we dismiss them over concerns about toxicity, we know that infants tend to respond to hep B better. They have a higher spontaneous cure rate. Shouldn't we also consider the option that infants might be much more responsive to interferon alone or to PEG-interferon at very low doses once a month, once every 3 months, because their immune system tends to be much more responsive to these viral antigens? And how do we design a study to appropriately look at this in infants rather than throwing them out entirely, because we may be missing the optimal time to treat?

DR. JONAS: With hep B, actually we think of them as more immune-tolerant to hepatitis B, and the younger you become infected with hepatitis B, you're vastly more likely to remain chronically infected. Their immune systems are not very responsive in the first months of life, the neonatal period, in the first year or two. The neonatal immune system is not my area of expertise, and I don't claim it to be.

But I think that until we demonstrate that, first of all, they don't lose the virus spontaneously in that period, and secondly, there are profound effects, not just neurologically, but this weight gain that I've talked to you about and anorexia and asthenia. I'm just not sure that anyone who has used this medicine would feel

comfortable using it for this disease that we don't understand so well in that first year or two. I'll ask my colleagues about that.

DR. BALISTRERI: Well, I would agree. I'm a little confused about the data you cite regarding hepatitis B, the immune tolerance effect. But the point that you raise is if you have a short duration of illness, perhaps you have a better chance of clearance with either monotherapy or some low-dose therapy.

I think until we have compelling data that we are doing harm by delaying the administration of an effective drug to these children, and I think entering the children, given the side effects, a very high incidence of spastic diplegia and some of the less dramatic side effects, I think we should exclude that population.

DR. CHESNEY: Yes, Dr. Ramsey.

DR. SCHWARZ: I like your question because I think we should always assume nothing. But perhaps a better way to think about the infants is that if we can agree on initiation of trials at age 2 and do carefully designed RCTs in 2 and up and try to look not only at standard endpoints but also predictors of response to therapy, lymphocyte, cytokines and so on, I think that by the time those trials are finished two, three, four years down the road, we'll know a lot more both about viral

clearance in ages 0 to 2, toxicity of interferon in young children, and predictors of response to therapy. I think at that point, that might be the time to ask again if we should be lowering the age.

DR. CHESNEY: Forgive me, Dr. Schwarz. I put your name and Dr. Lindsay's together and came up with Ramsey. Don't ask.

(Laughter.)

DR. CHESNEY: Dr. Nelson.

DR. NELSON: To continue the line of questioning here on outcomes, these are fairly toxic drugs, particularly if you're looking at ribavirin. And the notion of giving it to a 2-year-old. I guess my question is, in the adult data, is it possible that you see a reversal of fibrosis as opposed to a halting? And if you see a reversal of fibrosis, can you basically follow children closely, including even serial biopsies over a certain period of time, and be able to pick a moment at which you're intervening knowing you can reverse the fibrosis so that you're not intervening too early in those who will not have a progression? I'm trying to somehow balance the too early/too late problem.

DR. SEEFF: Your tax dollars are helping to pay me to answer that question actually. We do believe that one aspect of long-term treatment is that it may halt

progression or even reverse fibrosis, possibly even reverse early cirrhosis. The reason why I say that is because we're doing a big study at the NIH, the so-called HALT C trial, which is aimed at this very thing. But there are numbers of studies that have been done both in this country and in Japan in which the data seem compelling, which is the reason why we're doing the study in the first place, that indicate that long-term treatment may impede progression and possibly even reverse fibrosis. So, I do think that's the case. The question is how long and what might the toxicity be after long-term treatment, which is one of the reasons why we're doing the study.

DR. LINDSAY: Just to clarify what Leonard had said before, these three studies that have followed patients with sustained virologic response out 12 to 15 years beyond treatment have demonstrated reversal in hepatic fibrosis. So, in association with an SVR, there's clearly reversal of hepatic fibrosis.

DR. CHESNEY: Dr. Luban.

DR. LUBAN: I was wondering if many of you, not only one of you, could comment on the safety of serial liver biopsies, which is going to appear to be necessary in this population for us to really have an assessment of effect?

DR. SCHWARZ: I think we have acquired a lot of

knowledge about liver biopsy safety in children partly because of the liver transplant era. I think the number one morbidity is bleeding, and the prevalence of bleeding is, I guess the highest numbers are, 1 in 1,000 in high risk patients to 1 in 10,000. Would you agree with that, Bill?

DR. BALISTRERI: Yes.

DR. SCHWARZ: So, in general, we think of liver biopsy as quite a safe and accepted technique in children, and I think we have learned from the adult experience that liver biopsy is really the only way to assess what the virus is doing to the liver.

DR. CHESNEY: Could I follow up on Dr. Luban's question? How does the ELISPOT that Dr. Rehermann talked about correlate with degree of fibrosis in the liver? Do you see progression in the amount of virus in the liver, or is the virus actually eliminated? This is probably not immediately relative to what we're talking about today, but what is the role of the immune system? I assume enhancers or detractors of immune function have been tried and don't work.

DR. REHERMANN: Well, the ELISPOT is a measurement of the strength of the T cell response to the virus in the blood. We cannot correlate with fibrosis at the moment. It's also questionable how much peripheral

blood T cell response correlates with the one from the liver, but it's impossible to get enough lymphocytes from liver biopsies to study that directly. So, right now we can associate a stronger immune response and a stronger response in the ELISPOT assay in the blood with recovery, which is probably mediated by memory T cells which function much better than other T cells in chronic infection.

DR. CHESNEY: Thank you. That's helpful.

But I'm wondering if this progression is a direct response continued viral replication or is it the general immune response of the host that's doing the damage in the liver. Do we know much about that?

DR. REHERMANN: It's believed that's it's also the host response. So, the immune response can do both. It can mediate recovery and long-term viral clearance but also mediate liver disease and pathogenesis. At this point it's not clear what the difference is and what is necessary and what is required to mediate recovery. It's also part of the HALT C study that's ongoing.

DR. SEEFF: I suspect that the immune response is the predominant factor. We know lots of people have been infected for many years and don't have cirrhosis. This comes down to the issue of whether there's linear progression again. Do you just get damage and slowly this thing evolves over time regardless?

I personally have taken care of many patients. I started working at the VA before some people here were born, and I've been seeing the same patients now for over 30 years, some of whom I've got traced back to the time that they were originally infected. And not all of them have cirrhosis by any means. So, I think that it's not just the presence of the virus.

Now, I don't know whether the viral load makes a difference, unless Barbara has more on that or Karen or anyone here. But I think it's the immune response that is the major factor.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: We had the opportunity to look at the liver histology in children with hemophilia and hepatitis C in comparison to transfused groups. It was really quite interesting because these hemophiliac children had very high viral loads and very little liver injury. They also did not respond very well to alpha interferon. It's fascinating because the pregnant female who is relatively immunotolerant who has hepatitis C has a very similar pattern with progression of pregnancy as the hemophiliac children: rising viral load, declining ALT.

DR. CHESNEY: Thank you.

Dr. Balistreri.

DR. BALISTRERI: If I could just comment on the

question of the relationship of virus to liver injury. I don't think we're ready for a simple answer because of the complexity of the individual genetic variability, whether it be antifibrogenesis factors, their own native interleukin response, their own genetic tendencies. So, I think that may be why we have such a disparity in looking at viral load and trying to correlate it with injury.

DR. SEEFF: I do have the anecdote, of course, of the one patient whom we followed for 50 years who has the highest viral load I have ever seen. I have not biopsied him, but it's 50 years later. His albumin is 4.7. His platelets are 250,000. There is no evidence to me that this man has clinical evidence whatsoever, and he's the one who has nothing on physical exam. That's an anecdote, but it does make the point that it's not necessarily the amount of virus that is responsible.

DR. CHESNEY: Dr. Jonas just to follow up, and then Dr. Gorman.

DR. JONAS: I just want to make a quick comment to go back to your question, are serial liver biopsies necessary. I want to reexamine that for a few moments as well because, again, it depends on what the gold standard we're going to choose as a response to therapy.

We all do liver biopsies, I think, before any therapy is considered. We demonstrate there is liver

disease and we like to characterize it. Is it very advanced? Is it very mild? But whether it will be necessary in all of these studies to do serial liver biopsy as an outcome variable I think should be examined and not just taken for granted. I know that in adult studies it is pretty much a gold standard and everybody gets a liver biopsy and again these numerical scores are done, to be significant, a change of at least 2. But I think it may not necessarily be appropriate for the pediatric studies to do that. I don't know.

DR. NELSON: Joan, could I just respond quickly?

DR. CHESNEY: Yes.

DR. NELSON: My question was less the need for it within a study, but whether or not you need to follow children prospectively looking at the progression of fibrosis in order to only include those children who would have progression in the study itself and not those children who would have stable disease and therefore perhaps not even need any intervention at all. So, I was asking not the study question but the issue of inclusion and exclusion criteria to even enter into an intervention study.

DR. JONAS: Those changes, though, that you may be describing take 5 to 10 years to develop. So, you're talking about biopsying your child and saying, see you in 5

years, and then decide if we'll put you in a study. The rate is so slow.

DR. NELSON: Given the risk of the drugs potentially on growth and development, the question would be, if the rate is so slow, would it be appropriate to simply wait to intervene?

DR. CHESNEY: Let me let Dr. Schwarz respond to that and then Dr. Gorman has been very patient.

DR. SCHWARZ: There is one more risk versus benefit question that I would like to put on the table. It is certainly true that we want to design therapies to halt or reverse fibrosis. I think those of us in the room who treat children with hepatitis C and who deal with the families would say that the liver disease morbidity and mortality is a reality for these families more as a worry than an actuality. It is a major worry. Maureen alluded to it at the end of her talk. It is probably the single most important issue that we have to face with the children on a day-to-day basis. The pediatric hepatitis C epidemiology, at least in referral centers, is substantially different than it is in adults. So, we have many, many children who have survived one illness, cancer, hemophilia, thalassemia, and now they have hepatitis C. So, their parents have trouble getting baby sitters. The children are stigmatized. We need to figure out how to

quantify the emotional tragedy that these families endure. So, it's not just the hepatic morbidity that is a problem.

DR. CHESNEY: Thank you. That was perceptive.

Dr. Gorman.

DR. GORMAN: Despite or maybe perhaps because of the wealth of information this morning, I'm still confused as to what the post-viremic state looks like. After you treat these individuals for 24 weeks or 48 or 104 weeks and their viremia has been resolved, I've heard that the quality of life improves. I heard in Japan the incidence of hepatocellular carcinoma goes down. What happens to the endpoint that we seem to be most interested in, which is liver disease? Do we have definitive data in adults or is it still in the collection phase?

DR. LINDSAY: The three long-term studies that have ranged from 12 to 15 years of follow-up in patients with sustained virologic response at the end of treatment have demonstrated that the vast majority remain virologic responders, well over 95 percent, and in serial liver biopsies that have been done in those individuals, histology improves, including regression of fibrosis.

DR. GORMAN: Does their overall death rate from hepatic disease change?

DR. LINDSAY: I don't think that's really something that's been adequately measured. These are still

relatively small samples, as you can imagine, because 12 to 14 years ago, the numbers of patients who were receiving alpha interferon for what was then non-A/non-B/C hepatitis was pretty small.

DR. SEEFF: I've had the opportunity to review a paper from Japan in which the claim is that mortality has gone down. I insist, however, that there's a difference between the disease in Japan and this country. A lot of what has driven us has come from the Japanese and much of the data has been the emphasis on liver cancer, and I am staggered at the difference in the outcome. That doesn't detract from the fact that cancer occurs and may well increase to the level that people have suggested. I'm not sure it's going to do that, but that's the basis on which we're functioning at the moment. But at least in this one paper from Japan, they did suggest that the mortality decreased as a result of treatment.

DR. CHESNEY: Dr. Fink.

DR. FINK: I would like to take, I guess, a little side trip and disagree with Dr. Schwarz in terms of the importance of this because I would maintain that acquired hepatitis C in children is a transient problem. We've lived through the worst of it and it will disappear on its own without any clinical trials. What we really should be focusing on is the vertically transmitted

hepatitis C.

From that standpoint, then we get to the practical issues of how do you do informed consent, how do you structure therapy, how do you do follow-up in a population where, if my child had hepatitis C positivity, I don't know if I would enroll them in a clinical trial today.

But if you take a drug-abusing population, how do you even begin to approach the problems of designing a practical trial in that group because the transfusion-related, the chemotherapy-related hepatitis C is a passing phase. And we're really over the hump of that and it's going to cure itself without clinical trials.

DR. SANTANA: I don't know about that. I was talking to her earlier, and I don't have the numbers in front of me. But it's been said many times that there's probably about a million survivors of child cancer right now, and if the numbers from the Italian study and the St. Jude study, which are between 1 to 5 percent prevalence rates in those survivors -- now, granted, many of those kids were in the epidemic of the 1980s and 1990s, but that means that there's probably anywhere between 5,000 to 50,000 kids out there, childhood cancer survivors, that potentially may be infected and we haven't even screened them yet.

So, obviously, I'm throwing these numbers out without being a mathematician or doing the statistics, but I think still there may be populations, in which this is a problem, where the studies could be done. How relevant those studies would be to other populations is a separate discussion.

DR. FINK: But is it worth studying those populations with high risk drugs if the problem is transient? Because the current risk of transfusion-associated hepatitis C --

DR. SANTANA: For the individual patient, it's not transient. For the population at large, it may be. It may not be transient if that patient is at risk of developing fibrosis or other medical problems.

DR. FINK: Right. But for the population, the risk is very transient in a sense, and the risk of transfusion-associated hepatitis C now would then say if you have a million cancer survivors, you're going to have at most a few cases.

DR. SANTANA: I don't know what the numbers are. I have to look at my expert statistician to predict that. Naomi?

DR. LUBAN: Well, I guess I have some numbers. And I would disagree with you, Bob, and I would agree with Victor.

We've done a targeted look-back on a wide population of children transfused in the decade 1982 to 1992 and have identified a seroprevalence rate of 1.9 percent. That's a mixed group of children, premies, post-cardiac surgery, a few oncology patients, interestingly enough, and I think that's perhaps because we lost some to their primary disease.

We're now following these kids as best we can, without money from Leonard, I might add --

(Laughter.)

DR. LUBAN: -- in as much of a long-term follow-up study as we possibly can.

I would definitely agree with Kathleen on this point. The families are very, very concerned about the outcome of the children, most of whom, except for one sole child who has been co-infected with HBV, have mild disease on biopsy, but who live with a tremendous worry.

What we're now finding, which the panel might find humorous, is during our parent group meetings, which we hold regularly, the adolescent boys who are getting ready to go off the college now want to be treated so they can drink.

(Laughter.)

DR. LUBAN: An interesting concept. But they feel that if they can now clear their virus before they go

off to high-risk behavior areas, that they might well benefit. Now many of them are approaching 18 when, of course, we may lose them as pediatricians. They may go off to adult hepatologists who will freely treat them without the benefit of any kind of a controlled trial. So, I bring that group up as a unique group.

What I do agree with Bob about is the need, when we're designing clinical trials, to separate clearly the transfusion-related kids from the perinatal kids because, most definitely, they have a very, very different substratum upon which the treatment may be or not be as effective. The thalassemic kids, as Maureen has pointed out in many publications, very heavily iron overloaded, clearly having fibrosis on the basis of that, on top of which is their hepatitis C; the oncology kids also having some degree of hepatic dysfunction based on chemotherapeutic medications. And they're very different, I would imagine, from the perinatals.

DR. CHESNEY: Dr. Edwards.

DR. EDWARDS: I had a question about the spastic diplegia. I'm not familiar with that literature, and I wondered if there's any information in terms of pathogenesis, whether there's any information in terms of pathology or biopsies or any idea that this damage might extend outside of those first two years of life.

DR. BALISTRERI: Well, the data is outside of this circumstance, of course. It's in giving interferon for other conditions, other forms of interferon and perhaps larger doses. But there clearly was an age-related cutoff. In the Boston study, those patients who were over 2 did not develop spastic diplegia. Now, obviously, the vast majority of children who got it was for things like vascular anomalies and so on.

The pathogenesis was ascribed, at least in the Journal of Pediatrics article, to -- the antiproliferative effect and the effect on the growing central nervous system and neuronal maturation. Whether that's true or not I don't know.

DR. CHESNEY: Dr. Nelson, then Dr. Szefler.

DR. NELSON: This may take us in a slightly different direction. The question I want to ask is about the suitability of animal models, but let me make a couple of assumptions on the way of getting there, which may be debatable.

As I recall, it may have been Dr. Seeff who made the comment that the disease is the same. There may be some differences perhaps in the young age groups. But the question is why we would necessarily assume that we need an efficacy study -- let's say anyone from 6 years of age and up perhaps, just to take it out of the neonatal age

range -- and that all we would really need is appropriate dosing and safety.

On the safety point, one of the difficulties is the issues would likely be long-term safety, which then leads me to the question of whether there is an appropriate animal model of a developing animal, whatever, that would help us to extrapolate the impact of these therapies in a way that would be doable on a more short-term basis to provide that kind of information. Does anything exist as opposed to the kinds of long-term studies that would have to be done to look at real issues of growth and development safety, which is always difficult?

DR. SEEFF: Actually I'm flattered that you mistook me for Dr. Jonas because it was Dr. Jonas who said that the disease is the same I guess based on the histology. Was that right?

DR. JONAS: Yes.

DR. SEEFF: So, I don't know that it's the same. I think it's not the same. I think it's histologic manifestations may be the same. I think the natural history at this moment is such that it looks as though children have a much more either protracted course or a more benign course, and I don't know which it is. So, from that point of view, I'm not sure it's the same, and maybe Dr. Jonas or Dr. Schwarz or Dr. Balistreri can comment on

it.

Animal models have been a big problem. Other than the chimp studies, there really is no small animal model that's available to study this, no tissue culture system. I guess Charlie Rice is developing something, an early tissue culture. But we've struggled with this because there really hasn't been a small animal model that has been available for studying this thing.

Do you have any further information on that?

DR. REHERMANN: No.

DR. JONAS: I want to say that I think that it's same disease pathogenetically, I might have said, rather than by natural history. The same kinds of lymphocytes are in the liver, the same sort of bile duct injury, suggesting that maybe the immunologic targets are the same, more pathogenetically than natural history.

So, maybe your question about efficacy, does it need to be totally recapitulated in the pediatric group -- I'm not sure. Maybe not. Once you have a liver biopsy that shows chronic hepatitis C with varying degrees of fibrosis in a 7-year-old, is it that different than a 37-year-old with respect to treating? I'm sure it does need to be totally redone all over again. The natural history may be different, so patient selection of who you're going to biopsy and then enroll may be an issue. But once you

have the same disease established under the microscope, it may not be terribly important to determine a big difference in efficacy.

I think you were alluding to an animal model for interferon and growth. Is that what you were alluding to? Not for hepatitis C but more for what this cytokine does to --

DR. NELSON: Well, that would be the purpose, but also whether it would be a chronic hepatitis C model in which you could then extrapolate. But the main issue would be the safety of the medications in a chronic setting.

DR. JONAS: And is it the interferon you're more worried about or the ribavirin? There are animal studies in ribavirin. There's a lot of preclinical stuff.

DR. NELSON: A combination of both.

DR. SANTANA: But, Skip, remember that animal models are notoriously bad for looking at toxicity of any drug. I know that's a general comment, but from the oncology side it is true, that animals can give you some idea about issues of efficacy, but they're notoriously bad at predicting toxicity in humans.

DR. CHESNEY: Dr. Rehermann I think had a response also.

DR. REHERMANN: I have a question. I think for me it really comes down to the question, what would we lose

if we wait until these children are adults or adolescents? 30 percent or 40 percent would definitely recover spontaneously within the first or second decade of life, and even those that are still viremic wouldn't have much liver disease. So, a little bit of fibrosis but probably not so much because in all studies it has been described as mild hepatitis.

Given the significant side effects and also the impact on the quality of life, this has to be considered. I don't think that it's sufficient just to say that patients are viremic and we have to clear the virus. If the virus doesn't cause much liver disease and the response rate of adults may be the same, we can as well wait until they're 18, 19 years old.

Dr. Schwarz has said what she thinks about the age of treatment. I would like to ask the other physicians to get some more general impressions on this.

DR. BALISTRERI: Well, my posture is the same, and that is why treat, unless we have compelling data that if we do not intervene in a window of opportunity -- 18 years is what you cite -- that we have programmed that child to develop hepatocellular carcinoma or end stage liver disease.

In our transplantation program, which is 19 years old, we have transplanted only one patient for

hepatitis C, and I suspect that there are other factors involved. So, just like we talked about earlier on the way a patient would respond to a drug, pharmacogenomics, there may be some fibrogenomics going on here also. So, an unusual patient may well develop cirrhosis, but the vast majority of these patients are perfectly fine coexisting with their virus.

DR. CHESNEY: Dr. Szefler has been waiting a long time.

DR. SZEFLER: I think I was going to come back to the point Dr. Balistreri just mentioned. It seems like we've got a drug that we don't want to use in everybody. Is there a population that it should be used in where it's indicated? I guess it boils down to outcomes and inclusion criteria. Is there a population that you could define? If you were setting up a study, who would you set it up for? And that's what I haven't heard. Who is at risk for the worst outcomes? Are there any indicators at all that you would list in an inclusion criteria for a patient where you could talk to the parent and say, I think it's justified for your child to be in this trial given the risks of the drug? I guess I haven't heard that.

DR. SEEFF: In the adults, it's a little easier I think. I think there are some factors that are helpful. They're helpful but they're not sufficient.

I wish we had a test for fibrosis, for fibrogenesis and fibrolysis. We've been struggling with this for a long time. If we had something like that that we could use, that would be very useful.

Let me suggest the following. As I see it, there's no doubt in my mind that the natural history of hepatitis C in children in the first 20 years is more benign than it is in adults. I feel convinced about that.

The next question that we don't have an answer to is what happens beyond 20 years? Are they going to assume the rate of progression that occurs in the adult, or is the fact that the infection took place at an earlier age likely to set up a different kind of natural history in which the disease may not progress much beyond that? If it's 1 percent at 20 years, whereas in the adult it's 15 to 20 percent, do they, in fact, when they get to the adult age bracket, then begin to go up like this? I don't think they do, but I don't know the answer to that. And I don't think anyone does. Blaine may. He's got his hand up there.

The next question is, is the ideal time to treat early on when the likelihood of response may be slightly better? I don't know that. In doing that, one has to weigh out the toxicity. If we were dealing with something that eradicated this virus, no one would be

interested in the natural history of this disease. We'd treat everybody. But we're struggling with the fact that we have a disease that has a variable outcome, and it's a disease in which the treatment is effective and getting better, but it's by no means 100 percent. And it's a problem in which the treatment has many, many complicated side effects. We've got to put these three sort of vectors together to try to see what is the best approach.

Now, there are two options. I don't know at what age you would start considering treatments if you decide to do treatments, but it sounds as if you have to perhaps delay this beyond a certain time, or in fact to say we shouldn't be treating and we should wait until they get to a later stage and we can see whether they've progressed.

The question is how do you do that, and does that mean multiple biopsies? I don't know a good way.

The enzymes are of no benefit. By the time the platelets fall, by the time the albumin is down, it's too late.

The histology has been the best, and even that is not ideal by any means. There is sampling error. There are difficulties in interpreting it. It's a real problem trying to assess progression of this thing.

If I could spend the rest of my life trying to find a way of assessing in an individual -- because we've

talked about this in the aggregate. You take 100 people. We think is what happens, but when you have that one person in your office and you're trying to talk to that person and say, what's the likelihood you're going to progress and should we treat you, I don't know how to do that. I really don't know how to do that.

DR. SZEFLER: Could I just follow up on that? What I'm asking is to design inclusion criteria where you could predict some risk, and if you chose an outcome like cancer or morbidity -- that's a long-term outcome -- but could you at least select those patients, in terms of inclusion criteria, who would be the most likely to gain, and then follow the other outcomes. You're obviously setting up a long-term study and fairly large numbers, but could you then follow the other outcomes, the softer outcomes, like quality of life, along the way in that process and keep that population in mind and look at remissions, look at other relevant outcomes? But at least you're maximizing your chance for preventing the most deleterious outcomes.

I think we're kind of like around that issue. I guess we've concluded that it's not a drug we could use routinely where we could give it and not worry about side effects. Finances haven't even been discussed, but that's another relevant factor. But could you narrow that

population to somebody who you would definitely be more concerned about than the average patient walking in with a positive test and diagnosis?

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: I think that one could think about two broad categories, and these are more biological categories than they are predictive categories. And that is separation of transfusion-acquired hepatitis C which, although we hope it is disappearing, there are many thousands I think of children who are infected right now who I personally think need to be treated and studied appropriately. So, transfusion-acquired hepatitis C in the absence of co-infection, in the absence of HIV or hepatitis B.

Then the other category that will be of ongoing concern and is socially and perhaps biologically and immunologically different is the maternal/fetal category.

I will share our experience in Baltimore, and we're just at the beginning of the experience really. We are about to do a study of the epidemiology of hepatitis C in children of injection drug users. I was appalled to learn that in our little city, there are about 2,500 homeless children between the ages of 2 and 18. In our little state, there are 10,000. These numbers are, I guess, hard to come by, but there are somewhere between 1

million and 2 million homeless subjects in the United States, of which probably at least half are children. Trying to understand how to do the epidemiology, let alone the treatment in a rather chaotic population is going to be a major challenge, but I think it should be undertaken because the one published survey of hepatitis C prevalence in this very high risk pediatric group was 5 percent in an Oregon adolescent drug shelter.

DR. CHESNEY: Dr. Hollinger, I think you had your hand up a few minutes ago.

DR. HOLLINGER: No.

DR. CHESNEY: Dr. Danford, you have had yours up for a while.

DR. DANFORD: I was intrigued by Dr. Schwarz's remarks earlier about the level of concern among patients and family about risks of long-term problems from the hepatitis C. That was put forward without the other side of the coin, which would be the long-term concerns that might arise from the treatment of hepatitis C, especially since we're considering agents that potentially could be mutagenic.

I wondered if there was any knowledge about the risks of extreme long-term complications from the use of these kinds of agents in terms of late cancer or birth defects in offspring of female patients. And if there was

such knowledge, could you speculate about the magnitude of risk of those kinds of things relative to the magnitude of risk of life-threatening liver disease?

DR. JONAS: I don't have numbers for you as far as risk. In the animal studies, in the preclinical studies with ribavirin, first of all, the compound is cleared from the body and I think within a couple of weeks of use. I'm sorry I don't know the exact numbers. It's recommended that contraception be practiced for six months after finishing the end of treatment, but that's considered a very wide time interval.

The other thing I want to say is somewhat related. We talk a lot about the toxicity and side effects of these drugs. I haven't treated hundreds and hundreds of children, but in general, these medicines are very well tolerated by the children and much better so than in the adults. The kids do not miss school. They don't miss participating in their sports. Their biggest inconvenience is the blood tests they have to have to be monitored. I don't want to trivialize them, but it's not like they're on chemotherapy or they're totally disabled from these medications. So, I don't want you to get the sense that they're incapacitated by these medicines. Certainly we have concerns about long-term risk, but I think they rebound rather quickly in their weight, their energy

levels, and those kinds of things that you can measure on a fairly short-term basis.

The other thing is I think the strategy of waiting till 18 -- we know what it's like to try to get young adults, older adolescents, in for regular medical care and blood tests and this kind of therapy when they don't feel ill at all. I actually think that's a very difficult population to target specifically the 18-, 19-, 20-year-olds that are graduating from high school, that are going off to do their life. To say we're going to delay your treatment because you're under 18 until your 18 and then hit you at that point I think is not a very compelling strategy that I would propose to the families in my practice.

The quality of life issues are not trivial, and I can tell you that I get letters and e-mails from parents about this horrible, personal medical crisis in their children with this hepatitis C and how they are stigmatized. They're kept off sports teams. They are afraid to date. They're very serious and I don't want to blow them off and say, well, they're secondary and so forth because they do, a lot of times, run these children's lives more than the amount of fibrosis on their liver biopsy. So, I want to take that into consideration and weigh it against this toxicity.

DR. CHESNEY: I think you can get the adolescents as long as you can promise them they can drink.

(Laughter.)

DR. CHESNEY: Dr. Spielberg has had his hand up for a while.

DR. SPIELBERG: It sounds like we're struggling really with two things. One is the situation as it exists today.

Getting back to some of the things that Bob Fink was talking about and Dr. Luban as well, the 1982 to 1992 cohorts are 10 to 20 right now. They clearly need interventions, but by the time we're done with the study, they're going to be mostly adults. So, the remainder of that population that's actually not in the study will functionally be adults by the time we have enough data to know what to do with that cohort. That doesn't say we shouldn't do it, but that's just one of the realities.

The flip side is the perinatal issue which clearly probably is the horizon that's most distressing. The only miracle of the AIDS epidemic, in fact, was being able to stop vertical transmission. It's the only thing that in fact prevented the illness in the first place and really led to not having to use any of the other drugs during the course of these children's lives because the disease was prevented in the first place.

I got a sense that there are some behavioral, mechanical things that may help. Obviously, the drugs we now have available -- one is clearly teratogenic, so we can't use it long-term during pregnancy. But if I had to invest an awful lot, it would be trying to prevent vertical transmission right now by anything we can, mechanical, behavioral, surgical, and/or pharmacologic. We haven't gotten into the pharmacologic issues, recognizing that the drugs we now have in our hands are really pretty bad for pharmacologic agents in the last couple of days or weeks of pregnancy. But that seems to me one of the critical issues because if we can, in fact, prevent vertical transmission, that's the end of it for pediatrics.

We have to make a decision do we study now the cohort that now exists, do we try to optimize therapy and optimize these kids' lives now, or do we wait until they're adults. That's something I think all of us have to struggle with, but if we can prevent the perinatal, that's the end of pediatric hep C.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: A couple of comments, one about the perinatal, one about the drug side effects.

I think we have to be careful in our terminology to distinguish between vertical transmission and perinatal transmission. This is all very recent

knowledge, but I think there is no evidence that hepatitis C is transmitted in utero during gestation. From the data that Maureen presented, it looks as if actually the infant born to a hepatitis C infected mother may actually acquire the virus 2, 3, 4 months. We just don't know enough to know. So, I used to think that the number one priority was doing the equivalent of prevention of HIV transmission to the fetus. Now I'm not so sure. I think we need more epidemiology on that question.

The other is the question raised about the drug side effects. Having thought about this a lot, I would say that for me the drug side effects are not a reason not to treat because this is, after all, a great emotional burden for the families and I think potentially some liver disease. But it is definitely a reason to do the very best clinical trials we can with the very best measures of toxicity. So, having an observation group that would then be crossed over later to the best therapy, comparing two different arms plus an observation group, and then taking care to look at neuropsychological measures of toxicity or lack of toxicity, both during the drug treatment and after, I think is the best way to assess whether or not these drugs have important toxicities in childhood.

DR. CHESNEY: Dr. Hudak has been waiting for a while.

DR. HUDAK: Yes. I'd like to follow up on Dr. Spielberg's comments about the perinatal issues. Clearly with HIV, that was a huge boon to be able to reduce a 40 percent acquisition natural history, perinatal and vertical I think, in that situation to less than 5 percent for sure and maybe close to 0 if you identify these mothers and do elective cesarean sections before labor.

But the issue is here that that needs to be addressed somehow. I'm not sure what the best way to do that is. I don't think we have all the information we need. But I'm intrigued by some of the data that was presented about the duration of ruptured membranes and so forth. Gosh, if the solution were as simple as identify these mothers, do a cesarean section, and then discourage breast feeding until you know for sure whether or not that's really involved in a vertical transmission, that would be the answer, and it would be relatively simple.

The problem is we don't know which mothers have hepatitis C. There is no mandatory screening for that that I'm aware of in any state. Is that something worth considering? I guess you have to do the clinical studies first to sort of see.

But people may have some reservations about the issue of a cesarean section, but we do cesarean sections for other infectious diseases, particularly herpes. If we

know the mother has active primary herpes, the baby gets delivered by cesarean section. The morbidity to the mother is low. The morbidity to the baby is low if you deliver the baby at term. In fact, there's some evidence if you were able to deliver all term babies by cesarean section at term without having the mother go through labor and a vaginal birth, the babies actually do better in terms of long-term issues, intelligence and development and so forth. But I guess we won't go there.

(Laughter.)

DR. HUDAK: But I think that really is the key because it seems that there are really three populations of children we're looking at. One is the population who's got a transfusion-acquired illness or a drug lifestyle type illness. I guess those patients are now -- what has it been? 8 to 10 years since hepatitis C was screened effectively in blood banks?

DR. LUBAN: Most of the transfusion-acquired, exclusive of the hemophiliacs -- that's another population that we need to discuss separately -- are now between 7 and 19.

DR. HUDAK: So, basically there's that older group of patients and then there are the lifestyle patients who are acquiring it in the teenage years. There's the perinatal transmission who are in all phases of age now,

and the ones who are going to come up are going to be the ones who continue to acquire the disease by that route. So, I agree. I think that's where the money is, and the biggest load of children coming up having the disease is going to be in that area.

So, I haven't really heard anyone address these issues of the perinatal studies. I am intrigued by the possibility of whether or not pharmacologic treatment before delivery makes any senses at all from what we know of the natural history. It sounds like we really don't know whether or not that would have a role to play. But I think those are the sort of things that I, as a neonatologist anyway, would be very interested in.

DR. CHESNEY: Dr. Jonas can respond, then Dr. Rehermann, then Dr. Gorman.

DR. JONAS: I just want to say quickly that I agree with you that prevention of perinatal transmission would have a tremendous impact, I think, on the prevalence in this country of pediatric hepatitis C. We have a precedent. It was the pediatricians that are responsible I think for eliminating hepatitis B eventually from our country with the programs that were established. It's going to take a few more years.

But I just remind you that when universal testing of pregnant women for hepatitis B was originally

recommended, first of all, it took a long time to get instituted. It took some number of years. The only intervention we wanted to make then was the safe and efficacious vaccination for the infant. We didn't want to change major obstetrical practices based on that result.

So, yes, I think this is intriguing and I think there are studies ongoing to see if it's true that you can prevent perinatal transmission. But I think in practicality, before we have a national program for testing of all women and changing obstetrical practices in every community hospital -- because this is not something like hepatitis B that you can almost target in big cities and so forth. This is pretty much everywhere -- I think a good number of years are going to be between now and then. I think there will be a lot of children born in that period of time. So, I think that these things need to go in parallel, not one versus the other.

DR. CHESNEY: Dr. Rehermann.

DR. REHERMANN: I have two points.

First of all, I don't understand why we should treat transfusion-associated hepatitis in children as opposed to perinatal transmission. Most of these studies here in the binders have been performed with long-term follow-up of transfusion-associated hepatitis cases, and they demonstrate mild disease, if any, spontaneous recovery

or very mild disease, almost no fibrosis at all. So, if this is the case, then I think there's no need to distinguish between both causes, and we need to treat transfusion-associated hepatitis.

The second point is I'm really severely concerned that children should be treated because there's increased pressure on the parents, on their schools that they are virus-infected and may transmit hepatitis C. This may be something we have created also as physicians because hepatitis C has been dramatized as being the new killer infection and so on. And now it turns out that in long-term studies, it's much milder and more benign than we initially thought.

So, I think we have to spend more time educating the public and really saying that having the hepatitis C virus without having disease is not dangerous for transmission for infecting other school children. I would be concerned exposing young children to the side effects of drugs just because of public opinion really asks for that.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: Two questions that come. I'm trying to follow up a little bit on this. Besides to what appears to be a natural history study that's about to start

in Baltimore, is there a larger effort funded by any organization on the natural history of perinatally transmitted hepatitis C ongoing or about to be instituted anywhere in the United States?

And secondly, a piece of data that was dropped in one of the presentations was that when you treat mothers for their HIV infection, their rate of transmission of hepatitis C goes dramatically down. Is there any evidence that that drug already approved is effective against the hepatitis virus, or is that strictly a coincidence?

Thank you.

DR. JONAS: I can answer that second question. First of all, there was only one study that showed the transmission rate decreased dramatically when the mothers were aggressively treated. It was sort of a side bar to that study.

Women who have high levels of HIV in the blood have very, very high levels of hepatitis C. Not just pregnant women, I guess AIDS patients in general. So, the thought is maybe their hepatitis C viremia level goes down, and that's why the transmission rate goes down. I don't think it was considered a direct antiviral effect on the hepatitis C virus. But it was one study again, and I'm not familiar with more.

DR. GORMAN: Considered or studied? I guess

that's my question.

DR. JONAS: It was not studied.

DR. CHESNEY: Dr. Seeff.

DR. SEEFF: Dr. Rehermann beat me to the punch. I was about to mention this issue of stigma again. I honestly think that this panel, in considering whatever report it comes up with, should be talking about the issue of stigma associated with the virus, in addition to the question of treating the virus. There is enormous panic that has been created by this disease, by this infection. While I'm not a pediatrician, I happen to have been involved with some radio programs in certain circumstances in which I've been with parents who talk constantly about the stigma of their child being a carrier of the virus and that no one else wants to play with the child, that they are ostracized from all the various things that they do.

I think one of the very important things that this committee should do is -- it may in fact be impossible -- they have to educate the public that this is not an easily transmissible disease. It doesn't float through the air. If somebody falls down and cuts themselves and is bleeding, you have to be cautious. Other than that, it's simply not transmitted.

Personally I also believe -- and I could get myself into big trouble for this, but I'm going to say it

anyway -- that there is a lot of anxiety about this disease that has been created, and I think that we have to put this in some kind of a perspective. We do not have to look upon this disease as a necessarily fatal illness. We have to take it seriously. We have to consider the consequences. We have to watch what we do, but there is circulating on the Internet, circulating in the press, circulating all over the place this panic that has been created by this disease.

I keep saying it is important to recognize that this is an important disease. It has be dealt with. It has to be dealt with responsibly. I think we as physicians have to take into account what we also create in the minds of people and in the anxiety that we provoke by saying some of the things we do.

So, we need to be very cautious about that, and I wish that there were a way that we could put this into better perspective. For children, in particular, I think it's a terrible burden that they face. If we could eradicate the virus, it would be great. If we can't eradicate the virus, it does not mean that they're going to infect everybody in the school or in the class or even their close friends that they play with. I think that this is an educational thing that needs to be told to the public in a forceful way.

DR. CHESNEY: Thank you for that impassioned commentary and Dr. Rehermann for raising it. I think that we can certainly add that to our discussion today for the FDA, but I think that's clearly also in the province of the American Academy of Pediatrics, which is very responsible for educational issues.

But if you want to know something that really sends people into a panic and which causes absolutely no disease whatsoever, it's head lice.

(Laughter.)

DR. CHESNEY: It's not even as bad as the mosquito. It carries nothing.

Dr. Spielberg.

DR. SPIELBERG: This is true. The louse lady always comes to school. This is the one public health intervention that every school system has. Quite bizarre.

Right now in Philadelphia, there's a hepatitis C panic among the fire fighters, and it's become a major issue in the fire fighters' union. One camped out in the mayor's office for weeks over the issue of availability of treatment and everything. So, I think we need some appropriate reality testing of the realities of the disease.

This question gets a little bit back to what Stan Szefler was talking about earlier, just thinking about

clinical trial designs and risk-benefit issues. I think I got from the presentations on the benefit side, at least in terms of viral eradication, that there's a huge difference in serotype responses, 80 percent versus 30 or 40 percent. The issue then comes, in terms of clinical trial design, thinking purely in terms of risk-benefit in those patients who would benefit the most and in whom, at the same time, you can evaluate side effects, risk factors, long-term outcomes, and everything, whether or not -- and again, the numbers may not justify given the prevalence of the serotypes -- designing trials for those most likely to benefit purely on the serotype basis before you do studies in the general population where the benefit is at least under 50 percent.

DR. CHESNEY: Is there anybody on this side of the room who has a question? I'm sorry. Dr. Schwarz.

DR. SCHWARZ: Having spent quite a bit of time talking about trial design with pediatric hepatologists and also with some help from distinguished adult hepatologists sitting to my right, I think that since three-fourths of the children in the United States have genotype 1a or 1b, if we concentrated on those with other non-1 genotypes, we would only be focused on the minority of the population. So, I think what we kind of concluded was that it's certainly very important to stratify by genotype, because

otherwise you can make no sense of the response to therapy, but we wouldn't want to exclude genotype 1 because we'd be excluding the majority of children.

DR. SPIELBERG: But just for the sake of argument, you'd say the same thing in terms of cancer chemotherapy. If you had a drug that worked in a specific tumor type that's relatively rare, you'd study that tumor type, and if you really had evidence that that was much more efficacious, just again on a risk-benefit and understanding the compounds better and understanding the outcomes better, you might want to go after those patients who would maximally benefit, given all the other uncertainties of long-term benefit of early intervention. At least eradicate the virus maximally in those in whom you're pretty sure you can.

DR. CHESNEY: Dr. Lindsay.

DR. LINDSAY: This discussion really helps me to think back to a few years ago when the same kind of discussion took place, as you can imagine, among adults before these more effective therapies became available and factors associated with response were available. Just reflecting back on that and thinking about this discussion, I want to just raise a couple of issues.

One is that the concept of selecting patients who are likely to histologically progress is going to, I

think, be very difficult to do. We haven't been able to identify really anything other than alcohol as a clear-cut factor associated with progression of liver disease.

Second of all, we talk a lot about the side effects of the agents, and I think Maureen and Kathleen have pointed out that in children the side effect profile may not be anywhere what we see in adults. I think it's important to recognize that the side effect profile that we report in adults is largely neuropsychiatric. If you look at the individuals who have difficulty with this cytokine-based therapy, many of them have underlying neurochemical disorders, addiction disorders, underlying depressive disorders, and so forth. So, I think that's an issue that we just have to look at a little bit more carefully.

One of the major problems with selecting patients for treatment based on their histology is that if you select them out from a trial or treatment, it requires repeated biopsies to determine when their disease has advanced enough to select them for treatment. There are two problems with that.

One is that at least among adults -- and children and adolescents may be different, but I don't think so -- the perception is, well, then I don't have very significant disease, and if you tell me to come back in three years for a biopsy, I'll perceive that as meaning I'm

really not unwell, and I'll maybe come back in 5 or 10 years.

The second important point is that when we look at our databases, in terms of factors associated with response, the presence of baseline fibrosis or cirrhosis is a negative factor. So, patients with underlying fibrosis or cirrhosis have a less likelihood of response. So, if you wait until someone does develop fibrosis or cirrhosis, the likelihood of their responding to that treatment at least would be less.

I think the point, though, about using genotype and viral factors to select patients is a very important one because genotype is clearly the most profound factor influencing response and level of virus is the second most important. What we have decided and what we have done in adults is, because the baseline levels are not 100 percent or 0 percent effective in predicting the likelihood of response, we're now adding in on-treatment response. These paradigms are not well developed, but it's very clear that the likelihood of becoming a sustained virologic responder is highly influenced by whether or not virus becomes undetectable early during treatment. So, one could take the available databases in adults and design a study in which one uses on-treatment virologic response, a treatment trial, for example, as a design paradigm that could really

I think use the very important concept that one should only be treating those children who are likely to virologically benefit.

DR. CHESNEY: That's an interesting concept.

Maybe just one more question. Maybe two. Dr. Fink has been waiting too, but go ahead, Judith.

DR. O'FALLON: I have a question, but I'd like to respond, if I may, about these issues here. I think there's a lot of knowledge of methodology in the AIDS literature about using surrogate endpoints, which these viral load things are. The ultimate outcome are those clinical things of cirrhosis, fibrosis, et cetera. And we're going to wait 20 or 30 years probably before we see them. So, we've got to work with surrogate endpoints. But there's got to be a tremendous amount of caution about what we're seeing and who it is that we're seeing and how well it correlates with the final outcome. That we don't know in this disease. It hasn't been around long enough.

That leads to the other part, which is bothering me a lot. It is a long-term disease. It takes a long time. There were a couple of assumptions that were made here over and again. One of them was that if you couldn't see the ones that were nonviremic, I think is what you said, that they didn't transmit. The mothers who had no detectable viral load would not transmit to their

children. Do we really know that, or is that an assumption? Because it does have profound implications for how we go about detecting who needs to be involved in a study.

I keep remembering viruses of chicken pox in the kids and then shingles in us old guys. I think of the way polio is coming back. The kids who had polio and were total cures are now experiencing deja vu. We're seeing a lot of those guys now. I worry about the assumption that because a young woman does not show any sign of a virus to date, that therefore she is not going to transmit it to her children. This is a real concern to me in the assumptions that you've been throwing out here.

DR. CHESNEY: Dr. Jonas.

DR. JONAS: I'm the one who made that statement about the non-transmission from antibody positive, nonviremic women. That has actually been demonstrated in many studies of perinatal transmission. Almost all the studies start off with all of the women who are antibody positive which are viremic or not and then look at outcome in the infants. I want to say virtually every study I've ever read in that kind of vein has demonstrated no transmission from antibody positive, HCV RNA negative women. So, it's assumed that they've either recovered from their infections totally, been one of these spontaneous

recoveries, or it was a false positive antibody in that setting.

DR. REHERMANN: Yes. I want to add. Even more has been shown. The virus replicates in the liver. So, if you take a liver from an antibody positive, PCR negative organ donor, for example, and transplant that into an immunosuppressed recipient, that would be the best proof or the best approach to study this. There has been a study published by Dr. Hoofnagle, Dr. Everhart from NIH on a big transplant database, and in none of the cases analyzed was there any transmission shown.

Even the PCR positive mothers have very low viral load in general, and only about 5 percent or so of them transmit.

DR. CHESNEY: Thank you all very, very much. I think Dr. Weiss and I had the same feeling that although we were supposed to be addressing the questions, we were in fact doing that. It seemed like the questions were very directed to the questions.

So, I think if we could take a one-hour lunch break now and then immediately at 5 after 1:00 Dr. Weiss can introduce us to the questions.

(Whereupon, at 12:05 p.m., the subcommittee was recessed, to reconvene at 1:05 p.m., this same day.)

AFTERNOON SESSION

(1:07 p.m.)

DR. CHESNEY: Dr. Murphy is scheduled to talk to us for half an hour at the end of the day, but in fact she's going to be here all afternoon. She tells me she has more than a half hour's worth of information to tell us. With the renewal coming up and the congressional hearings next month, I think we all would very much like to hear what she has to tell us and to again ask her what we can do to help. I'm sure many of you have questions for her.

So, I wanted to be sure to get started and see if we might be able to get through our questions by 4 o'clock. I think also Dr. Balistreri has to leave at 4:00 and we want to hear from him, as well as everybody else, as much as possible. So, let me ask Dr. Weiss if she would mind just giving us a very quick overview of the questions and then we'll start with the first one.

DR. WEISS: I just, first of all, want to say that I think the discussion just before lunch has been absolutely fascinating. There were a lot of issues raised that sometimes raised more questions than had answers. Some of the discussions touched upon the specific questions the FDA has posed to the committee. Some of them are the fundamental questions of who to treat, when to treat, how best to treat.

So, what I would think, given some of the time frames we're under right now, is just to ask that we start to just tackle the questions. Again, some of them might already have been addressed to some extent, but it's helpful for us, years later when we go through the transcripts of the meetings, to have this format and to have the questions addressed in the order that we have them. So, I would ask Dr. Chesney if you wouldn't mind reading the background and then the question for the record, and then we can have a discussion on each of those points.

DR. CHESNEY: The easiest thing I have to do today. So, question number 1. The treatment of hepatitis C virus infection in adults raises concern about the relatively low rates of success and the durability of response; lack of information on the impact of therapy on long-term outcomes such as cirrhosis and hepatocellular carcinoma; as well as known and unknown toxicities. Given these concerns, please discuss the need for and the appropriate timing during drug development of agents developed to treat hepatitis C infections in the pediatric population.

So, our first question is, is there a need to treat hepatitis C infections in the pediatric population which we might roughly designate as children under the age

of 18 years. Comments. Dr. Schwarz.

DR. SCHWARZ: I think my bias is probably obvious, but I can think of four reasons to argue for the treatment of hepatitis C in children.

The first is to prevent liver disease.

The second is to improve emotional well-being and decrease stigmatization.

The third is to understand the immune responses of children to hepatitis C therapy because there are tantalizing suggestions that the immune response in children may be different, may be better, may be more effective.

And then a fourth is the ultimate public health consequences of the economic benefits of eradication of hepatitis C.

DR. CHESNEY: Thank you.

Comments, questions in response to Dr. Schwarz's bias? Dr. Balistreri.

DR. BALISTRERI: Well, just to play the devil's advocate, the last issue, the public health implications. If this were hepatitis A, for example, children play a massive role in the transmission of hepatitis A. What is the data that children -- again, we'll keep them children for a long while -- play a role in the transmission of hepatitis C? Because if it was a major impact, at least

for the next 15 years, then we should do everything we can to decrease that pool. It's a rhetorical question.

(Laughter.)

DR. SCHWARZ: I was actually thinking about the economic consequences, the liver disease burden, the doctor visits burden. I think the transmission question is going to be addressed, but it will be little to none.

DR. CHESNEY: Does anybody else feel strongly that we should treat children under the age of 18 years? If so, please let us hear from you. Dr. Luban.

DR. LUBAN: I think I'd just add an adjective and that is "selected" patients.

DR. CHESNEY: Which selected patients do you feel we should treat under the age of 18?

DR. LUBAN: I was afraid you were going to ask me that question. I think that for me is really where the dilemma is. It's in selecting that group with the minimum amount of knowledge that we currently have as to the natural history and progression in the U.S. that limits the true definition of a patient population that for sure needs to be treated versus that group that perhaps could benefit versus that group that we could allow to see whether those kids cleared. It's very, very muddy between those three categories in my mind.

There certainly is one group that categorically

I would say we absolutely should be treating and that is children with chronic hemolytic anemias, thalassemia, sickle cell disease on chronic transfusion programs with iron overload, and clearly defined liver biopsy evidence of fibrosis and not even necessarily progression of disease, but a single biopsy. That would be a group that for sure I think should be treated.

DR. CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: On the other end of the spectrum, I haven't heard anything today that convinces me as a nonexpert in this area that we should be treating preschoolers with the therapies that are currently available. I hear we've got a therapy that is marginally effective or effective in a minority of patients and patients with certain -- except with certain genotypes of the virus. We have a lot of unknowables right now about these drugs in terms of their long-term effects. In kids within that age range, it sounds like it's highly unlikely that they're going to be symptomatic or progress to clinically apparent disease. It seems to me this is a unique situation. We are usually pretty aggressive about treating infections early on, as early as we can diagnose them, but this may be an exception to that. So, I would argue that we ought to seriously consider excluding at least the preschool and maybe up to 12 for those reasons.

DR. CHESNEY: Dr. Jonas.

DR. JONAS: I guess I have to say I have a different point of view. I certainly would like to target therapy to selected populations, and I certainly don't know how to do that yet either. There are some children who have advanced serious liver disease from this either in late childhood or early adulthood. It would be, I think, a shame to be so concerned and we let the time go by. As Dr. Lindsay mentioned earlier, I think there is a time at which you identify significant fibrosis on biopsy and you have missed the moment. I think if there's a cohort of those children as well to say we had a therapy that was certainly not 100 percent -- as you've seen, at worst 30 percent, at best 60-70 percent in some genotypes. But we could have intervened. I guess what I'm trying to say is I think the focus is how do we pick out the children better rather than just say it's an aged-based thing because I think we will miss the boat in certain circumstances.

DR. HOLLINGER: I think along those same lines, I guess the real question then comes up at what point do you determine the "advanced" disease. That usually has to be a biopsy. Anybody can diagnose cirrhosis, particularly if they have significant cirrhosis. You can usually see it biochemically or hematologically or other things or how the liver feels.

The issue is that very large gap of people in there. Depending on which staging you're using, if you use a four stage with fourth being cirrhosis -- so it's between one and three, and even in to transition towards cirrhosis, that becomes very difficult without a liver biopsy.

So, the first step I think you're going to need to do is to decide at what stage would you consider biopsying a child to get a baseline level.

DR. CHESNEY: Thank you.

Dr. Jonas.

DR. JONAS: This is my opinion. I have no data to substantiate this. But, again, we did our own internal look at liver biopsies in children with hepatitis C. We had I think 45 biopsies, and 78 percent had at least some fibrosis. So, the majority did. Now, this was a mixed bag of patients. They were perinatals. They were relatively recent infections from the Gammagard outbreak. We had a mixed bag. So, I can't stratify them in that regard. But they were done at least 6 months after the documented start of infection. That was when we decided and when we would consider doing something about it. We didn't do biopsies just for the purpose of that study. We saw probably selection bias in that group towards more because we were biopsying kids with abnormal liver enzymes at that time.

DR. CHESNEY: Dr. Fink.

DR. FINK: I might take a different approach to this dilemma, and the approach I would take to it would be to say that I would think pediatric trials would be appropriate when an adult therapy has been proven to be greater than X percentage effective. Since a spontaneous remission or cure rate is around 30 to 40 percent, or appears to be in that range in children, I would probably pick something in the range of 70 to 80 percent so that whether it's in a subgroup or a global when adult therapy has proven efficacy above 70 or 80 percent, that then it would be appropriate to do pediatric trials where the likelihood of benefit is greater than the risk of toxicity.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I know we're supposed to be past our question-asking stage, but are liver biopsies done routinely by the gastroenterologists for all diagnosed cases of hepatitis C in pediatrics?

DR. JONAS: I can give you my own practice and then you can ask my colleagues. Typically I have not recommended a liver biopsy unless we were going to use the information to make a therapy decision, either enrollment in a trial or sometimes the child needs anticonvulsants and you want to know if there a serious baseline liver disease. So, not just because hepatitis C virus RNA is present in the serum, because we don't know what to do with that

information necessarily.

DR. GORMAN: Without a biochemical abnormality, you don't do liver biopsies then, except if there's a therapeutic need.

DR. JONAS: No. That was early on. I think now that we know that some of the therapies in adults are effective -- interferon monotherapy was not successful, by and large, in adults with normal ALT. So, we weren't using interferon monotherapy in children with normal ALT. When it became more apparent that combination therapy may have a role in the adult patient with normal ALT, then we started doing some liver biopsies in normal ALT patients to look at them for therapy.

DR. BALISTRERI: I agree.

DR. CHESNEY: Dr. Lindsay.

DR. LINDSAY: I think this whole discussion is very useful and complicated and difficult and I don't think there are really simple answers to any of the questions that we're trying to address. But it seems to me that the first criteria that needs to be present is demonstration that chronic infection that's not likely to resolve spontaneously should be present. The question is can we define that in a pediatric population based on either duration of infection or age, given the information that's available. I don't know if we can, but it certainly seems

possible that by looking in more depth at the databases that are available, that we can come up with an age or length of infection at which point it was highly unlikely to be spontaneously resolved after that point. So, that would be the first criterion.

I like the idea of using the treatment in a population where the treatment has been proven to be 70 to 80 effective. That gives you a really good target. I think that it's important to realize that when we talk about effectiveness with this treatment, we're talking about something that's really biologically quite unusual; that is, that we give a treatment for a fixed length of time. And from everything that we have available, it appears that we eradicate a chronic viral infection. Now, I don't really know that there is really good evidence that we do that with any other antiviral therapy. Almost all others are suppressive. So, we're talking about the potential for eradicating a chronic viral infection and, if we're successful, providing that individual with long-term clinical benefit.

So, effectiveness I think has to be interpreted in a number of different ways, but if we just use the conventional definition of SVR, or sustained virologic response, we have genotype data. The 70 to 80 percent target in individuals infected with genotype non-1, 2 or 3,

is in that range with the current available therapies or evolving therapies. In genotype 1 patients, I think again by reanalyzing the existing databases, one could take the on-treatment virologic response as a parameter and identify a subgroup at a time point during therapy where that target could be reached.

I think that the issue about concern about side effects is a very real one. Until the agency has an opportunity to really look at the Rebetron database and so forth, I don't think we'll have answers about toxicity or concerns in children. But that is something that will just have to be left open.

Finally, this issue about selecting patients based on where we think their liver disease is going to go in time I continue to think from a practical perspective is not likely something we're going to settle. If we defer therapy, I have great concern that these individuals, as they evolve into the age and the length of infection when liver disease is occurring in their late teen years, 20's, early 30's, this is a therapy that requires paying attention to your disease and paying attention to your treatment. Adherence to therapy is very important in terms of maintaining a virologic response.

Personally in my practice and years of caring for young adults, it's just not an age where people are

likely to commit a year to this type of treatment necessarily. Now, maybe I just haven't had the right experience, but I would be very cautious about advising deferral of this treatment to teenage years and the 20-year-old age group.

DR. CHESNEY: Let me come back to the question. Is there any point in time when you can be certain that this child is not going to revert to viral negative status? Anybody. Dr. Schwarz.

DR. SCHWARZ: I believe that Miriam Alter at the CDC is currently doing a prospective follow-up of infants who acquire hepatitis C from their mothers. I think that this study may be a year or two along. I think that it is this large scale study that will address that question for young infants in the U.S. population.

DR. JONAS: But I don't think you have the answer to that question in a 6-year-old who is brought into your office because the mother's hepatologist said you might want to get your kids tested because you have infection, and the child is brought in at 6. I think the crux of your question is, is there anything I could do that day or over the next year following that 6-year-old to say this is one that won't be infected at age 12 or will? And I think the answer to your question is absolutely not. I don't think we have any idea of either genotype or ALT or

anything at that point that will predict that.

DR. CHESNEY: If you biopsied on that visit, would you be able to tell us what you anticipated?

DR. JONAS: Not viral clearance. I think you could do a biopsy and see minimal, if any, liver disease, and you might, with some reassurance, say we really don't need to address this disease for at least another 5 years. We could rebiopsy in 5 years and see if there's been progression. I think you could do that with some safety.

I think if you saw significant fibrosis, you still couldn't predict whether there would be viral clearance or progression in 5 years. There really aren't predictive factors. So, to be able to defer therapy under those circumstances, I don't think you're going to have that information.

DR. CHESNEY: I think that's what makes those of us who aren't in this particular area very nervous, that we would be exposing children to effective, but not 100 percent effective, therapy with significant side effects when they might revert to negativity. I guess that's the crux of this question.

DR. JONAS: But I think it's still the minority will revert to negativity. The chances are that 6-year-old will not and will remain chronically infected. How long before she gets serious liver disease, if ever, is a

related but different question.

I think in these studies that show this drop-off from positive infected to uninfected over some number of years, there's probably a small percentage of them that were going to do it and did it early and the rest of them are just going to stay infected. I'm guessing again, but I don't think that's linear so that every year you can expect a percent to lose the virus. I don't think it's going to be that simple. It's going to be, those who are going to do it did it, and everybody else is going to stay infected with it. We all have kids that we've followed for years now, because there hasn't been good therapy, and they come back once a year and their PCR is positive, and okay, see you next year.

DR. CHESNEY: Dr. Lindsay.

DR. LINDSAY: I guess what I was thinking about was just reexamining these databases again as we've read about them, as you've presented them and we've discussed them. There's data that if you sample individuals at a certain point in time, just like the Irish and German women cohort and Dr. Seeff's cohorts, a certain percentage has become negative. And Dr. Rehermann has been involved in this.

But the issue is at what time points have children actually been observed to clear virus. All of the

data that you're telling me that I've heard in terms of clearance has all been observed during the first few years of life. So, does that mean that they never clear after that? Well, no, but the bulk of the data suggests that that's when they are observed and followed and demonstrated to clear. So, it would seem reasonable to make the presumption that there is some sort of a cut point where at a certain length of infection or age there is more likely to have been clearance.

DR. CHESNEY: You're asking that like it's a question.

Dr. Hollinger.

DR. HOLLINGER: You can take it a couple of ways. We know that hepatitis B clears about a half percent to 1.5 percent a year, the HBS antigen and so on. But that's pretty consistent throughout the follow-up of these patients. If you follow them long enough, you see it. You don't see this with hepatitis C. If they have chronic disease and you follow them, they rarely, if ever, seroconvert from positivity to negativity unless you introduce a treatment or something of that nature.

So, the assumption that I would make just from that is that they clear, and the clearance probably occurs very early in the course of their illness, as I think Leonard mentioned. I would certainly agree with him that

it may be in the first one, two, three years at the most, and after that things seem to be pretty stable. I would doubt, just on the basis of other follow-ups, intuitively, at least to me anyway, that it would be unlikely that this is going to occur much after a few years.

Now, children are a little different. From a pediatric standpoint, immunologically and so on, there may be some differences very early in the course of disease, the first year or two or three years, but then I think there's probably less of an issue at that point.

DR. CHESNEY: Skip.

DR. NELSON: I'd like to comment specifically on the portion of the question about appropriate timing during drug development. There's a lot of uncertainty. But in listening to that uncertainty, I guess I'd like to try and articulate what might be a point of agreement which would be surrounding this whole debate which we're having about risk-benefit and whether you can identify a cohort of children that would be most to benefit, less at risk, et cetera, that you really can't do that with any degree of confidence until you have an idea of the efficacy of the intervention and the kinds of toxicities that might be observed. Given the chronicity and the very slow time line of the disease, I would certainly conclude that you wouldn't want to do studies in pediatrics until you had

efficacy and safety data in adults, as opposed to doing it earlier.

You've also got some data that's going to be coming out in pediatrics of one particular intervention which we've been focusing on, but the question here is worded in general. So, whatever the next intervention is, I would still conclude that it shouldn't be studied until you have adult efficacy and safety data on which you can begin to make some kind of assessment of the risks and benefits of the research alternatives and the clinical management in pediatrics, which would be different perhaps in other diseases.

So, I offer that as much for debate, but that's at least what I take away from this, not that it shouldn't be studied, but the timing relative to drug development -- we're talking about timing in terms of ages, but also timing in terms of drug development -- would be after there's adult data to begin to try and come to some conclusions about the risks and benefits.

DR. CHESNEY: Dr. O'Fallon.

DR. O'FALLON: What's happening here is we're really talking about two different problems. One of them is the problem of the child who already is demonstrating in a certain sense that they're sick. The other big problem is that it's a smoldering disease and no one really knows

what the effect is going to be 30 years from now. I think those are the two issues here. The ones with the silent disease, what is the effect going to be 30 years from now in terms of the transplant units and so on.

I would also point out in terms of having children maybe in terms of this vertical transmission, the silent smolderers may be passing along something to their children. We don't know.

It seems to me that in addition to the things that Dr. Nelson mentioned, I think we need more information about the natural history of the disease because we cannot accurately assess the benefit if we don't have a pretty good idea of the risk that these kids are having. We're making the assumption that their disease is going to act basically like the adults, and that may not be the case. The evidence that you've shown us so far is that it's a more benign version of the disease. We don't know what's going to happen at the other end of it, and I think that's a very important issue in balancing the benefit versus the potential costs because we can look at the toxicities in the adults, but the adults are not growing and the adults may not have their fertility affected, and there may be a number of other things that the kids could have that the adults are beyond.

DR. CHESNEY: Talking mainly to the committee,

Skip, could you formulate your response? It was very good, but could you do it one more time? Then let us just see if most of the committee are in agreement with the way you formulated it or if we need to continue with our discussion.

DR. NELSON: I don't want to get into the second question by formulating this, so I'm ducking the issue of whether you need efficacy studies in pediatrics. But what I feel is clear in my mind is that you wouldn't be able to evaluate the risks and benefits of conducting a trial in pediatrics until you had efficacy and safety data in adults. So, this would be a circumstance where I would want to see some phase III data in adults before you would begin to do clearly phase II and phase III. I'd even question whether you would want to do dosing studies until you had some idea of the safety and efficacy, given the chronicity, the benign nature of the disease, by and large, for most kids, et cetera. So, I would, in this case, probably delay pediatric studies until you had safety and efficacy data in adults.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: I want to play devil's advocate with that because if what you're saying is that the disease is very similar to adults -- now, there may be some little things that are different. But the consensus is it's

really the same disease. There is some preliminary safety data on the use of at least one of these medications in children. Then you don't need a large cohort of pediatric data to justify its use.

DR. NELSON: I was trying to answer question 1 without answering question 2. I agree with you that I'm more inclined to think the disease is similar enough that I wouldn't require large cohort sort of efficacy studies and would look more towards dosing and safety studies personally. But I was trying to answer 1 without answering 2.

DR. SANTANA: So, I think the issue for me would be if I make the assumption that the disease is very similar -- and considering I'm not an expert, but from what I've heard, it probably is very similar -- that my main concern, in terms of balancing the risk-benefit, is the issue of side effects. And I would want to see more safety data in children and not necessarily studies that demonstrate a greater efficacy.

DR. NELSON: I would agree. The point at which I would even start doing safety studies is when you think it's worth it, which means you've got some efficacy results in adults. This wouldn't be a case where I would start doing pediatric safety studies until you had a notion that there would be some efficacy.

And I also would say if you're going to exclude the kids that are going to spontaneously resolve, which hopefully we could come to some consensus about where we might choose that to be, I don't know if I would demand a 70 or 80 percent where we might do that.

DR. SANTANA: But I think you could address some of those concerns by the study design. I heard a comment over here that there may be some information that you could identify the early responders early in the trial and you then wouldn't subject the nonresponders early in the trial to further therapy.

DR. NELSON: I think we're agreeing, Victor. Let me just restate it to make sure. I'm trying to generalize past the particular compound that's been studied and just say that you wouldn't want to subject children to a safety study until you had some sense that whatever compound you're studying has efficacy, so therefore it's worth finding out if it's indeed safe.

DR. SANTANA: I agree with your comment.

DR. CHESNEY: And the reason we don't want to jump in is because it's a benign disease in childhood, for the most part.

DR. NELSON: I guess I'd rather call it indolent rather than benign or chronic or something. It's certainly not immediately life-threatening.

DR. CHESNEY: Asymptomatic maybe.

Dr. Hollinger.

DR. HOLLINGER: Just on those same lines, I wouldn't call it benign disease in adults too, but that doesn't stop people from being treated at a certain stage of the liver disease. They're asymptomatic. The liver disease itself is not something that's going to result in their death in decades by the time you start to treat them. So, those issues are pretty clear.

I'm not so sure that there's very much difference between the child and the adult. I think there are other factors in adults which play a role, particularly such as alcohol and perhaps even injection drugs and a variety of other things which may play a role in the progression of the disease. But clearly alcohol does. Leonard and I had a paper out recently, a couple of months ago, on the effects of alcohol in patients with hepatitis C. When you look at adults who do not drink, their liver disease is actually pretty slowly progressive, if progressive at all.

DR. SEEFF: You know, there's a real philosophic difference of opinion. Even among adults there is a philosophic difference of opinion. There are those people who will treat everybody who's infected who have abnormal ALT and even those without an abnormal ALT if a

liver biopsy shows a little bit of inflammation and even early fibrosis. There are others who wouldn't. Were it not for the fact that this is such a protracted disease and one in which the outcome is so variable, and one in which the treatment is not always that effective and has many side effects, we probably wouldn't be struggling with that.

So, the issue is what do we do with children who mostly fall into the situation of being in that more benign situation. This is almost impossible to be able to discuss with any data. This now becomes a question of one's philosophy and one's belief in the fact that we are doing good and not harm.

I am of the opinion at the moment -- and I state this and I write this -- that I think there are times when I would not treat adults even though they're HCV RNA positive, even though they may have mild enzyme abnormalities, if their histology is minimal. By that I mean very little fibrosis. Now, you may ask how often that happens. Maybe not often, maybe 20 percent. I don't know. But I think that's a choice.

I think that we hope that in the near future, in the foreseeable future, there will be better, more benign hopefully or less painful drugs to take. I've always wondered whether the people who prescribe this had thought about taking it for themselves to see what it is

like, because it's a very unpleasant form of treatment to have to deal with. It doesn't mean to say we shouldn't be doing it. We have to do something, and we've made huge inroads. There's no doubt about it.

I'm still struggling with the question about what to do in pediatrics. I don't know the answer. Again, it comes down to the vectors. What is the likelihood that we're dealing with a disease that is progressive? I have no doubt in my mind that over the first 20 years of infection in the pediatric population, that the rate of progression is not the same as it is in a 50- or 60-year-old person. I feel absolutely convinced about that. I have no idea what happens beyond that time.

Therefore, it comes down to knowledge that we don't have and the kind of knowledge that Barbara and other people working in this field we turn to to say what are the factors that will give us the information or that will show us that the progression has promoted. And we just don't have that information. So, we're struggling terribly here.

As far as the issue of once you get it, will you lose it, I think that we all agree that once the person is chronically infected, the likelihood of losing the virus is close to nil. It doesn't disappear. It stays. The pediatric population is one that I just don't simply know enough about because, on the one hand, we do know that

there is a higher rate of loss of the virus in the pediatric population than there is in the adult population. So, therefore, it must occur sometime early on.

Now, let's take the 6-year-old that comes to see you and is found to be hepatitis C positive. The question is when did the infection take place. I think it's reasonable to assume at the moment that if that infection took place two or three years ago, the likelihood that this is going to disappear is virtually nil.

DR. JONAS: Most of these will be perinatal.

DR. SEEFF: Under those circumstances, I think you are talking about an infection that's not likely to disappear. It's going to stay. So, we've got that to deal with. I don't think the issue about spontaneous loss at this point is an issue. I think it's earlier on. I really do think it's in that first year. None of us have that information, and we can speculate until the cows come home and it's all speculation. We just don't have those data. So, I think that, number one, once you get it, it's going to stay.

Is it going to progress? If it's going to progress, the treatment is needed and particularly if that treatment is going to be effective. My sense from what I'm hearing is that it's a little bit more effective in children than it is in adults. I'm not sure whether that's

true or not, but that's the sense I have. I don't know whether Bill or Maureen or Kathleen can talk about that, but I get the sense it's a little bit more effective.

Whether the side effects are the dominating issue or not I don't know. I don't have an answer to that. I really don't have an answer.

I think maybe what we have to do is to grab the bull by the horns and say we've got to do something. Either we do nothing and just let this thing go and wait until they become adults and then once they're adults, we sort of redefine what we're going to do. The question is when. 16, 17, 18? Is there any difference between the 18-year-old and the 19-year-old? The NIH Consensus Conference says you don't treat anybody under the age of 18. We're going to change that I'm sure. We have a new consensus conference that we're figuring on for next year. But is the 17-year-old any different from the 18-year-old? Where is the cutoff where the child becomes the adult and then assumes the outcome of the adult? And does that outcome, in fact, differ between the person who is infected at age 1 and reaches 18 or the person who is infected at age 18 because they use drugs? Is that a difference in outcome? And we just don't have this information.

So, to me it seems to me the committee has to say either we do nothing or we do something, and if we do

something, we start treatment and we try to choose the group that is most likely to respond and the age at which we should begin to consider treatment and do the study and do it very carefully under terribly close supervision and observation. Our job is first do no harm. So, we want to make sure we don't cause harm. Because I think the rest of it is just pure speculation at the moment. We can sit around here and talk until forever. And we don't have the data. We have to come up with a decision about what's the best and appropriate thing to do.

DR. CHESNEY: Thank you very much.

Dr. Jonas.

DR. JONAS: I just want to make a comment again addressing timing, when pediatric trials should be done compared to adult trials. Dr. Schwarz can tell you that a few years ago we spent I don't know how many hours in meetings, investigator meetings, to do an interferon monotherapy trial in children. I think it was what? Three or four years ago. And it was probably two years' worth of work in the planning, just the same exact issues that we're having here. Which kids to treat. Is this safe? What's the natural history? By the way, we don't know any more today than we did two years ago.

But we eventually scrapped the protocol because newer therapies were available, parents weren't going to

enroll children in monotherapy trials with placebos anymore because they had heard so much about hepatitis C. If we had done that trial, I'd have the data for you today, saying this is monotherapy. Here's safety for you. Here's efficacy data of interferon by itself. Here's the placebo. Here's the natural history. We never got to it because of these discussions. They were appropriate discussions and we worked very hard I think, but we threw the paper in the trash on the way out and said, next.

So, now people are still using interferon monotherapy in children, some in the community. They're using it some to try to scale down ribavirin. And we don't have this information. So, there's a case to be made for doing a carefully monitored trial to answer some of these questions that we're struggling so much with.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: I'd just like to add to that and talk a little bit about the relationship between the formal deliberations of this expert body and community practice.

I am so happy that the group is discussing these many issues, but I can say that if the decision is the ultimate conservatism, which is not to do any pediatric trials, I think the reality is that what will happen in the community is that there will be fairly large scale uncontrolled treatment of children with hepatitis C.

It's interesting. I remember when the Pediatric Gut Club met in St. Louis about 25 years ago. It was in a classroom at Washington University, and our Society of Pediatric Gastroenterologists is now 700 or 800 in the United States and North America and there are several thousand worldwide. So, the subspecialty of people who treat children with hepatitis C has grown tremendously.

We have an e-mail bulletin board in which uncontrolled discussions go back and forth. It is amazing how people debate doses of drugs without really any controlled basis.

I think that it is our responsibility to talk about the very best study design, very best controls, very best endpoints, rather than just making the decision not to do pediatric trials because if that is the formal consequence, it won't stop children from being treated in an uncontrolled fashion.

DR. CHESNEY: I think that's an important point. My conservatism would go along with Skip. Let's wait until we get the adult results. On the other hand, the whole reason we have the pediatric initiative is not to wait until we have adult studies, although there are good reasons. This is a different kind of disease. But my other instincts say, being in infectious disease, that the earlier you treat things, the better off you are in

general.

Kathy, you had your hand up earlier. I'd be interested in your thoughts.

DR. EDWARDS: It seems to me as a nonexpert that what we need is to clearly outline progression of disease and to understand the disease process. I guess one of the things that seems so important that perhaps we can ask our adult colleagues about is that it seems that there are a number of pediatric patients that may be receiving treatment in the communities with adult colleagues. Maybe in the Gut Club or the group that you have, if there is a prospective way to monitor these children in terms of how often do they need liver functions, how often do they need biopsies and try and get all of the children into the fold rather than having people on off-label therapies where we're gaining really no information and not even monitoring toxicity. So, it seems that we really need guidance in terms of how children should be monitored, guidance in terms of getting all of the children into a database that can be assessed.

Then finally, I guess this morning really made me feel more comfortable about hepatitis C. Obviously, it's a disease but it made me really much more comfortable than I had been before that this in children may not be such a horrible disease.

So, I think that you also could do a great service at education or asking the NIH we need such and such more money for this large trial from our group to do education, to do monitoring of these children, and to try to get all of the kids into one fold. So, I think this may be more of a research initiative, but I think that's how we may help you, by really getting all the patients to address the questions.

DR. CHESNEY: Dr. Nelson, and then I wanted to ask Dr. Weiss if we really have to answer this.

(Laughter.)

DR. CHESNEY: Go ahead, Skip.

DR. NELSON: Just to make some modifications to my earlier comment, it was not my intent to suggest we should do post-marketing studies on these drugs, so trying to work out where that window of opportunity exists where you've got enough data in adults to be able to begin to draw some conclusions about the risks and benefits in children, but before it would be open for off-label use, which I agree is always a problem. I will say I'm always conflicted over the argument that because pediatricians will do it anyway, therefore we ought to study it. I think that argument in and of itself, though it may apply in this case, needs to be critiqued based on pediatricians' propensity to believe that anything will work and have no

toxicity.

The other comment is just putting on my IRB hat, now that the FDA has adapted Subpart D, this would be considered under section 405, and it would require under that that the risks and benefits of participation in the research would be similar to the non-research alternatives. So, the risks and benefits of the trial are going to be judged in the context of the risks and benefits of not being treated. All of the things we've been talking about that we haven't been able to come to any firm conclusions on an IRB will have to struggle with, and they will only approve the study if the risks and benefits are, indeed, similar enough to the alternatives, not equal, but at least in balance. So, that's how it's going to be considered.

DR. CHESNEY: Dr. Szefler.

DR. SZEFLER: I've been listening to the discussion and then trying to parallel this with something I have some familiarity with, which is asthma. We deal with a drug, inhaled steroids, where there's been a concern in the disease of progression. Not everybody gets it but some people do. It's viewed I think as a little bit of a safer drug than this drug. But there is kind of a push to use it more widely and prevent this progression.

We're going through the same steps in trying to understand who is at risk for progression. I think we have

a little bit of a better handle on who is at risk for persistent disease, which I think you have to kind of go through these steps. I tried to do it this morning to push you to say what would be the criteria for doing a trial.

I think if you don't do a trial, the opportunity will be missed and it will be the off-patent drug of the future where we're struggling to try to do trials and nobody wants to fund them. You have the opportunity now to do a trial, potentially with the FDA saying a trial should be done or at least put on paper before we approve this drug, please design the trial. So, you're going to be sitting on either side of the table, either helping the FDA design the trial for industry or helping industry design the trial. So, this seems to be the forum to help put in line what the format of that trial should be.

There seems to be a polarity -- and you're both sitting at the same table -- of one saying we don't need to treat everybody, and then another one saying I think there's a wider spectrum that eliminates almost nobody to treat because of this emotional impact. I think we were getting there through Dr. Lindsay's comments about a population who should be considered for treatment where most people would agree they have some risk because you have the disease and then there's liver disease. Not

everybody that has infection has liver disease. But how could you screen that down to say who's going to have liver disease and at least address that population?

I think what I haven't heard real clearly is we can diagnosis who has the disease, but then I'm not clear who's going to get liver disease or how you detect that. Is it just by biopsy or are liver enzymes the next screen? Maybe we ought to move in that direction to try to help formulate what population should be studied.

DR. CHESNEY: Thank you. That was very helpful.

Dr. Weiss, you do want us to come to some kind of consensus on that. Is that correct?

And the second question is maybe we can just discuss the need for rather than design, although I think design is important, but is there a need -- that's the first part of the question -- for agents to treat hepatitis C infection?

DR. WEISS: I thought the discussion was very good. Maybe I'm misinterpreting, but I thought there was at least some consensus. And a lot of it is going to be addressed in the next question, question 2. But it seemed like there were certainly some disagreements but certainly the majority of the hepatologist experts that we have thought that there probably is a need for treatment. I

think that that seemed to be a consensus that some pediatric patients should be treated.

We're not talking about the currently approved therapies, but things in development, future therapies. What should be the timing of future therapies? I think your answer was, like with a lot of other therapies that are being developed for adults that also occur in pediatric patients where we're talking about non-life-threatening diseases, chronic diseases perhaps, the timing in your answer should probably occur somewhere but certainly not before you had some preliminary evidence of efficacy and safety. Exactly when I think maybe can't be answered until we have more hard data on whatever those products are down the pipeline and what we're seeing in terms of the safety and efficacy profile in adults.

So, I actually thought that at least question 1 seemed to be -- I could eke out sort of a consensus from the committee, at least for the first part. You've established that there is a need for treatment. Exactly who and how and when is going to be addressed in the subsequent bullets, which we can hopefully get to. But there is a need probably for treatment and maybe we should just then move on, if my assumptions or my hearing is correct, to question 2 which really addresses I think some of the nuts and bolts of that type of response.

DR. CHESNEY: Is the committee comfortable with that summary? Okay.

So, we'll move on to question 2. As previously noted, the 1994 Pediatric Rule allows extrapolation of adult efficacy data to the pediatric population when the disease and response to therapy are sufficiently similar in both adults and children. Determination of when extrapolation is appropriate can be difficult and controversial, unlike question 1.

(Laughter.)

DR. CHESNEY: Please discuss whether the course of hepatitis C infections and the response to therapy are sufficiently similar to allow extrapolation of adult efficacy data, and please be sure to consider, first of all, the small number of pediatric patients available for enrollment and, secondly, the potential role for exposure/response studies.

Dr. Kauffman.

DR. KAUFFMAN: I have a comment and then a question of the gastroenterologists. I got the impression this morning that there is some evidence that the kids may respond better than adults in general in their disease. If that's the case, that implies that there may be something different about not the infectious agent but the host response. But it also tells us that if we use adult

efficacy data, we may underestimate the effectiveness of the therapy too and overestimate the adverse reactions. We also talked about the morbidity that comes out of the therapy being less in the children than in the adult population. So, using adult efficacy data to guide us could potentially mislead us in either direction. In this particular case, it could underestimate the efficacy, and that concerns me if we go this route totally.

DR. CHESNEY: Dr. Balistreri.

DR. BALISTRERI: I'm not sure that we have enough data to say that the child does respond better. I think a whole host of factors must be taken into account. Body mass. Even though we think we correct, I'm not sure we do.

Secondly, you have compliance issues. You have two people who are involved by definition. You have a parent. So, it's more likely the children are compliant with this regimen of injections.

So, I'm not sure that we have enough data to say that they respond better, but I think it's pretty clear they don't seem to be any worse in terms of the efficacy.

Now, the safety issue is a whole different set of questions that we'll need to discuss later. But I think that if we conscientiously apply this drug in the same fashion, the efficacy data that Karen and Lynn and all the

others have put together, I think we should feel fairly comfortable that the child is not going to respond in a worse fashion.

DR. CHESNEY: Dr. Fink.

DR. FINK: I think part of the solution to this is really looking at the role of the exposure/response studies. It may require either reanalysis of adult data or gathering of further adult data because it strikes me that if you took such combinations like PEG-interferon and ribavirin and you could expose a child to it for 4 weeks and, based on reduction in viral load, predict the good responders or the "cures," then you have changed the weight of risks and benefits dramatically.

It really strikes me if we need more adult data, the adult data we need is either reanalysis of the trials or new adult trials to say what in a 4- to 6-week time frame with exposure to this therapy predicts good response, and then can we use that in pediatrics to limit the toxicity, knowing from the adult data that the worst patients, in terms of toxicity, will also fall out in that 4- to 6-week period, and we don't have to expose large numbers of children to a year's treatment that may not be beneficial.

DR. SEEFF: I think that's an extremely important comment that you made. Maybe there are data here

already. Certainly at the NIH the study that we're discussing tomorrow I guess that's coming up is looking at viral resistance, and in the process of looking at viral resistance, we're also trying to find out at what point in time can you predict what the outcome will be subsequently and get it as close as possible to the time of initiation of treatment. So, that's being done.

But already there may be data. I don't know whether Karen has or the Roche people have data to show that. But I think that that's very important. The trouble is, unless it's already available, it still has to be gathered.

DR. LINDSAY: This is the data set that I was referring to before where, as we were saying, the individuals who ultimately develop an SVR tend to have a response early during treatment, just like you're saying. I think that it really is probably just going to require intensive reanalysis of existing databases. You have to see whether you'll get the answer.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I would also evaluate the question of efficacy trials in the context of the kinds of information you would need to collect. So, for example, to argue that the histopathology is similar would suggest to me that if you wanted to design an efficacy trial based on

a surrogate marker such as clearance of viral RNA, as opposed to maybe in an adult trial where you would do liver biopsies, you would choose not to do that in a pediatric trial because you have information that would allow you to infer similarity. So, I think it's not whether you do an efficacy trial or not, but certainly from someone analyzing these from an IRB perspective it's the risks of the interventions necessary to evaluate the efficacy. So, if you're talking about a blood test in a viral RNA, it's a much different -- if you want to do an efficacy trial, I'll feel a lot better about that than if you've got a couple liver biopsies tucked in there.

DR. SEEFF: The issue about a liver biopsy is a very complicated one. As you probably know, the NIH Consensus Conference required a liver biopsy. That was one of the bases for treating a patient. You had to show a certain amount of fibrosis in order to get in.

I can just tell you we are, as I mentioned, planning another consensus conference, and one of the issues up for discussion is the liver biopsy. Is the liver biopsy still absolutely essential? There are two major liver biopsies. One is the first one to get the patient in, and the other one is often the last one to decide whether you've really had an impact.

Most of us I think believe that the last one is

probably less important than the first one. I can tell you there are some people who feel that you don't have to do liver biopsies. There are many of us -- and I happen to be among those -- who believe the second thing, which is that they do require that.

It's more important I think in the adult. Again, it comes down to the philosophy. The reason why I say that is that if I have a fairly good database to suggest to me that a given patient has been infected for 30 years and I do a liver biopsy and I see minimal fibrosis, I believe that I can reconsider whether or not I need to treat that patient. That's not true for the pediatric population because we are very early on in the course of the disease and it becomes very difficult to do that.

I am very cognizant of the fact that one has to be very cautious about a liver biopsy. It's very safe but it does have occasional problems and one has to be cautious.

On the other hand, if you're going to do a study which is to study the progress of this disease, I guess the question is going to come down here of whether you're going to have a non-treated control group as well. If you have a non-treated control group, you need to know what the natural history is in the group that's not treated compared to the group that is treated, and that's where the

liver biopsy may become important. You may reach a point in time where you can say you don't need it anymore.

Now, the question I guess you're asking is, can you extrapolate this data from the adult to the children and say you don't need it because we've got all the information in adults? I don't know the answer to that. I guess it depends on how well children respond as compared to adults. So, I think it becomes difficult.

I think the liver biopsy is going to be rediscussed at this meeting and there are people, as I say, who have felt that it's not as important, and we're going to have to rethink the whole issue about whether this is mandatory. Up until now, it's been mandatory if we use the 1997 NIH Consensus Conference data.

DR. NELSON: I think one important difference is how a liver biopsy would be evaluated in an adult trial versus a pediatric trial. An initial biopsy for diagnostic purposes I don't think would be as much of an issue as a follow-up biopsy which wouldn't offer any benefit to that particular child. You can do a lot of things to adults for the sake of knowledge, which in pediatrics we're much more limited in whether we think that's ethical or appropriate. So, we would end up with differences there. If the adults decided it was unnecessary, then clearly that would settle the issue in pediatrics. But even if it was felt to be

important for the knowledge, it wouldn't settle the issue in pediatrics.

DR. CHESNEY: Dr. Hollinger.

DR. HOLLINGER: First of all, I would agree about the biopsy. I personally am one of the people who believe that a baseline biopsy is critical. I do not believe a follow-up biopsy is essential. I think there's a lot of data now in which is compared the sustained virologic responses, the liver enzyme abnormalities, and so on with biopsy to the point that it's fairly convincing that this is a fairly good predictive factor. I think the FDA has been wrong in requiring that as an endpoint anymore. I think they're way behind the times in doing so.

The other thing, too, I wanted to mention is that most the patients we see already are past the childhood time because, when we see a patient as an adult, they've already had their disease about 15 to 25 or 30 years already. They got it during the drug era often in the 1970s and maybe early 1980s. So, they're already like a child that's gone through 20 or 25 years. So, we've passed through that time period before we're making some decisions anyway.

DR. CHESNEY: I would just like to comment about Dr. Balistreri's comment about the efficacy in children is very unlikely to be worse than adults. And I

really liked Dr. Kauffman's comment that it might be better in children and that would modify the duration of therapy and the total dose of therapy if it turned out it was even more efficacious than in adults. And the concept of the on-treatment response. I feel like we probably shouldn't extrapolate adult efficacy data to children, that we should look at it in children.

Dr. Danford.

DR. DANFORD: Intimately involved in this question is whether or not there are going to be control groups and what kinds of control groups are there going to be. One question that I would have, based on the comments of the hepatologists earlier today, I think we need to ask whether there are going to be any takers for a control group. If you offer participation in a study that either does or doesn't get the treatment, is the fear of hepatitis C so strong in the community that you're going to get people running off to get their off-label treatment? Or can you even do a controlled study?

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: I'll be happy to tackle that one because we spent a great deal of time addressing that question. I think it's very important.

I think the consensus of a group of pediatric hepatologists that was a multi-national group was that

there definitely needs to be two therapies compared, one to the other. The real issue was the untreated observation group. And no one is going to give interferon/placebo therapy. Nobody is going to give subQ saline for a year. So, the real question was and I think the controversy was the observation group.

I'd like to hear Bill and Maureen, but I think the notion that seems to be coming more and more to the fore is that we probably do need an observation group within any trial, but that ultimately the observation group would be given the option of being given the most efficacious, safest therapy at some point along the way in the trial. Would you all agree with that? Otherwise, you're right. We won't get anybody to enroll in a trial.

DR. BALISTRERI: If you put it in the context of the IRB, obviously a placebo group is not appropriate if there is a standard therapy. We don't have a standard therapy. So, as Maureen talked about, we deliberated for all those years about what we should do. I think you summarized it well.

DR. JONAS: On the other hand, just to bring this up, if our primary outcome is the sustained virologic response, we're not talking about the biopsy now. We're talking about a year of treatment and six months later looking at sustained virologic response. You've already

heard a lot of people say people who aren't treated in the observation group are going to remain viremic. So, if we're not using histologic criteria, because we've decided for the reasons we've just talked about, and we're not going to get natural history data, because it's only a year and a half and we've already talked about that this is natural history in decades, I'm not really sure what we'd learn from that observation group. They may grow a little better and we may see those weight loss effects that I talked about. We already know interferon is going to do that.

I don't know what the right answer is here. I'm just bringing this up because we angst over this forever. But if we're using sustained virologic response as a primary outcome variable and we expect it to be 0 or close to 0 in the observation group, what have we done for those families and what have we done for science? I don't really know yet.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: Well, I was just looking for the numbers in this interferon monotherapy in children. This was an abstract that you mentioned, Maureen, and this was our group's effort to review the entire English literature on interferon monotherapy. In all of those 11 manuscripts, we only found 37 children who had been observed for a

certain period of time. So, the published data on spontaneous viral clearance in any pediatric cohort is extremely limited.

So, that is why it seems to me that we probably do need a bit more data on spontaneous rate of viral clearance and would argue for some scientifically observed control group for some period of time.

DR. CHESNEY: I think, Dr. Nelson, you were next.

DR. NELSON: I wonder, in the trials that have been conducted, how many parents, after listening to the risks and benefits, the drugs, the course of the disease, et cetera, decide not to enter the trial. In fact, in this case I assume they come in highly motivated, in this case change their mind after having listened.

And then the follow-up question would be -- and the statisticians will probably shake at this -- is whether or not one can choose something other than randomization as a way of selecting that observational group because often the randomization is what most individuals struggle over if they really want to get the intervention.

DR. JONAS: I'm trying to remember a parent who declined to participate because of listening to the side effects. We have a pretty rigorous IRB that makes you spell everything out two or three times very carefully.

But it is a motivated group that comes to seek treatment for hepatitis C. We're not looking at the homeless shelters and the things that Kathy was alluding to earlier. We're talking about kids referred to Children's Hospital, Boston for hepatitis C after they had leukemia therapy or after they had their congenital heart disease fixed. So, they are motivated. So, I cannot recall people saying they didn't want to participate because of side effects.

We had one or two that actually had liver biopsies that were so trivially involved that we decided to wait because there might be a long-acting interferon kind of thing, not because they didn't want therapy. They wanted a little better therapy and they'd wait for that. So, that wasn't a concern.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: If I remember some data correctly from this morning, somewhere between 10 and 15 percent of people enrolled in clinical trials with interferon withdrew secondary to adverse events. The placebo group would probably have a slightly lower incidence of those adverse events. I've often had the parents in my clinical trials say they hope they get randomized to the placebo arm.

It brings up the issue of when you go to study a disease, it often disappears. I remember Lyme's disease and being involved in a vaccine trial for Lyme's disease in

my practice. And suddenly this disease that was the number one question in my practice for two years became a non-issue. It's just amazing. As soon as there was a potential vaccine, boy, we're not nearly as worried about this.

I don't doubt that the people who have had leukemia or congenital heart disease who have been corrected or cured by the health care system are an incredibly selected group in the sense they've already bought the medical model and they believe you really do effective things because you've cured them. I suspect the groups that come in who haven't had their cardiac disease fixed or children now suffering from secondary disease from leukemia might not be as nearly as enthusiastic about participating in another clinical trial.

With the risk of a thunderbolt from Dr. Nelson at the other end of the hall, I still have a lot of difficulty with the Helsinki declarations of no placebos under any circumstances. Do I duck now?

(Laughter.)

DR. CHESNEY: No standard treatment.

Dr. Luban.

DR. LUBAN: I just wanted to make a comment about the observational group and suggest that perhaps it's more appropriate to not put an observational group within a

clinical trial, but rather to have some sort of an HCV registry. I don't know who would pay for it. In some way you could then perhaps get a little bit of a greater handle on the natural history for those families who, for whatever reason, still were in some part of the health care system but would not be appropriate for a randomized clinical trial.

DR. SEEFF: I'm aware of, obviously, the Helsinki report which says no placebo if we have a known effective form of treatment, which we don't have.

But the other thing is that this is such a protracted disease that if you had two groups, one that was treated for a year and one that was not, I don't think it's going to make a bit of difference to that untreated group over the course of that one year. If indeed in the treated group you see real effect, you can then put the people at the end of the first year onto treatment, and you really haven't seriously altered the outcome. So, this is not a disease that is rapid. It takes forever to reach its endpoint.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: We struggled with that issue. I think that the proponents of the observation group made two important points.

One was what we would learn in a larger number

of children than have been studied to date about spontaneous viral clearance because right now we have almost no good information.

And then the second is, if we're talking about some form of interferon and then some form of ribavirin, to look very carefully at the neuropsychological side effects and growth side effects. So, it may be that the observation group is more important for the assessment of toxicity or lack of toxicity than it is for liver disease.

DR. CHESNEY: Two excellent points.

Dr. Weiss, I think the consensus is that we can't extrapolate efficacy to children. So, do you want any more information from us on question 2?

DR. WEISS: Let's just go back to this again. I guess it may be somewhat of a catch 22. We're saying you can't extrapolate. And if everybody agrees that you can't because perhaps the responses, et cetera are better, then that speaks towards trials that are other than just PK and safety trials. So, what you've talked about doing is perhaps a delay in treatment, using some type of concurrent control, whether it's a registry or some other type of control population, perhaps delaying treatment for a year in those and then offering them treatment, which are designs that we've certainly seen and utilized before.

This may be a moot issue because oftentimes

when we're talking about extrapolation, it's when it's very difficult to do efficacy trials. What you're talking about looking at in terms of measuring response rates, sustained viral response, similar to what we do with the adult settings, you could get those types of information in a reasonably short trial. You could probably look at numbers that are not very huge numbers. That's part of the second set of bullets in question 2.

I guess the fundamental question about whether or not the course of disease is sufficiently similar to whether or not you can extrapolate is a fundamental question that we address that we have been looking at ever since the 1994 rule went into effect. But maybe for this disease, it's somewhat of a moot issue because you're going to be able to get your efficacy/activity data anyway in the course of controlled trials, whether using historical controls, a concurrent observational control, a registry control. I guess I just want to make sure we clarify that particular point because I think it is an important point with this disease.

DR. O'FALLON: Oh, please, let's not talk about historical controls. You've already spent the whole morning telling us how the face of the disease is changing over time. Historical controls are absolutely the wrong thing to use in this. We won't be able to interpret the

data when we get done.

DR. WEISS: But you're saying, though, in this disease very, very few spontaneous remissions, spontaneous resolution of the virus, occur. I agree. Historical control trials are problematic, but in certain settings where the course of disease is very well documented, certainly historical controls have been used.

DR. O'FALLON: But we're talking about the face of the disease changing from being the blood transfusion to the vertical transmission and nobody really knowing how similar or how different they really are. You're going to have to have concurrent controls of some variety or another. Dr. Nelson asked whether we could have the choose what they wanted to have. Well, that's just fraught with all kinds of problems, but it's still better than nothing.

DR. CHESNEY: Dr. Jay Siegel from the Center for Biologics.

DR. SIEGEL: I just want to clarify this difference. I feel funny being here as an advocate for historical controls, and I assure you I'm not. But I think to follow on Dr. Weiss' points, there's been a lot of discussion about what you want a control group for, and there's no question that a control group will get you a lot of information, and you may not know the spontaneous remission rate, and you may not be able to determine

effects on development and safety endpoints as sensitively if you don't have a concurrent randomized control group.

On the question of efficacy, if you take sustained virologic response as an endpoint of efficacy, and if you do a study and you get a 37 or 45 percent sustained virological response, I don't think there's anybody here who would say, well, you couldn't conclude from that that there's a drug effect on sustained virological response. There's no suspicion that the control group would have had that level spontaneously. I think that's what Dr. Weiss was saying so that one can in a crude sense from historical controls at least determine that there is an activity which we're equating with efficacy.

There are a lot of other questions like dose optimization, like sensitive detection of adverse events, like whether in a combination therapy both elements of the combination or one element -- that you may well argue for all sorts of designs other than a simple cohort study.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: Just to provide a little bit of a counterpoint, I agree with the comments that Dr. Weiss made. As I think about the purpose behind trying to extrapolate efficacy data, it's to try and allow us to introduce information into pediatric use that doesn't

require exposing children to unnecessary risks. So, if we are willing to construct an efficacy trial that's based on interventions that are of minimal risk, we're then debating something that I certainly wouldn't feel strongly about serving on an institutional review board.

But if efficacy was interpreted as requiring invasive testing in such a way, I'm not convinced that one couldn't infer from the adult data to at least avoid what would be considered invasive testing. The devil is in the details when you get actually down to those kinds of designs.

I agreed with what Ralph said, but not to the point where I would say let's design a classic adult efficacy trial and do three liver biopsies and whatever we can do to adults. I know that's an overstatement.

DR. CHESNEY: I agree. I don't think any of us were thinking to go back to the absolute bottom line initial therapy.

Dr. Hollinger.

DR. HOLLINGER: Well, I guess I would have to disagree that I think that you can't extrapolate the adult data to the pediatric data. I completely disagree with that. Monotherapy doesn't do as well as combination therapy. Genotype 1's don't do as well as genotypes 2's and 3's. High concentrations of virus don't do as well as

low concentrations of virus. I'm not sure what other extrapolation there is except that it seems like the sustained virologic response rate may be slightly higher, and there may be things, as mentioned before. I think, Bill, you mentioned some things about compliance or other things.

Can you tell me, just for my own information, what the relative concentrations would be based upon the -- I think, Dr. Jonas, you mentioned also about the dosing on a per meter squared basis. What would that represent in an adult? Instead of 3 million three times a week, what would that represent approximately?

DR. JONAS: It would be about 5.

DR. HOLLINGER: See, 5 million units. That was the other thing. The higher the concentration you give, the longer period of time you give it, the better response rates. So, that doesn't surprise me. These numbers would be comparable in what I might expect in an adult receiving 5 million units three times a week. So, I'm not sure what the issues are about extrapolation between adults and children. I think they're very comparable.

DR. CHESNEY: Go ahead.

DR. HUDAK: I'd just like to ask a couple questions to clarify things because I'm really a bit confused at this point. I sort of started the day having

read the materials here and being fairly persuaded about the efficacy in adult studies. I'm not exactly sure what we're trying to decide right now.

Clearly, there's been a lot of use of these agents in the pediatric population. You're doing studies in Boston. You're doing studies in Baltimore. Other people are doing studies. We're having all sorts of editorial comments about we think this therapy is more effective in children. What does that mean?

It seems to me that if you have appendicitis and you've got an 80 percent death rate if you don't operate, and you start operating and don't do a controlled study, and you find out that your death rate is 0, I think you're pretty safe in concluding that your operative intervention is very effective.

In this situation, I'm fairly persuaded that if you have a 6-year-old child who comes in who's got HCV and that child is going to have HCV the next year and the next year and the next year, I'm willing to grant you that with 98 percent confidence from what I hear.

Clearly, there have been children coming in for treatment who have been treated for some period of time, and people have been following this for some period of time and looking at responses. What is the information? Is this, in fact, effective in eliminating viral load in the

blood? Number one.

The other issue is in terms of the trial design. I think, rightly or wrongly, I sort of look at this from the point of view of if it were my 6-year-old child coming in who had HCV in the blood and I was going to try to make some decision about enrolling in a trial or what to do, I think there are some safety issues that have been brought up. I'm not knowledgeable about what all the issues are. I've heard a lot of things, but I'm not sure how severe they might be, what the incidence is. Clearly the spastic diplegia in an infant is a concern. I don't think that's operative at 6. But some of the long-term psychological issues would worry me.

So, I'm not sure at this point, having listened to everything that everyone has told me, that if my 6-year-old child was asymptomatic and was otherwise healthy, with incidental or indolent HCV in the blood -- I certainly I don't think would go ahead and choose willy-nilly to put the child on treatment. I think I'd be much more likely to go into a clinical study, which would be placebo controlled because, as a professional, I know that the risk of side effects is a real issue.

Certainly in my field, we've done a lot of things, most frequently treatment of babies with steroids for lung disease where everyone jumped the gun on this, did

it for 10 years, and now we're finding out that these kids have a much increased chance of having cerebral palsy, which wasn't found out until 10 years after the fact.

So, I guess I'm kind of unclear as to which direction we're going here. I think if there is evidence that there's efficacy, which I think there must be some, is a placebo-controlled trial looking at side effects appropriate? How long are you going to look for side effects to develop? Is it reasonable, if the placebo group shows no acute side effects but still has viral load, to cross them over to treatment only one year later? You may lose all the information you're going to get about the long-term side effects, and you don't know that treating at 6 as opposed to 12 is going to make any long-term difference in the issue you're facing. So, I'm really quite confused.

DR. CHESNEY: Yes, please clarify for us.

MR. FLEISCHER: No. Can I add to the confusion?

We've heard a lot today about sustained virologic response, eradication, cure. But I wonder if we could just talk a little bit about what the lower limit or undetectable viral load really means. We have a number of research-based assays that have various lower limits of quantification. Those have never really been validated.

We don't know what the lower limit of quantification is with certainty for a lot of these assays. We know with HIV that just having no measurable virus doesn't mean it's not there. In HIV we have lots of sanctuary sites, lymph nodes, CNS, which we don't have good drug penetration into and good ways of measuring. We don't know whether we have some sanctuary sites for this. We're only measuring so far serum HCV RNA. I know there has been some work, but I don't know very much about it, the work in looking at actually the viral load in the liver. So, I was wondering if the experts could talk a little bit about what it really means to have an "undetectable" viral load.

DR. SEEFF: To some extent, the proof is in the pudding, isn't it? If indeed 10 years later, if we use the current cutoff -- I guess the lowest level is what? Is it 50? All right, 10 copies. The fact is that if you follow these patients out using that as the endpoint, 10 years later and 12 years later and 13 years later, they still don't have detectable virus. It hasn't come up.

Now, it may be in the liver. I think we're beginning to find that with hepatitis B, by the way. Maybe we never recover from hepatitis B. Maybe there is hepatitis B in the liver even though we now even have antibody in the blood.

The fact is, though, what the effect of all of

this is. What is the outcome? Maybe 20 years from now it will change. I don't know, but certainly 10 years later, in those people who have responded by the criteria that we have used, they still don't have virus. Their enzymes are generally normal. They don't have any clinical manifestations, and their histology is better. So, I can't deny the possibility that there may still be residual virus that we can't measure, and what the effect of that will be over 50 years, no one really knows for sure.

We still have to accept the view -- and the proof is not yet fully in -- that treatment is going to reduce mortality. I think it makes sense, and at least there's some preliminary data that would suggest that. I guess we could do studies looking in the liver and see if the hepatitis C virus is still there in individuals in whom it's not in the blood. But after all, as I say, what we're trying to do is to make the patient who is infected feel better and remain better as best we're able to determine, which in liver disease is progression to fibrosis.

To me the whole essence of hepatitis C -- and I know again there's a little discrepancy in this view -- is progression to fibrosis. If we could cut out progression to fibrosis, we can use all these instruments and say, well, in retrospect I didn't feel so good for 25 years. Most of the time, people just don't feel very good for the

last 25 years.

(Laughter.)

DR. SEEFF: But they don't know about this until they're told that they have hepatitis C and they've had it for 25 years.

So, it's when they progress to fibrosis and ultimately to cirrhosis, their portal hypertension begins to develop, and then you run into trouble that you have an increased likelihood of development of cancer which in hepatitis C rarely occurs without significant fibrosis and/or cirrhosis or that they have hepatocellular failure. So, that's what we're trying to prevent, and if we can prevent that, I think we've done the best we possibly can.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: In my own simple logic, I'm going to try to summarize what I've heard. I think what I've heard is that this disease is really no different in children than it is in adults. It's probably the same virus. It's the same pathogenesis, probably produces the same end result if you give it enough time to do what it's supposed to do. So, I don't think basically the disease is very different.

What I've also heard is that when you intervene with X treatment, that there is a wide variation of responses, and if you use the serologic viral response as

your endpoint, some people will respond better than others. Well, that's true for many diseases. That's what prognostic factors are all about. So, you do get good responses in a good number of patients, and when you use these treatments in children, you get similar responses. You may get some better responses. There may be some pharmacokinetic differences. There may be some issues of genotype, et cetera that may explain why children may respond better. But I haven't heard that children respond worse.

So, the central issue then is not doubting the potential efficacy of the intervention, but how can that intervention be used in a safe way in children. So, the issue to me becomes then what studies do we do with the endpoints that we know about, not endpoints that we don't know about because we don't know whether these children 30 years later are going to get hepatocellular carcinoma and are going to die. But we do know that we can measure viral response. We know that maybe fibrosis is a good indicator too. Using those endpoints, how can we design trials to maintain that efficacy or improve on the efficacy and then try to answer the real question, which is the safety.

So, maybe we shouldn't be talking about randomized studies with placebo controls or observation groups. Maybe we should be looking at studies that look at

different dosing regimens or different exposure regimens because ultimately to me that's what would convince me that the therapy then is both efficacious and safe and not just efficacious with a lot of safety issues.

That's my summary.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: I think I may have heard the information this morning slightly differently. I think I heard that the best prognostic factor you could have when you develop hepatitis C is being a child. 20 percent of adults 20 years later have cirrhosis, and less than 1 percent of children have cirrhosis. So, when you were talking about prognostic factors, the best prognostic factor that I heard presented was to develop this disease while you're an infant.

I'm sure that it's the same disease virally and in eventual outcome, but the slope of the progression of that disease seems to be remarkably different in children. You can bring in other extraneous factors such as alcohol consumption that adults have that children don't, but they're not extraneous. The progression of the disease is slower in children. So, I think it's the same disease but the confounders have been eliminated and it doesn't progress as rapidly and doesn't seem to be as severe as it

is in most adults.

DR. SANTANA: I'm not sure. I'm beginning to think that this is a new disease of kids that happened in the last 20 years where it's been a disease in adults probably for the last 40 or 50 years. It wasn't until we had these "epidemics" in the 1980s and 1990s that it became a pediatric disease in terms of children who were exposed perinatally -- period -- because how else would kids get exposed? It's bloodborne. Or unless it was through transfusion. So, we have two groups of patients. We have the patients that are now entering their 20's and 30's that we cured from other diseases who now have hepatitis C or we have the kids who are getting it perinatally. Perinatally is a new disease. It only has occurred in the last 20 or 25 years.

DR. GORMAN: But with any new disease, the most serious cases percolate to the attention of medical providers first. So, you would assume that in our particular epidemic -- I agree with you it's new in the sense of the incidence, but we should be seeing the more severe cases first. They should have percolated to the top, and that doesn't appear to be the case. It seems like we're getting milder disease even though it's more common.

DR. CHESNEY: Dr. Weiss, I'm almost embarrassed to ask this because it will demonstrate my ignorance, but I

do that all the time anyway, so I don't know why I'm worried.

(Laughter.)

DR. CHESNEY: But I interpreted this as that if we were going to look at efficacy in children, it would take much larger groups of children, that if we just extrapolated efficacy from adults to children, that then we could just focus on the side effects and the PK/PD parameters.

DR. WEISS: It may be just semantics because in a lot of settings, you measure efficacy endpoints. There are a lot of times, because of the smaller numbers of children affected, where the trials that are done -- and my colleagues in CDER, maybe Dianne, could speak with respect to all those written requests that have been issued over the last couple of years with those hundreds of different written requests and several hundred studies that have been asked for, and many of them have come in. There's been sometimes some confusion because they have to, for their tracking purposes, identify which trials are efficacy trials, which trials are activity trials.

Sometimes you might consider an efficacy trial -- if you consider it the same way you might do it for adults for the first approval, those trials probably wouldn't meet that criteria. But, nevertheless, they do

show response rates or whatever it is that's the important aspect of the disease that you're measuring. Some of them are controlled. Some of them look at the response rates in light of what's been documented from the adults. So, sometimes it maybe gets to be semantics as to what you want to call it.

DR. MURPHY: What Karen has identified I think and what you're struggling with is what we're all struggling with, which is it's not just semantics, but it really gets to are we willing to extrapolate completely or partially. That's sort of a terrible thing to say because the way that the 1994 rule is, it's sufficiently similar.

We have a category that we've put in your questions as exposure/response. I'm going to shorten that to PK/PD, even though it may not always be appropriate. Because we have felt that there are situations in which you think the disease and the response are sufficiently similar that you can extrapolate the efficacy, but you wished a test of hypothesis, if you will. But it's the same endpoints. It's the same viral loads. Again, it's a test of a hypothesis that you can extrapolate. The numbers are small, so you can't really call them efficacy trials.

About 10 percent of our written requests now are in that category where we think we can extrapolate, but we want to have this test of hypothesis in addition to dose

finding and safety because the safety issues are clearly different.

So, that is what we were trying to get at with the question. If you think that you can extrapolate, how would one design this test of hypothesis if you're not sure, in addition to what safety studies do we need. I think that's the shortest way to put it.

DR. WEISS: You could almost consider it a little bit of a Bayesian approach. Your priors are going to be high because you already have adult data and you know that there is a fair number of similarities. Given the fact that you have these priors, what additional kinds of data would it take? It's probably not going to take the same large numbers and possibly not the same kinds of controls because you have those priors already.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: Sort of drawing on what Bob Fink talked about earlier on, if you really wanted to look, say, at dose ranging and PK/PD, what you'd want is an early marker and having, say, three dose-ranging groups. At 6 weeks, you look at your decrease in viral titers, and you say, this group is clearly better than that group. You may want to continue that from a safety point of view because you may want to work it out another 12 weeks and see if, indeed, some of the lower doses caught up efficacy-wise.

I'm still concerned, even though we talked about some of the older patients having various behavioral problems and suicide problems, we have clear evidence of neurologic damage in the little ones. So, if you have it in the real little ones and you've got it in the older ones, my guess is you've got it in the middle ones too. I don't think we've looked in a structured way at cognitive function and behavioral outcomes and CNS toxicities. Since we know nothing about the mechanisms of the CNS toxicity, I think we're going to have to look very, very carefully.

But doing interim analyses, we really don't have to have an 18-month study and then start another 18-month study at another dose if, in fact, the data in the sequential manner allows us to begin with three or four strata and then drop a stratum very quickly because it's not doing anything. Now we're down maybe to two strata, but we want to continue those two strata out another 12 weeks, see where they are, follow safety during that period of time so that we're getting now more and more about risk/benefit. We can do that if, in fact, there are enough adult data to suggest what the time points will be.

That's probably the quickest way of getting at the kinds of PK/PD. We talked about this in ICH E-11 as well, of bridging data between the adult data and the pediatric data that increase your confidence that, in fact,

you're getting the same kinds of outcomes that you saw in the adults.

DR. CHESNEY: Skip.

DR. NELSON: I think one of the big challenges would be to establish some of that neuropsychiatric toxicity which would likely require long-term studies and likely large scale studies. So, my question is whether there could be a registry approach of some kind. All the pharmacies I know inform all the pharmaceutical companies when I write a prescription for X. So, why couldn't we begin to harness some of these databases in a positive fashion rather than just a marketing fashion to begin to try and generate that kind of data? Would that be received well? You know, not holding up approval in marketing but having some way that, 20 years down the line, we'll know if there has been some subtle neuropsychiatric problems when kids hit 7th through 12th grade, having got this as a 2-year-old.

DR. SPIELBERG: Absolutely. I think it will be probably a combination of the two, intensive examination of the kids during the course of a year trial and at their 18-month follow-up with intense investigation of cognitive function and behavioral testing and attention span. There are a number of paradigms for doing this that have come primarily from the anticonvulsant literature of looking at

cognitive and development effects of anticonvulsants.

But then for the long-term kinds of things, absolutely. I think those kinds of longitudinal, long-term sorts of examinations are exactly the kinds of things we're going to have to look at in this and other diseases.

DR. CHESNEY: Dr. Weiss.

DR. WEISS: That was very helpful. I just want to point out that that is actually question 4, so if and when we ever get to that.

Actually when we started these discussions at 1 o'clock, I thought we'd have tons of time and be twiddling our thumbs with all this free time. So, I'm actually pleased that there's lots of controversy and discussions, but in an attempt just to try to get through at least questions 3 and 4 -- we touched a little bit on 4. 3 hopefully may be more straightforward.

What I'd like to maybe propose or ask if this is okay to do, we've heard a lot about the issues of the need for a control group, and it's ranged from maybe you don't need a concurrent randomized control to dose-ranging types of controls to placebo controls to observational controls. I guess I take away from that there isn't really one right answer. There are perhaps advantages and disadvantages to a number of these different options. That's helpful, I think, as we think about the advice,

which again we could probably debate all day long.

But one of the points on question 2 that I would actually just want to make sure that I personally get the information about is the third-to-the-last bullet on that first page, which is the identification of those children whose HCV infection should be treated and therefore could reasonably be included in a clinical trial. I know our experts have already discussed some of that. I would just like to maybe be able to have a little bit clearer criteria of what you would be considering in your exclusion and inclusion criteria for putting children in trials.

DR. CHESNEY: Dr. Jonas.

DR. JONAS: I'll give my opinion for discussion. As I sat here and listened to everybody, I was scribbling it down myself. I think we're pretty much agreed that maybe at this point we're not prepared to just say the diagnosis of hepatitis C infection, virus in the blood at one point. It's probably not enough.

Then we've talked a little bit about the definition of chronicity. We want to have chronic hepatitis C infection. You've heard Dr. Lindsay's several definitions of that, but at least I think we want to be sure we're not treating anybody who's very, very early in infection who may clear the infection on his or her own.

So, I propose we can have some sort of definition, maybe nobody under age 2 or 3 and then have defined infection, viremic at least 6 months, two separate points in the preceding period. So, infection, then chronic infection, and then chronic infection with liver disease. So, do we want to avoid treating children with no liver disease from this hepatitis C?

This doesn't come up very often in my experience, but I suppose a cogent argument could be made, a liver biopsy at that point and have to meet certain criteria for chronic hepatitis on liver biopsy. So, infection, then chronic infection, then chronic infection with liver disease with maybe a cutoff age of 2 or 3 or something like that is what I'm taking away from all this to distill it out.

I think it gets a little hairier if you start saying a certain level of liver disease for the reasons we've discussed.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I'd like to add to your inclusion list people who have an increased risk of liver disease for other etiologies. Dr. Luban talked about frequent transfusers, children who are receiving multiple transfusions. Comorbid viral infections such as hepatitis B might also be reasons to include people in studies

earlier.

DR. JONAS: Actually we usually use those for exclusion criteria.

(Laughter.)

DR. JONAS: You're sort of defining our list of exclusion criteria there.

DR. GORMAN: Knowing the desire for clean data by the industry and the FDA, I can understand those being used for exclusion criteria. However, we have difficulty treating basically healthy children otherwise. Even liver disease, depending on how you define it, may be perceived as basically healthy children. If you're talking about a minor elevation of the AST or the ALT or GGT, or whatever liver enzyme you wish to say, if you're going to talk about phase 2 cirrhosis or fibrosis without bridging, I think people will get a little antsy about that as a diseased child.

DR. JONAS: Just note that I didn't say anything about transaminases.

DR. GORMAN: I noticed.

But people who have other risk factors for progression of their hepatic disease I would consider even if the agency and the pharmaceutical industry would be less than enthusiastic about those.

DR. CHESNEY: Dr. Fink.

DR. FINK: I don't disagree with anything that was said, but I would probably add to that that I would look at least a two-tiered approach saying 12 and above first. Even for antibiotics and many other drugs that are less toxic, we look at 12 and above first and then we look at 6 to 12. In this disease where I haven't heard any real compelling argument that waiting to look at 12 and above first would impair the 6- to 12-year-olds, I would think it would just be the wise thing to stick to 12 and above first and then, as a second tier, look at the 6- to 12-year-old age group particularly since there are neurologic toxicities that are of concern.

DR. JONAS: Can I just make a comment to that? I just want to remind you that interferon is approved for chronic hepatitis B in children down to the age of 1, and it's double the dose.

DR. SCHWARZ: 2.

DR. JONAS: The studies were done to the age of 1. It says 1 on the label, and the dose is double of what we're discussing here, and it's a 6-month course of therapy, just so you know.

DR. CHESNEY: Are there other issues on question 2 you want us to -- shall we go through all the bullets?

DR. W[illegible]SS: I was just looking at the clock and

the fact that we want to try to finish up within the next hour. That's fine. We can go through the bullets and make sure that we've covered them. A lot of them we somewhat covered in the discussions, but it would probably be helpful to go through them, and if there is no more discussion, that would be fine.

DR. CHESNEY: In addition, should it be determined that extrapolation may be appropriate, comment on the following. The first one, the identification of subgroups whose disease may be sufficiently different that extrapolation would not be appropriate.

DR. SANTANA: I think the only group that I can think of would be the transfusion patients because they have so much other comorbidity that potentially they could be different both in terms of their efficacy and safety. So, rather than including them, I would probably do it as a separate stratum or something. I don't know. Some study design. But I think those may be sufficiently different clinically that they should be treated in my view, but they should be separate from the others in terms of the analysis of the endpoints.

DR. CHESNEY: That's a good point.

What other groups do you exclude, Dr. Jonas?

DR. JONAS: Typically we exclude other viral infections, HIV infection, hepatitis B co-infection. We

certainly look for other causes of chronic liver disease in patients with chronic hepatitis. So, we look for Wilson's disease and alpha-1-antitrypsin deficiency. We look for autoimmune hepatitis because there is a danger if we misdiagnose someone, just as in adults with autoimmune hepatitis, as having hepatitis C because they have a positive test and if we use interferon, we may worsen their condition. We exclude people who have other autoimmune diseases that might be worse, and then anyone who has an obvious contraindication such as pre-existing serious depression, substance abuse, unwillingness to use birth control. We talked about that before. So, we have to do pregnancy monitoring monthly and a birth control questionnaire.

DR. SCHWARZ: Active malignancy. Hemophilia is probably different biologically. It's certainly different when it comes to the liver biopsy. And then some young age of exclusion.

DR. JONAS: Decompensated liver disease was the other big one. If anyone is very ill, starting to have a lower albumin or prolonged prothrombin time or has had bleeding varices or jaundice or anything. So, anyone who has very advanced liver disease. They respond very differently and they're at much greater risk with these therapies.

DR. CHESNEY: Yes.

DR. O'FALLON: I interpreted that question a little differently when I saw it. I thought which children are not like the adults. And there were the vertical transmission. That's obvious. And then to a great extent the cancer survivors, all those pediatric cancer survivors who are now young people who are at high risk. So, I just wonder if you can truly extrapolate from the adults to those groups. They might have a different variety.

DR. CHESNEY: I think Dr. Schwarz did mention active malignant disease, not cured though.

DR. SCHWARZ: Right.

And then of course, if we're talking about extrapolation from adult efficacy data and if the existing data suggests that young children might have a better response, then I think that the age should be open for discussion. I personally think it's wrong to look at a cohort of young children with a low viral load and pre-cirrhotic liver disease and a short duration of disease and then extrapolate from the adult experience to them. I don't think that's correct.

DR. CHESNEY: Dr. Luban.

DR. LUBAN: I'd just like to add that there will be and is ongoing data collection on hemophilia and hepatitis C from any number of different studies. So,

you'll have a subgroup to compare to another subgroup.

DR. WEISS: What I'm taking away from this too is that there are a number of different groups, if you're going to treat and you've defined your parameters to treat, many of them appropriate to treat. But like most analyses that are done, you would look at certain important subgroups after the fact. If you're doing a randomized controlled trial, you might want to stratify, but if you're not doing that, if you're doing a single-arm type of trial, it's probably less important for stratification, but you certainly want to be able to define up front those subgroups and be able to look at them afterwards and determine whether or not you can come up with some types of conclusions regarding their responses or similarities or not. Does that make sense?

DR. CHESNEY: Study designs that may provide for the optimal collection of safety, pharmacokinetic, and activity data.

DR. SPIELBERG: Again, I'd need to really see what the chronicity data looked like in the adults because if you want to set up things in a relatively clean population to get an idea of dose-ranging, you want the shortest-term study you can do, if you will, a phase I. It's not really a phase I study, but basically it's a PK/PD viral clearing study to get an idea of dose-ranging.

The one thing we've learned from this whole FDAMA experience is in some of the younger kids, the clearance of their drugs may be even vastly greater on a milligram per kilogram basis, and we may in fact be underdosing drugs such as ribavirin. I have no idea how that applies to biologics. I don't think we have any real data on clearance of biologics in the middle age toddler population who just chews up small molecular entities at two to three times the rate of many of the older kids.

But we need those data first, and I hope we would be able to do that kind of an initial study in a relatively short study looking at a relatively short endpoint so that at least when we start the longer-term studies, we're in better shape dose-wise.

We'll only get acute safety out of that. We already have acute safety because of the exposures we have.

Then the idea is designing the longer-term study for safety, having recognized already that we've begun optimizing the doses in those populations.

But we are going to have to be careful. Again, around the time of puberty, we know again there are going to be fairly significant pharmacokinetic shifts for many drugs. I have no idea how that applies to a drug like ribavirin, but we've got to establish that. Otherwise, again, we're going to be doing what we laughed at our

internists friends for doing, treating a ballerina and a sumo wrestler with the same dose of drug.

DR. CHESNEY: Skip.

DR. NELSON: Just to be clear, Steve, you'd do that as a population pharmacokinetic and with adjustments so that everyone in the trial would hopefully over a reasonable period of time end up on an optimum dose so you could see it as a therapeutic trial at the same time?

DR. SPIELBERG: You could actually do it in that way so that you would fold your initial dose-ranging, if you had rapid enough feedback, which sometimes doesn't happen because of the amount of time it takes to get the levels back and everything else. But if you did have a rapid enough feedback -- and maybe that could be built in -- you would start off again with several different strata, following the viral titers, and then fold the patients into the longer-term observational study once you had determined the dosing.

But also don't forget you're also going to need different endpoints for cognitive effects in different kids. So, it gets very difficult. You're not going to have 2-year-olds read Shakespeare back to you, and the kinds of attention span issues and the kinds of assays that you're going to be using for looking at CNS effects are going to also have to be age-stratified. So, it gets a

little complicated around the edges, but it can be done.

DR. NELSON: I only ask because I think designing trials that favor the possibility of benefit for an individual participant I think is always a good thing and having that kind of population approach with an ability to adjust dose for the individual as opposed to the "you're in this cohort for the next 3 months, come hell or high water" approach.

DR. SPIELBERG: Yes. Again, remember, we don't have something where, if you're not at the right dose in the first 2 days, you die. This isn't a meningitis trial. This is a long-term kind of thing so that we're in a very different kind of situation in terms of dose-finding, and individuals can dose-find into the right range. That's actually maybe a nice design for this.

DR. WEISS: The biologics are a little bit tricky in terms of pharmacokinetics. It might be a little bit clearer with the ribavirin or other compounds coming down the pike, but traditionally with a lot of our biologicals, especially if we're talking about a pegylated molecule, the paradigms may be a little bit more difficult in terms of trying to determine optimal dose response/exposure.

MR. FLEISCHER: I'll just tell you that basically was the design of the first Rebetron study:

three doses, then rollover into the one at 4 weeks based on antiviral response and actually hemoglobin response for the ribavirin patients.

DR. CHESNEY: I sense that we need to start thinking seriously about taking a break. Shall we discuss the choice of control groups before the break and then come back to tackle the other three questions?

DR. WEISS: I think we already did choice of control. We beat that horse into the ground. Hopefully it will be brief before we break. Maybe we could talk about what are appropriate endpoints, particularly liver biopsy. A number of people have talked about the role of liver biopsy. It's controversial in adults as well, but more so in children. I don't think anybody probably has an issue with looking at other types of -- the HCV RNA assays perhaps, but maybe we could just focus on liver biopsy as a measurement.

DR. LINDSAY: It would seem, given all the concerns that we all have about long-term effects of the disease, long-term natural history of the disease, that a baseline liver biopsy is important in terms of the design. But I think it would be extremely reasonable to extrapolate the adult data on histologic effects of a sustained virologic response to the pediatric population, and instead of doing liver biopsies as an endpoint of efficacy in the

short run, enroll these SVR pediatric patients into long-term follow-up studies where the liver biopsy would be planned for year 5 or some distant point just to demonstrate that the histologic benefit is there.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: I'd just like to second that because, as Maureen said, the histologic changes in children, even those referred to a referral center, are fairly minimal. So, I think we're just not likely to see a change 12 months down the road. So, for both the safety and the lack of utility of the liver biopsy, I would agree we shouldn't do it as a short-term endpoint.

I might also share our disappointing experience in trying to come up with a serum marker of liver fibrosis as a surrogate endpoint for liver disease in hepatitis C. We looked at plasma transforming growth factor beta and serum procollagen peptide 3. And there were data in adults with hepatitis C that these were useful noninvasive markers of liver fibrosis. What we found out was that the growing normal child has so much TGF-beta and so much procollagen peptide 3 that until we got to the 15-year-old with hepatitis C, we couldn't tell a difference between our hepatitis C-infected children and the controls.

DR. CHESNEY: Thank you. I was wondering if there wasn't some kind of collagen marker that could be

followed.

Dr. Danford.

DR. DANFORD: Am I to conclude that because nobody has mentioned them, that MRI or other imaging modalities that are noninvasive are not useful in this setting?

DR. SCHWARZ: Yes.

DR. NELSON: Will that always be true, or do you think the imaging could improve to where it might become useful? Is there anybody working to extend the envelope in that direction? Because it would certainly be helpful.

DR. SCHWARZ: It would be wonderful, but I think that with those few exceptions of the young children with severe liver disease in whom the imaging techniques are useful, that the differences are just too subtle.

DR. CHESNEY: Let's take a break and plan to be back at 25 after 3:00 to tackle our last three questions.

(Recess.)

DR. CHESNEY: I guess we can go ahead and get started with question 3. I particularly wanted to thank all of you who are still so incredibly energized. I think I need to go and have my hepatitis C test done to see why I've been tired for all my life.

(Laughter.)

DR. CHESNEY: Question number 3. The marketed treatments for hepatitis C infection in adults include polyethylene glycol conjugated to interferon, various non-PEG interferons, and combination therapy consisting of Intron A, interferon A, and ribavirin. The data to support an indication for PEG-interferon plus ribavirin in adults have recently been submitted to the agency; preliminary results suggest marginally higher response rates, but possibly more safety concerns such as more severe neuropsychiatric events, bone marrow suppression, thyroid disorders, and cardiovascular events.

No products are currently approved for the treatment of hepatitis C infection in children. Studies with the interferon A/ribavirin combination are underway. Interim pharmacokinetic and safety data have recently been submitted to the agency. The interferon manufacturers are interested in studying the combination of PEG-interferon and ribavirin but not PEG-interferon alone in children.

Two questions. First of all, are additional studies of interferon-based therapies in pediatric patients warranted at this time? And I interpret that to be interferon alone or interferon plus ribavirin. If the answer is yes, then should only combination therapy be studied or is it appropriate to also evaluate PEG-interferon monotherapy in pediatric patients?

So, the first question, are additional studies of interferon-based therapies in children warranted at this time? Dr. Nelson.

DR. NELSON: Can one infer that the increased safety concerns are from the PEG-interferon, and if so, is there any evidence of dose response in terms of those safety issues?

DR. WEISS: We have marketed PEG-interferon monotherapy. It's the first approval that came along, and that was I think in January of this year, just a few months ago. In that study, there were three dose arms. There was definitely a dose response with respect to toxicity of the PEG-interferon. If that was your question.

DR. NELSON: Most of the toxicities we're worried about are in the long-term issues, neuropsychiatric and the like. So, to pick something that has a higher rate of those when we don't have good ways of studying them just strikes me as risky.

Then I was trying to ask myself, well, under what circumstances would I do that? And that's if maybe I could get away with a lower dose that would not have those safety issues and maintain efficacy and perhaps have other tradeoffs that would make it worthwhile. So, I was trying to wrap my mind around that question.

DR. WEISS: Actually in the controlled trials

that led to the approval of PEG-interferon monotherapy, it was a head-to-head comparison of three different doses of PEG-interferon versus Intron A. So, it wasn't really a comparison to Rebetron, which is interferon plus ribavirin, which is probably a more important question because most people do not use Intron A monotherapy. Response rates were probably about doubled when using the PEG-interferon, especially the two higher doses of PEG-interferon, but the toxicities were also somewhat higher.

A lot of this is theoretical because there isn't a large, large database with PEG-interferon right now, but given the longer half-life, the longer that these levels last, there's certainly a concern about toxicities, the fact that a main way to treat toxicities of interferon are to either dose reduce or take drug holidays if something lasts for quite a long period of time. It may be that the actual toxicities themselves are not different, but they last longer and so they may be harder to treat. So, those are the kinds of concerns.

A lot of this is theoretical, and in a sense it may not be a terribly fair question to ask this committee because we don't have the data analyzed thus far in adults on PEG-interferon plus ribavirin. It's a little bit premature. And we don't have the full data set in pediatric patients being treated with Rebetron yet to ask

that particular question. So, realizing that it may be somewhat of a difficult question to ask, given the database that we have right now, nevertheless we decided to ask it.

DR. CHESNEY: Three hands went up instantly over here.

(Laughter.)

DR. CHESNEY: I'm not sure who was first, but let me start with Dr. Schwarz who's our guest.

DR. SCHWARZ: Addressing the question as to whether additional studies of interferon-based therapies in pediatric patients are warranted, I'd like to respond to both Dr. Nelson and something Dr. Spielberg said having to do with both the safety and the way the safety is measured. I want to address particularly the neuropsychiatric side effects because I think that's something we're all concerned about.

I believe that if we're going to treat hepatitis C in children, we have to use interferon-based therapies because all the therapies to date have some interferon basis.

The neuropsychiatric side effects may be quite different in newborns, growing children, and adults. I did want to comment on this spastic diplegia business because it is very frightening. The spastic diplegia that was observed was in newborns treated for cavernous hemangioma.

I believe it was 1 million units of alpha interferon subQ daily for 4 to 6 months. That is I think probably biologically quite different than using interferon in older children. So, none of us want to get into that in newborns with hepatitis C.

But very cautiously studying the cognitive, neuropsychiatric endpoints of the use of interferon in growing children and interferon plus/minus ribavirin has not been done. We're not going to know anything more about it with the Rebetron trial because that's combination. It's not a controlled trial. And it may also be quite different than the neuropsychiatric effects of interferon in adults which are primarily depression.

So, I personally think we really have a responsibility to look very carefully at these cognitive endpoints with validated testing instruments in the young population.

DR. CHESNEY: With interferon alone.

DR. SCHWARZ: And with different doses.

Well, my bias is that there should be interferon plus placebo, interferon plus ribavirin, and then some observation group, again primarily so we can compare neuropsychiatric endpoints at least during, let's say, a year of therapy before a crossover.

DR. CHESNEY: Great, very helpful.

Dr. Spielberg.

DR. SPIELBERG: Karen, what do we know about pegylated proteins in kids? I know there are some products out there that are a replacement in various enzymopathies where there are pegylated versions. Do you get similar increased durations of exposure? Do we have any way of guesstimating before we actually start putting such a pegylated compound into, say, a 2-year-old, whether once-a-week therapy is going to be adequate or whether we're going to need twice-a-week therapy? Is there any basis at this point for us to make any judgments?

DR. WEISS: In terms of pediatric patients, relative to the adult experience, I don't know if there is. There is experience with other PEG proteins, PEG-ADA for instance, approved on the basis of, I think, 10 or 6 children. It was one of the smallest clinical trials ever that led to approval. PEG-asparaginase, which is now used in the oncology setting, primarily in children with ALL that have hypersensitivity to native asparaginase.

But I certainly can't, off the cuff, tell you that we have enough priors already with our experience with PEG to know. Victor, you've probably have had more experience in dealing with the PEG-asparigenases maybe. But even that's a different molecule, and there we're talking about the antibodies that affect the clearance of

the half-life of the molecule. It's probably a little bit different.

But even so, even in interferons, there is an issue of neutralizing antibody developing with the native interferons. Thus far we don't have any evidence that that impacts on efficacy responses, and pegylation is supposed to actually minimize that.

DR. SPIELBERG: So, we are breaking new ground then. Clearly, in terms of understanding PK, we're going to really need to look at it very carefully.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: Is one of the mechanisms of action of interferon, in terms of its toxicity, considered the interruption of angiogenesis? And if so, do we have any evidence that that is going to cause irreversible deficits in the brain? Spastic is clearly one, but my concern would be during the development. At different phases there may be very critical times during childhood where brain blood vessel growth might be fairly important.

I was surprised. I'm often surprised because, unlike Dr. Chesney, my areas of ignorance are immense.

(Laughter.)

DR. GORMAN: I was surprised to hear that interferon had already been approved for hepatitis B. So, we have data now that we are interfering with the cognitive

development of an entire group of children?

DR. JONAS: I don't know that anyone has looked at the angiogenesis part outside of antitumor therapy and experimental models in animals. I'm sorry. I just don't know anything about it.

DR. GORMAN: But it seems to me the reason we try it on cavernous hemangiomas is --

DR. JONAS: Oh, yes, it is an anti-angiogenic substance. Yes, for sure.

DR. GORMAN: And with the doses that are lower than we're treating hepatitis B but still substantial -- pharmacologically active I think might be an appropriate word -- we may be interrupting the blood vessel development in the brain.

DR. CHESNEY: Well, that's that.

Dr. Lindsay.

DR. LINDSAY: I just wanted to comment a little bit on the frequency of reporting of neuropsychiatric events in the PEG-interferon versus standard interferon trials. As I mentioned this morning, I think that the instruments that we use to measure, quantitate, understand, define these events are very crude, and we're just now doing the first full extensive cognitive testing on patients receiving interferon. I think it's the first extensive study that's being done in adults.

But when you look at the frequency of reporting symptoms in the instruments that were used, in one of the studies, both depression and impaired concentration -- impaired concentration is a very common complaint of patients -- were numerically higher in the standard interferon recipients and lower in the PEG-interferon groups, but not statistically different. The frequency of irritability and insomnia were not statistically different comparing standard to pegylated interferon. So, at least in adults, numerically there's no statistical difference.

What's interesting I think -- many of us think -- because of the sustained, relatively constant levels of alpha interferon in the pegylated interferon product therapy, the patients don't have what they describe as a constant up and down kind of difficulty with thinking and sleeping and irritability and so forth. So, it may actually be that when we do these formalized cognitive evaluations, there will be a difference in favor of the pegylated compounds. We'll have to see what we find.

DR. CHESNEY: I'm getting very uncomfortable with interferons. What do we know about interferons in infants? I was already to go with it, but now that I hear about angiogenesis and subtle cognitive things that children aren't going to tell you, or you really have to go looking for them. What do we actually know about

interferons and neuropsychiatric side effects in children?

DR. WEISS: We do not have a lot of experience with neuropsychiatric adverse events. I'm not sure how good our assessment tools are for them. I think that's a big question mark, and I think that's something that needs to be kept in mind when you consider potential benefits and potential risks of these therapies. It may be harder to identify subtle changes in certain age ranges. You have the confounding factor of adolescence, for instance, where there could be behavioral changes and other events happening. Those are just all things that have to be taken into consideration.

DR. SPIELBERG: Karen, following up on what Skip had asked a few moments ago, is there a registry set up for the hepatitis B indication and do we know how many kids have been treated for hepatitis B at this point?

DR. WEISS: We did not ask, as I recall, for a phase IV commitment for a registry. The actual trial itself was an observational controlled trial, children ranging in age, I believe, from 1 up to 18. There were approximately 150 children randomized, 70 to treatment and 70 with observation. It was a 6-month dosing and then a follow-up period of an additional 6 months. We did not ask at that time -- and that was perhaps an oversight -- for specific long-term follow-up with respect to the

neuropsychiatric or developmental types of issues. There were very, very few children at the younger age range, as I recall, in that trial.

The big factor that we were looking at was sustained response rates. From my discussions way back when with some of the pediatric gastroenterologists, I think everybody was very interested in treating and having things available on the label for hepatitis B. It was hepatitis C that was more of a question mark about whether or not treatment was actually indicated.

DR. CHESNEY: Dr. Luban.

DR. LUBAN: I don't know, Karen, if this will help you or not, but I believe Dr. Folkman at Boston Children's does have a registry of the hemangioma interferon-treated infants and perhaps some data can be abstracted from that.

DR. WEISS: This is jumping ahead to question 4, but I think it's clear from the discussions thus far that we're going to need, no matter what we do, to follow up children for long periods of time and to discuss what kinds of sensitive tools should be used to evaluate them. My colleagues in the Center for Drugs can mention probably what's being done or is going to be considered perhaps for the Rebetron trial. But that's an important question that I hope we get to today.

DR. CHESNEY: Dr. Fink.

DR. FINK: Two comments. One, I think again as we look at the young infant, as we look at the PEG-ribavirin combination, we also have to keep in mind that besides the ribavirin toxicity, you're dealing with immunomodulatory drugs in a group, at least if you go below age 6 where the immune system is really maturing. To say that we can safely extrapolate adult data on ribavirin to the under 6-year-old I think is extraordinarily dangerous with systemic ribavirin because its use as an aerosol in RSV infection showed immunomodulatory effects when it was only aerosolized, not systemically administered. So, if we go to the young child with this without any clear-cut way of studying it, I think we're just asking for trouble.

On the registry end of things, the one comment I would like to make is I think registries are great. They teach you things in retrospect, but in today's environment I'm not sure I see what the utility of a registry is that goes beyond maybe 5 or 10 years of data collection in that it's hard for me to imagine, in the rapid evolution of treatments we have today, that PEG-interferon/ribavirin will be the treatment of choice of hepatitis C in 5 or 6 years. So, I have a feeling these registries are going to tell us the long-term consequences of therapies we no longer use. They're probably not going to contribute much

data to current therapy.

DR. CHESNEY: Dr. Jonas, am I right that you've already entered some patients into the Rebetron study? Is that correct? And did you have anxieties about interferon and angiogenesis?

DR. JONAS: The angiogenesis part, actually no, because these are short-term and we treated for hepatitis B. We had a fair amount of experience with hepatitis B and interferon at higher doses. People do report bahavioral disturbances in adolescents, and in the large studies, there are always one or two where you hear about the question of suicide ideation. But we don't have all kinds of children with learning disabilities and failure to develop in terms of the study.

First of all, I can't think of any that are below that we entered. They're pretty much school-aged children, 7, 8, 9, 10, and so forth. As I said, they attend school. They participate in gym. They're tired. You get a history that they may be tired or they don't eat very well, those kinds of things. Some of them have no symptoms whatsoever, no side effects.

I guess you may be getting the wrong impression of this group of children who are stumbling all over themselves and then can't speak anymore. It really isn't like that. I don't mean to trivialize the concern. I'm

saying that it's not something that is easily apparent.

Actually all of my children are off therapy for a year. They're in the follow-up phase on the Rebetron.

DR. GORMAN: Have you done pre- and post-IQ testing?

DR. JONAS: No.

DR. GORMAN: Have their grades in school fallen?

DR. JONAS: The grades are an issue. Some of them actually are better, but you don't know if it's because people are paying more attention to their grades and their study habits and their sleeping and things. In the teenagers, I've seen volatility. When you stop and they're worse, the parents go, can you put them back on.

(Laughter.)

DR. JONAS: I don't mean to trivialize it because I think your concern is very real, but it's not like we have all kinds of suicide attempts or children who are not functioning in their daily lives in the activities of daily living and relationship disorders. The older children on the higher doses -- because if you dose the 17- and 16-year-olds like a kid and give them the 5 million and 6 million units, sometimes you notice the problems there, and I've actually dose-reduced to an adult type dose for the really older teenagers.

My experience is limited.

DR. SCHWARZ: I would agree. I think that without doing the detailed cognitive function that I personally think should be done, the general impression is that the children tolerate interferon quite well and they do attend school and their grades don't suffer. So, I think the neurotoxicity -- this business of very high dose daily interferon in newborns -- while it's very sobering and should be considered, is probably the very worst toxicity of interferon. So, in the growing child, it should be studied carefully, but I don't think we should be too alarmist about it. We should just recognize it and study it appropriately.

DR. LINDSAY: Just from a design perspective, this might be an area where during a lead-in evaluation screening phase, during which time viral testing can be determined to demonstrate chronic infection, 3, 6 months serial cognitive testing could be done to determine baseline in the children. It may be very useful.

DR. CHESNEY: Dr. Fink.

DR. FINK: The neurocognitive testing and evaluation obviously is something we're all concerned about, but it also strikes me that if we're talking about patients who have received blood transfusions for treatment of leukemia or particularly in the in utero drug-exposed

infants, how are we possibly going to separate neurocognitive differences due to this treatment of hepatitis C from the whole issue of in utero drug exposure?

DR. SCHWARZ: I think you have to use each patient as his own control for that. I agree with you.

DR. SANTANA: I certainly don't like to quote anecdotal data either, being a scientist, but we did conduct a study at St. Jude of very high doses of interferon alpha in children with neuroblastoma who were in remission. It was an immunomodulatory phase of therapy after they had had standard induction and bone marrow transplantation. It was very high dose interferon alpha. It was a dose-finding kind of study too. It was up to doses of 32 million units three times a week for an initial phase of a month and then alternate weeks for a total of 16 weeks of therapy. Although the study prospectively did not look at cognitive issues, neuropsychiatric behavioral issues, I took care of many of those patients. In general, it was very well tolerated.

I was thinking of the data as I heard the discussion. I don't remember any major issues. Obviously, they were not prospectively being looked at. These are kids between the years of 4 and 8 years of age. So, it was rewarding that we were giving such very high doses of Intron A and we were not seeing a lot of issues.

The only toxicity we did see, which was very surprising and actually we did report it to the FDA, was a kid who developed a myocarditis and became quite ill, and it was totally unassociated to anything else. This was one of the kids who had gotten the very high doses, up to 32 million units. And that had not previously been reported, so it may have just been a spurious adverse event. The kid did eventually recover from it, but it was kind of scary.

So, that's the only data I have in very high dose alpha interferon.

DR. CHESNEY: Maybe the quick answer to the first bullet is yes, we do think, and unless you want us to define that further, the next question, should only combination therapy be studied, or is it appropriate to also evaluate PEG-interferon monotherapy? Is it all right to move on to that?

DR. WEISS: Yes.

DR. CHESNEY: Skip.

DR. NELSON: As I recall, there was a suggestion -- it might have been, Steven's or Ralph's -- that given the potential improved response in infants, for example, that monotherapy might still be a justified question. So, I guess I raise that. I think that came up earlier just in passing in the discussion. I mention it to see if people still think that that's the case. I don't

have the expertise to comment one way or the other.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: I think it is very important to do a prospective controlled trial. One of the reasons for the importance is the effect of the predictable anemia from ribavirin on intellectual functioning. Frank Oski did very, very careful studies in Baltimore showing the impact of iron deficiency of anemia on intellectual functioning. So, I think that we really need to understand how the combination affects that versus PEG alone. As we said, we may see fairly high response rates to PEG monotherapy.

DR. CHESNEY: Dr. Fink.

DR. FINK: It would strike me that could also be built into the study design in a single trial, that you start out with PEG monotherapy and in those patients who don't reduce their viral load, you then consider adding ribavirin in. You don't have to even do it as two separate trials. The ribavirin could sort of be the poor responder add-on.

DR. CHESNEY: Naomi.

DR. LUBAN: I just have a question for the group. What do you do about immunization during the length of time that the kids are being treated? How does one handle that?

DR. JONAS: Immunizations are very early

childhood, and so we're not talking about treating in the primary immunization series. You mean just a general flu shot or something preschool?

DR. LUBAN: Well, that plus H-flu at a later point in time. If you look at the whole schema, there are the early immunizations. Rich can go over these probably in about one microsecond. But there certainly are serial immunizations preschool, H-flu, boosters, and whatnot.

DR. JONAS: We haven't taken that into separate consideration and we give them as recommended mostly.

DR. WEISS: Have you administered immunizations while people have been on interferon therapies? I'm just curious to know if you looked at that.

DR. JONAS: Again, back to anecdotes again, but I'm sure I have. I'm sure that it has come up and we have just kept them in their general scheme of immunizations.

DR. WEISS: It's a very good question, Dr. Luban, because we've been actually asking that more and more with some of our newer immunomodulatory therapies that we've approved for chronic use, like the anti-TNFs for RA that are being used for years, beta interferons for multiple sclerosis that are being administered for several years, actually a lifelong type of treatment. Again, we're talking there more in adults where you might be giving the annual flu shots and whatever. There are phase IV studies

that we've been asking, and so that's something that can be built into phase IV commitments to look at responses to various types of immunizations.

On the other hand, too you could just, I suppose, delay an immunization because this is a year therapy, and I guess if the time frame isn't so critical, if there's a concern about not being able to mount an immune response, you could delay the immunization.

DR. SANTANA: We delay the cancer kids for a whole year and really, with few exceptions, don't have that much problem. They catch up when they're done.

DR. JONAS: Excuse me. But it's my understanding this is more immunostimulatory. Is there a concern that they wouldn't respond as well to immunizations, or that it would interfere with their therapy?

DR. CHESNEY: One of the ways you get better from a live virus is to generate interferon. So, maybe it wouldn't be as --

DR. JONAS: Yes. I was just wondering if there was a specific concern that the committee had about that.

DR. GORMAN: I have none about the dead vaccines. I guess there is some concern about hyper-response maybe even more so for live vaccines.

DR. CHESNEY: Just one thing. You didn't ask

us if we're comfortable giving ribavirin. That's an assumption here. Should we use only combination or the interferon alone?

DR. WEISS: I'm going to refer that to my colleagues in the Center for Drugs.

DR. CHESNEY: Can we leave that alone? I'm happy to leave it alone, but I actually have more anxiety about the ribavirin.

MR. FLEISCHER: We've done it. We'll know better probably in the next six months to a year whether we did anything bad. I think one of the things that was interesting is how fast the trials were enrolled and the comfort level of the investigators who are following those kids in the Rebetron trials, and some of those kids are now out after receiving the drug for 48 weeks. So, we'll maybe have some information once the final results come in, once the trials are completed.

DR. CHESNEY: Dr. Weiss, did you want to say something before we went on?

DR. WEISS: No. I think that answers our question that we have regarding the PEG-interferon monotherapy. It was put down because one of the arguments was, given the smaller numbers of children, if truly PEG-interferon plus ribavirin is really a much more optimal combination, is it appropriate to expose kids to a less

effective therapy. That's the whole issue, whether or not one should actually study PEG-interferon as monotherapy or should you just ditch that as a regimen and just wait and use the combination treatment with the idea that you want to optimize treatment as much as possible. But I think we got some good answers, so I'm happy with moving on.

DR. LINDSAY: Could I just ask a question? Certainly a major indication potentially for PEG-interferon monotherapy would be anemic patients. So, are there sizeable numbers of children who have anemia in whom just PEG-interferon monotherapy might be a reasonable study? Chronic anemia?

DR. JONAS: I personally think that if the anemia is the issue, it's actually very dose-dependent, monitorable, and I think that our children tolerate a couple drops in hemoglobin better than adults. The risk in adults is cardiovascular disease, coronary artery disease. Children don't have those kinds of risks, and they will tolerate. So, the patients who are being transfused are a separate issue altogether. I think the issue is more the teratogenicity and immunogenicity of ribavirin exposure. I don't know if that's your major concern. The anemia is a problem but can be watched with good safety monitoring and dose reduced.

DR. LINDSAY: The issue that I was thinking

about was among children who have chronic anemias and require transfusions. Would it be better to do a trial using PEG monotherapy rather than PEG plus ribavirin?

DR. JONAS: I think that should be separate from this trial. I think those considerations should be made, but not what we're discussing today.

DR. LUBAN: That's actually the easiest group to take care of because you just increase their transfusion during the next transfusion. So, that group I wouldn't worry about.

I think the little ones who have a natural nadir of hemoglobin which is age-dependent and growth-dependent are the more critical ones, but they may not become part of this trial because those are usually the 6-month to 2-yearers.

DR. CHESNEY: Issue 4 has to do with the long-term follow-up of both adult and pediatric patients who have received treatment. Information is needed to address the impact of therapy on the clinical endpoints of cirrhosis, carcinoma, and mortality. Please discuss approaches to maximize the collection of long-term follow-up data in pediatric patients who have been enrolled. Who should receive follow-up? How long should the follow-up be, and what parameters should be followed?

DR. WEISS: And this doesn't need to be limited

just to the efficacy outcomes that are outlined in the lead-in. Obviously, we're also very interested in the long-term safety as well.

DR. CHESNEY: Everybody should be followed up forever.

(Laughter.)

DR. CHESNEY: And what parameters? I don't mean to trivialize it either, but it seems to me that there is going to be such a small number that we really need every bit of data we can get from those that we can follow.

Dr. Fink.

DR. FINK: I would think until there is some agreement from Congress on a national medical data bank, that that undertaking is relatively impossible because unless you bank this data someplace by Social Security number at a national level, there are some surprising studies that I'm aware of in asthma that about 60 percent of adults don't recall that they had significant childhood asthma with hospitalizations. Are they going to remember their hepatitis C history?

DR. CHESNEY: Kathy.

DR. EDWARDS: I don't want to belabor the point, but I do think that there is an opportunity, actually at least coming up in the next week, where large numbers of pediatric subspecialists congregate. This may

be something where you might want to discuss this. Certainly the NIH in other situations has been interested in large databases of common diseases, of investigators such as Jerry Winkelstein at Hopkins who has done the patients with CGD. So, I think this may be something that people want to discuss and how follow-ups both of kids with various types of disease processes with hepatitis C might be followed and funds could be garnered for that.

DR. CHESNEY: Is this something, Dr. Schwarz -- is it called the Gut Club? Am I correct? Is that something that they could pull together?

DR. SCHWARZ: Well, we don't call ourselves the Gut Club anymore. We have graduated to the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition, NASPGHN.

DR. CHESNEY: I'm sure something you all have talked about a lot is how to -- these children are all going to be in the care of a hepatologist, surely.

DR. SCHWARZ: It is a concern, although I share Dr. Fink's conservatism about the kind of information we're going to get from a registry versus prospective controlled neuropsychiatric function studies.

I can share our experience with our liver transplant program. We're trying to look at ways to improve neuropsychologic outcome following pediatric liver

transplantation. So, we're now doing those very detailed neurocognitive function studies. We're learning so much, not necessarily cheerful news, about our neuropsych outcome in our transplant patients that we really would not have known from just the casual clinic visit or even school performance. So, I have my doubts as to the amount of quality information we can get from a registry.

The other thing that I would like to comment on because there may be folks here that have influence with the CDC. One of the important long-term questions about hepatitis C morbidity and mortality is does the virus cause cancer. We are just completing a study with the CDC looking at primary hepatic malignancies in children in the U.S. in the last 25 years, cross referenced with the SEER database.

It was very sobering because I think we found 927 cases of primary hepatic malignancy. CDC doesn't have histologic bases, so we had to cross reference with SEER, which is histologically based. About a third of these children, we think, have hepatocellular carcinoma, the adult disease, not hepatoblastoma. Of the 927 cases, 17 had an associated etiology, 14 of which were hepatitis B.

So, I think getting much better quality information from the CDC mortality data bank will be important in the future to find out if children do get

hepatocellular carcinoma from hepatitis C.

DR. CHESNEY: Naomi.

DR. LUBAN: I guess you heard me use this reference to hemophilia quite a bit today, and I'll use it again along these lines. Certainly the Maternal and Child Health/CDC initiative in growth and development of hemophilia and the serial follow-up of those initially children now young adult and adults for virologic disease has been one of the most successful programs, at least from a hematologic perspective. I think it really could be a model for hepatitis C. It is not just a registry. It is actually involved in looking at growth and development. It follows the children at least yearly. It monitors the children serially with a wide spectrum of viral serology, and because it's organized and it's a multi-institutional kind of data collection, it can provide for clinical trials. It's expensive but so are many things in life.

I think that a model like that would be really superb for this setting. That way you would have a data collection set that would be serial, that would be managed by CDC which has got those capabilities, and you have a group of investigators that are pulled together that can respond to clinical trial initiatives.

DR. CHESNEY: Any other comments on who should receive follow-up, duration, and parameters to be followed?

DR. WEISS: Just a follow-up to what Dr. Luban was saying. Currently, though, our mechanism at the FDA -- it would be very nice if there was a government-funded organization that could undertake to encompass all the children that had been not only treated but infected and to do these kinds of follow-up. But what we have available to us right now to any company that's coming along and doing pediatric studies, our mechanism is basically phase IV commitments, to ask these companies to continue to follow up the patients that have been in trials longer term. That could be a couple years. It could be 5 years. It could be 10 years, whatever it is. But that's all spelled out carefully as we go towards approval for the pediatric indication as we discuss how long studies should be, what kinds of measurements to evaluate, something sometimes about how it's going to be reported to the FDA annually or whatever, and those kinds of things.

In the absence of some other more centralized organization to do this, that's what we have and that's what we would need advice on I think for right now, as of 2001, if we're going to be discussing with our manufacturers -- these are going to be pharmaceutical companies -- their pediatric studies and what kinds of commitments that we would want from them once something is indicated for pediatric use.

I could use some practical advice on how long children should be studied, what kinds of things to look for. Should it be a questionnaire after X number of years to be sent out to the parents? Check for significant psychiatric problems or whatever. It could be anything. These are very difficult questions and they're not, obviously, unique to this particular situation. We've been struggling with that very issue in a number of other areas. So, if the committee has any advice or any experience with those kinds of longer-term follow-up, we'd really love to hear it.

DR. CHESNEY: You don't have any control over that, though, do you?

DR. WEISS: We're getting a little bit better able to control it in the sense that under FDAMA there have been new requirements not so much to force companies to do studies if they don't do them, but the information about the phase IV commitments is now going to be publicly available. They're going to be put up on a website. The companies have to actually provide us, on at least an annual basis, with the status of their phase IV studies and the progress, whether or not they're delayed and the reasons why. That information is going to be publicly available. So, there is that incentive, the public pressure to comply with these commitments, but there's no

other disincentive. You're not going to, obviously, withdraw approval or other types of things.

DR. CHESNEY: Dianne.

DR. MURPHY: There is, as Karen noted, the increased attention that will be paid as far as phase IV. Under the exclusivity, under FDAMA, section 111, exclusivity, we have a couple of trials -- and I think we've mentioned this to some members of the committee before -- where we have issued a written request which has in it a long-term follow-up for 10 years in which we have said that part of the construct is that you must bring in 5-year data plus the evidence that you have developed an infrastructure for the longer-term follow-up because of the numbers that are involved sometimes, and that you would get your exclusivity when you bring that interim data in. So, we do have some experience with that.

These are more than large, simple trials, some of them. They get to some of the endpoints that are not terribly complicated, but still they are endpoints that you are measuring along the way. So, that has been one approach, but that's very difficult.

In addition, we recently had an NICHD meeting on adverse event reporting in which we were trying to get some idea of what long-term follow-up was. As you all realize, most of our studies are weeks. Long-term follow-

up is months. We clearly got the message that one year was not long-term follow-up, which for us has really been long-term follow-up.

So, it's a whole new universe for us to be stepping into, and that's why we keep bringing this issue to the committee because we know it's an evolving field and there will be different, I'm sure, paradigms, depending on the disease and the safety profiles, et cetera. But we do see it as a very important issue.

DR. CHESNEY: Skip.

DR. NELSON: My question relates to whether there's authority to require, within whatever mechanism, long-term follow-up of any child who receives the product. Often studies are powered on efficacy endpoints and not safety endpoints. You don't see serious safety concerns until you have a large population who is administered a medication. Can you require data collected on kids that were not in the studies as opposed to the kids that get that particular product after it's marketed?

DR. MURPHY: First of all, as far as requiring, that word means we have regulations that say, yes, we're approving your product with the following phase IV commitments. But as Karen has indicated, we and the industry don't have a very good record in this area, and there are efforts to try to improve that process.

For the agency to do anything about somebody who's not meeting their phase IV commitments, basically we have limited tools. This is what the lawyers tell me, so I'm stepping way beyond my expertise here. The tools are: an imminent hazard, misbranded, take it off the market. You can imaging what level of evidence we'd have to have to be able to do that. So, we can require it as part of the approval process, but the tools that we have presently are really often humiliation, bully pulpit. As we've seen in pediatrics, it really hasn't worked too well. So, these are the kind of quandaries that we're in.

One of the reasons we like exclusivity is they don't get it until they bring in some of that information that you need. But that means that we have to have the ability to construct a trial that can last for more than a year and still have the potential for benefiting from exclusivity, which we hope to have as we move into more products that haven't been marketed before because one of the issues has been so much of what we're doing right now is the older products that have been on the market.

DR. NELSON: But to follow up, I would assume if you design a trial for exclusivity, you wouldn't design a trial that would include everyone who would be receiving that medication regardless of whether they were in that initial trial.

DR. MURPHY: That was the part of your question I was selectively disremembering.

(Laughter.)

DR. MURPHY: To require them to study every child who took the product is not within our purview at this point. I think you need a nationally funded study that would look at something like that. We often refer to things as putting on the table this pediatric Framingham type of follow-up or studies. What are the big public health issues and where do you want to put your tax dollars to work for some of these long-term follow-ups?

DR. WEISS: You can also ask, though -- and we've done this before. People may like the word "registry" and maybe there's a better way to call it. In addition to longer-term follow-up -- it's a little different with hepatitis C than, for instance, with JRA where our anti-TNF therapies are going to be used for long periods of time on these children. But we ask for not only longer-term follow-up of the children that were in the original trials, just to continue them out -- they were no longer controlled trials at that point -- but also for an additional registry to be established. You could limit it to, say, the first X hundred people that come in will be enrolled in a registry.

I don't remember all the details. I don't

know, Bill, if you remember the details more about it, but we asked for that to happen with additional patients coming on to look at various aspects of disease treatment and confounding medications and other types of conditions. So, it's something that we actually can ask for as a phase IV commitment.

DR. GORMAN: Knowing how focused pediatricians sometimes are on labeling, I don't think we ever read the label, but we really like to have stuff on it. If I was trying to design a phase IV follow-up study for the experimental group, leaving the registry out, especially in this particular disease where we don't expect to see anything in the first 20 years other than cirrhosis, things such as hospitalizations, if there's a difference between the treatment and control group, would be very suggestive. If diseases and their incidences were dramatically different from that of the general population. Again, the neuropsychiatric effects.

Dr. Oski in his iron studies was looking for the ability of teenage girls to pay attention and noticed that there was a 6-second difference in their ability to pay attention, which in my normal clinical exam I would not have noticed. But with iron deficiency, it appears to be 6 seconds longer, and it affected their academic performance. Maybe high school graduation rate might be a reasonable

surrogate, perhaps not. Maybe their SAT scores, things that would be relatively painless for the company to gather.

I think their adult heights and weights might be awful interesting, especially since we heard about the fall-off and we hear that they rebound, but do they get back to their original growth curves, their growth velocities, or is it lost forever?

DR. SANTANA: Karen, what are you really asking for? It may be an unsurmountable task to ask the drug companies to do this. They'll do it for the first couple years, and then after that, they won't do it. It costs a lot of money. Paediatric patients move when their parents move. This is not a disease that they may remember 10 or 15 years later. If they're cured from their hepatitis C, nobody will ever know. And we may be putting the companies here in a position of something they just can't do.

So, are we really asking that you want some long-term safety data on these patients that were treated with X and you define a reasonable interval for that? Because you're not going to be able to identify the hepatocellular carcinomas 30 years later. That's impossible to do unless you have a national registry, which is what you're asking for.

So, I think we've got to be careful because I

think we're confusing national registries for long-term follow-up information of patients versus a very limited focus of a patient got drug X and I want to make sure that I can identify that patient forever in case something happens to that patient. To me those are two different models, and I think you're probably talking about the latter, not the former. Am I correct?

DR. WEISS: You're right, Victor. There are two separate areas. One is knowing better information about natural history and long-term sequelae regardless of treatment, which is a very important issue and one that I think is still probably a real need. But then the responsibility of our pharmaceutical manufacturers who want to come in and have these obligations -- you're right. It's the latter.

It's really more looking at what is a reasonable request to ask for -- and we want to be reasonable here -- in terms of duration, in terms of the kinds of follow-up, in terms of the kinds of information we want to get collected that would be important for pediatricians to know about, to be able to update the labeling several years down the road or 5 years down the road, or whatever it is with outcome data of both kinds really. Durability of response probably isn't as critical because we think if we're extrapolating from the adult

experience, there are very few people that lose their response after a certain period of time. But there are these long-term safety issues and the effects of interferons, in particular, on children.

DR. SANTANA: I guess you guys have the best models. Don't you do that for devices when some of these experimental devices like pacemakers or subQ ports, which I have experience with --

DR. WEISS: We don't have the device people here.

DR. SANTANA: Those get identified up front, and that's prospectively monitored.

DR. SPIELBERG: The issues of follow-up are obviously critical, and the practical aspects are very, very difficult. Things that increase long-term follow-up is if you have a chronic disease and there are very few subspecialists and you keep going back to their subspecialists and your third party payor allows you to keep going back to that same subspecialist, and falls off dramatically if you don't have a defined chronic process with a parent support group and all the other things that keep you going back.

Rates of attrition for intercurrent illness. You're going to lose 50 percent in six months. You're going to lose another 25 percent at a year, and then

they're all going to disappear into the woodwork, and it becomes harder and harder to get long-term follow-up.

For a process like this where you're on a drug for a year and it requires going back to the same specialist for a year, you might do a little bit better. But once you are "cured," you want to disappear into the woodwork as fast as you can, and your third party payor wants you to disappear into the woodwork as fast as you can, being now a healthy person who can go to the GP once every other year for well child care.

Because of the mobility of American society, as well, people don't stay in the same jobs. They don't stay in the same cities. They move around a great deal. In an interesting way, having spent a large portion of my academic life in Canada, it's a little bit easier on the Canadian scene because people tend to not move as much and because you have a single third party payor. So, at least if you stay within the province, you have a single third party payor. If you move provinces, your third party payor changes, but at least the national system allows for longer-term follow-up.

So, I think we do have to be a little bit careful in terms of long-term promissory notes. It's extremely hard to do and it's extremely hard to keep cohorts together for long periods of time.

DR. FINK: Even when you have an ideal situation -- I've dealt with the Cystic Fibrosis Foundation registry for close to 30 years now. There's a twofold difference across the United States on what is the upper limits of normal for liver enzymes for AST and ALT from different labs.

(Laughter.)

DR. FINK: There's a fivefold difference in IgE levels, and trying to get reliable height and weights with a stadiometer with the shoes off and only socks has required yearly reeducation and site visits.

(Laughter.)

DR. FINK: And that's probably an ideal disease where you've got good capture.

I think the answer is a registry is never going to have research quality data that will allow you to decipher small changes. If you're talking about neuropsych testing, I can't even believe that a registry can begin to address those issues.

DR. WEISS: So, what shall we do?

DR. FINK: I think you do short-term prospective data collection and you live with it.

DR. CHESNEY: Dr. Schwarz.

DR. SCHWARZ: My question is going to reveal my ignorance about the regulatory process. But it seems to me

that we don't have enough information right now to make a wise recommendation about long-term follow-up. In other words, we haven't done those carefully controlled neurocognitive function tests during and immediately after therapy. To me, since the long-term follow-up is so very difficult, particularly in the maternal/fetal population where we're talking about homeless individuals and so on, the importance of the long-term follow-up would be very different if there were intellectual defects discovered during interferon therapy that persisted 6 months after therapy. Then I think it really would be important to try very hard to get some longer-term follow-up. If, on the other hand -- and I think Maureen and I might guess that we wouldn't see too much deficit at 12 months, at the endpoint, and 6 months afterwards. Then it would probably not be fair to the pharmaceutical companies to demand very long-term follow-up.

DR. CHESNEY: Judith.

DR. O'FALLON: We haven't talked about ethical issues. This is all very practical, whether it can be done, which is of course important. Ultimately it's the bottom line. But if you have a disease that the patients are not going to die from -- it's not like cancer where they're likely to be dying soon. Here is something that they're likely to live with for many decades and some

fairly substantial percentage of them never will suffer any major sequelae, according to those numbers that we saw, really bad stuff.

If we treat a whole lot of people that are really not going to have all that much trouble from the disease and we cause them trouble that will stop them from having the kinds of jobs that they could have had, have the education that they could have had, where they're going to be limited, I think there's a problem here. It's one thing to treat the life-threatening diseases. It's another one to be treating ones that are smoldering and actually may never cause major problems to the sufferers.

DR. SANTANA: But that's the whole point. The serious stuff you should be able to identify early on in the first year or two years of the therapy. Those you will identify, and then that serves as a baseline for you to define how much more aggressive your follow-up should be for everybody.

The counterpoint to that is you also have to have a mechanism, as we learned in cancer, to identify patients so even those that do not have early issues can still have issues 10 or 15 years later. So, you can capture those. But those you don't capture by being very stringent on the pharmaceutical company to follow them very closely. There has to be another way to explore that.

I would be more concerned that if you do a trial and early on in the first couple of years you do identify that there are serious issues, then you have the information you need to define your long-term follow-up.

DR. CHESNEY: Do you need any more input?

DR. WEISS: No. I think we need to digest our input that we have. This has been very, very helpful. For the sake of time, I think we've decided that we do not need to -- the last question was an optional question, and I think we actually touched upon a lot of those issues already in our discussions.

So, I want to thank everybody on this committee for their enthusiasm and their discussion, and we will be anxiously awaiting the transcript to review what you all said and take it back with us. Thank you.

DR. CHESNEY: Well, let me thank you and Russell for setting this whole day up and for finding our invaluable experts for us and for providing us with very difficult questions, difficult issues, which we've all learned from. So, let me thank you both because I think we've all learned a tremendous amount here too.

Dianne Murphy is going to give us an overview of what's going on at the Center now. Dr. Rehermann, Dr. Schwarz, Dr. Jonas, and Dr. Lindsay, if you all want to stay, that's fine, but if you feel like it's time for you

to go, we all thank you tremendously. You've been a wealth of information today, and we could not have done any of this without you. So, thank you very much for your time and expertise.

DR. MURPHY: I'm going to go through this pretty quickly because you have a handout. Hopefully that is really all that you would need.

I'm going to talk about the response to exclusivity, the health impact of the new labels -- and that's really the bottom line of what we want you all to know what we're seeing already with only 18 new labels. I could also comment on the things that I know that are coming. We really are seeing important changes that are being made to labels.

I am really not going to spend time on our report to Congress, because we don't have it and it gets very complicated. If you want to ask me some questions about it, that's fine.

And then a quick update on the Pediatric Rule, again remembering that we could not require studies under the rule until this past December, but to give you an idea of the number of deferrals and waivers.

The stats that you've become very familiar with at this point are that we now have received over 200 proposals from industry to study products. We have issued

over 188 written requests and over 40-some other letters to sponsors about incompleteness or what else, that we can't issue a written request. So, well over 200 responses.

Products that have gone through the entire process, meaning they have received a written request, they have conducted the studies, they've analyzed the studies, and they submitted them, are 34. Again, it takes a while. Even though exclusivity by law is required to be denied or granted within 90 days, it takes a while after the submission of the studies to get the label written. Our usual is up to a year.

So, of those 34, we now have 28 that have been granted exclusivity. We have 18 new labels. I'm going to quickly talk about the 13, just to give you the breadth of the diseases for which we now have an extended age group or an extended safety profile, but mostly talk about the 5 where we think we have important dosing changes out of these 18.

These, very quickly, are the ones which we've extended the age or they have additional information that is either similar or some specific comment we can make about pediatrics in these indications which include not only fever but HIV, gastroesophageal reflux, diabetes, conjunctivitis, hay fever, ichthyosis, rhinitis, urticaria, type 2 diabetes, hypertension, and anesthesia.

Now, these five products we think have particularly significant changes in them as far as pediatrics is concerned: midazolam, which is used for sedation in conjunction with anesthesia; etodolac for treatment of JRA, fluvoxamine for treatment of obsessive-compulsive disorder, gabapentin as adjunctive therapy in the treatment of partial seizures, and propofol for induction and/or maintenance of anesthesia.

Because I thought the committee might want to have some idea of the numbers involved, we've tried to include on this slide a synopsis of the moiety that was studied, the studies we asked for, the age ranges that were included and the number of patients.

As you can see, in midazolam, we asked for single-dose PK/PD study comparing at least three dosage levels. We asked for a controlled dose response study in the age group 6 months to 16 years involving about 500 patients.

What we found is with midazolam we were able to get an effective dose at which they should start from the dose-ranging studies, defined the volume of distribution, and its similarity to adult protein binding elimination, the additional information on AEs and warnings about concomitant medications, and particularly important, identified a subpopulation of children with congenital

heart disease and pulmonary hypertension who are at very high risk for having severe respiratory problems if you didn't start at the very, very lowest end of the dosing regimen and go slowly up. Importantly, we had a new oral liquid formulation.

Etodolac. This product had an osteoarthritis indication in adults. We asked for a 12-week open-label study, a PK/PD study really, to look at can we extrapolate one of those tests of hypothesis type of things using endpoints that you would for arthritis. 6 to 16-year-olds, 68 patients. I don't think you could all these efficacy trials.

This basically did pass muster, if you will, by feeling that there was an appropriate dose response. However, what was interesting was that there was a higher dose on a per kilogram basis in the younger children. We're finding that this 5 and 6-year-old group -- we're finding very different clearances in children in this age group in some products. It was approximately two times the lower dose recommended for adults. Not always depending on the product and how it's eliminated, but again, these are our first 18 labels.

This is fluvoxamine. This study was asked for because we were getting information about concerns that adolescents were being underdosed, that there seemed to be

out there some concerns that the adolescents -- apparently for reasons people were looking at them -- were not reaching the levels you would have expected. So, we actually had an open-label PK study in 7-year-olds to 17-year-olds and a long-term open-label safety study in 8-year-olds to 17-year-olds.

It always kills me. We get all this good information and we end up synthesizing it down to a sentence or two. I think there's actually been an abstract published on this. Maybe Dr. Kauffman can comment later, if he knows, on what was actually found, which is in essence, yes, the adolescents were being underdosed, but not only were the adolescents potentially being underdosed, but girls between the years of 8 and 11, again in limited numbers, but in disproportionate numbers, would have sometimes up to two times the AUC levels. So, we found this very different distribution of serum levels by physiologic state.

Gabapentin. We asked for quite a bit for this product, a double-blind, randomized, placebo-controlled, parallel group efficacy and safety study as an add-on therapy. Patients 3- to 12-years-old. Then we asked for a double-blind, randomized, placebo-controlled efficacy study in the next age group. So, we had about 250 and 75 patients here.

The third study was a PK performed on a subset of the efficacy because we try to be efficient, if at all possible, in these studies. Four, an open-label extension study, and five, a single-dose PK study in the 1-month to 12-year-olds. You can see the numbers are getting up there, over 1,000 patients.

These studies were able to establish effectiveness down to 3 years of age. Because we were looking, they were able to identify neuropsychiatric events in the 3- to 12-year-old group that were not present in the control group. It had to do with hostility and aggression, poor school performance, et cetera. Again, even though these had hundreds of kids, still when you're finding it in studies that are relatively small with hundreds of kids, you're concerned that it definitely is occurring.

Oral clearance was normalized per body weight, was increased in children less than 5, and a higher dose of gabapentin was required in the children less than 5. And we had a new oral liquid formulation.

The last of our five products, propofol. A randomized, double-blind, comparative dose-ranging trial to evaluate the efficacy and safety in 0- to 16-year-olds, over 300 children. Study two, randomized open-label comparative parallel group to evaluate safety in the 0- to 3-year-olds, 157 patients.

This was a very interesting result. They were able to extend the age down to 2 months for the indication of for maintenance of anesthesia. For induction of anesthesia, it remained at 3 years of age. We're going to get to the PICU aspects of this.

They identified concomitant administration with fentanyl may result in serious bradycardia, and the abrupt discontinuation following prolonged infusion may result in flushing of hands and feet, agitation, tremulousness, and hyperirritability, sort of emersion effects that you may see coming out of anesthesia.

Data we put in the label. We felt it very important to get out there because we know these studies in the pediatric ICU are ongoing, and we don't know the reason. We could spend hours talking about the analyses that were done, looking at this is a chelating agent, magnesiums, numerous studies done, multi-center. Was it center-driven? It did seem to be one center more than another. But what we put in the label is that propofol is not indicated for pediatric ICU sedation as safety has not been established. In a single multi-center trial of critically ill ICU patients, there was an increased mortality, causality not established, of 9 percent in the propofol arm versus 4 percent in the standard sedative arm.

So, you can see with the first 18 labels we

think there is very important information being generated at this time.

Our report to Congress, as I said, was submitted in January. It addressed the effectiveness in obtaining pediatric information, the adequacy of the incentive, the economic impact, and suggestions for modification. You can ask me questions about that. It's up on the Web.

The Pediatric Rule. Very quickly, to give you some follow-up on what's been happening with that. Again, we can require studies for certain new and marketed drugs and biologic products. The important part about the rule is that it makes thinking about pediatric studies a part of the drug trial development process.

Again, if anybody thinks that FDA just sits here and waits for the truckloads to unload, you don't understand what we do. It is very important that we're involved in drug trial development in the early stages and that we can ask the questions: is this product going to be used in children, what do you know about the safety, what do you know about the pharmacokinetics of it, do we want to consider developing it for children, when do you want to consider developing it for children? All of that goes on pre-IND into phase II and pre-NDA discussions.

Again, we could not require studies to be

submitted up until December of this past year. As of right now, we have deferred 114 products, which means that we have not said you don't need to study them. We have said we need more safety information. We need more phase IV information in adults. Or we've said this is what you need to do, bring it in later, and we've set a date. But they didn't have them at the time of the approval.

We have waived 149, and I knew some people were going to say, what? 149? You don't think it's important to study 149 products? So, I thought we would give you an idea of what those were.

I think you will agree that most of us don't want to go out and start studying facial wrinkles in children or some of the acne vulgaris. We can extrapolate at certain pubertal stages we feel for certain things. Age-related macular degeneration, osteoporosis, again mostly diseases that are related to age in onset at a later time in life.

One of these, however, you all had this discussion on sleep disorder for which there is an indication -- the sleep disorder that is labeled presently for adults is different and not the same at all for sleep disorders that may occur in children. So, that's why that is on there.

Post-menopausal breast cancer, et cetera.

This is just a few more: fertility, contraception, abortifacients, and chronic obstructive pulmonary disease.

Important points just to remind everybody. We cannot delay the approval of an adult indication. That's why, as we move through this process, we do have a number of deferrals, and we expected that. Unlike exclusivity, the rules limit it to the indication that is under review or in development. It doesn't permit us to ask for off-label development. And promotes early consideration, as I said, of pediatric use and drug development plans.

You all should have this handout of the announcement about the interim rule that was published on the Web this past week about additional safeguards for children in clinical investigations of FDA-regulated products. This is in response, as you heard from Karen, to the Children's Health Act, but I also think that the committee deserves some credit for saying, we think this is important and this needs to be carried forward and, working with the Academy and other interested parties, to make it clear to people that Subpart D did not apply to regulated products. And it does now as an interim rule. It is still open for additional comment.

Now, I'm not up here to discuss the revised consensus bullet points. It should have "draft" on here.

I hope you all have "draft" on your copies because it is not final, and it was supposed to have "draft" on there. This is in response to the meeting we had on placebo-controlled trials and the ethical issues.

We have a pediatrics ethics working group internally. They met. They tried to reconstruct that we thought would be points that were a consensus. We sent this to the committee. We received a number of comments back. We revised it again.

I think at this point why I'm bringing it back to you is because so much has happened. Unless we go back and look at an all-day videotape, we're finding it hard to determine what was actually discussed at the meeting versus everything that has intervened in the meantime. So, we're asking you again, not today, but we really would like you to look at these points in brackets because we're not sure that this was fully discussed. It may have been mentioned, but because of increasing discussions with Helsinki and other issues, we wanted to make sure that we hadn't passed over our thoughts into what really should be a consensus statement from the committee. So, that's why we're asking you one more time to please look at this.

We did put it in a slightly different order, talking about placebo-controlled trials in general, and then add-on trials, and then withdrawal trials.

We think we're at a watershed -- this is my concept of a watershed -- event right here which is reauthorization of FDAMA, section 111. We know even if it is not reauthorized, there's a huge amount of work that is in the pipeline right now for pediatrics, and this committee is contributing tremendously to that scientific and ethical base. But we do feel that you are going to be here for a while, contributing to many of our questions both science-based and ethically driven, as we go through this process.

Tomorrow we enter again another arena, which is how does one study a product which I think will be for discussion, but we certainly hear people think is needed in a population which may have difficulty communicating their concerns to us, and certainly the ethical issues.

I always end with this one of my daughter overlooking the mountains because we look forward to the future and being able to keep this arena moving forward because I think it's just tremendously exciting to us about the number of scientific issues that are being looked at and thought about, not that we wouldn't do it anyway, but it always helps to have a lot of other players, who can fund some of these studies, participate in the field too.

Any questions?

DR. CHESNEY: Can I just make one comment? In

the folder are the three bullet points that Dianne has asked us specifically to comment on. So, I just wanted to be sure you recognized they were there and not just in the slides.

Skip.

DR. NELSON: First of all, a phenomenal effort. I think it's amazing, given how many pediatricians there are within the FDA, that in fact you've been able to accomplish as much as you've accomplished.

So, my questions are as much to ask how do we take it to the next level, which is related to the extent to which there's pediatric input within the various divisions as they begin to generate written requests, as they begin to discuss with various sponsors the design of particular trials, whether you feel there's adequate pediatric input at that stage so that when sponsors are designing trials or receiving requests and then they're being brought to IRBs, which is where I see them, that they're felt to be pediatric-appropriate.

And then a follow-up question to that would be the extent to which this committee could do more than it's currently doing, whether you feel it could be used more effectively in different ways to facilitate the design of appropriate pediatric trials.

DR. MURPHY: Clearly there's not enough in the

way of resources at FDA right now. We refer to it as the thin line. It's really very thin for the volume, if you consider the number of NDA's that we approve in a year, 30 or 40, and we're cranking out 188 written requests. It gives you an idea of the disproportionate number of activities. So, yes, we need more resources, and we made that very clear I think to everybody. We just can't continue the way we are right now.

That relates also to the people within the division, because the people within the division are not assigned to pediatrics, even if they're a pediatrician. It's sort of like what happens in industry. They're assigned to do drug development for certain diseases, and it's very seldom just a pediatric disease. So, all of this activity is carved out on top of their additional efforts. We know that most of the pediatricians do not have time to participate at the level we wished they could because this regulatory history, this scientific history, this ethical discussion is really being limited to very few of us, and it's impossible for us to be able to disperse all of this information in an effective way and a timely way.

So, clearly what we're looking for is more resources so that we can assign people, at least 50 percent, to pediatrics because we don't want them to leave their divisions because they leave their science. It's

sort of like having a faculty member who doesn't see patients anymore. They sort of lose their credibility. If you're not in your science division you tend to lose some of your credibility. So, we really do want to be able to target people maintaining their division activities while being clearly identified for pediatrics.

As to what could this committee do, I think one of the things that we're always struggling with is timeliness versus efficiency versus when does the issue cross to the point where you really can't move forward. When we don't think we can move forward without additional external discussion -- now, sometimes that external discussion will be that we can call up people and say, we've searched the literature; we need a clarification. We do a lot of that. We do a lot of talking to investigators, a lot of talking to NIH and CDC. It's when we need more information like that, like the discussion here today, that we do bring it forward.

Do I think that we will look back and wish we had done a better job on some of our requests? Absolutely. I don't think you can put a program in place with this many written requests and say that you're sure that every one of those written requests were stellar. I think they are the best evidence that we had, the best science that we had.

Do we want to improve upon that? Yes, but

that's where the resource issue comes in because if we can bring enough people into an active discussion, then I think you have more consistency. You have more communication and therefore better consistency in the way that some of the trials are requested.

One of the reasons we have so many different divisions is that each product -- it depends on the stage of information that we have, or as Karen was saying, how many priors we have. Is it already approved in adults? What's the safety profile of the product? What are the needs in kids? All those things have to be addressed. I don't think any committee could address 188 of those. So, it has to be those which we have difficulty with.

DR. NELSON: Just a quick follow-up. Are you, as a representative I guess of the pediatric initiative within the FDA, seeing all the written requests? Part of the reason I ask is my impression is that there's a different willingness on the part of pediatricians to have an appreciation for the risks of trials and whether you need to subject children to those risks to get certain information. It is a different kind of risk-benefit calculus than someone who is an adult physician in adult trials would consider. Often some of what would be considered an inappropriate trial design by a pediatric IRB would look more like an adult study. My bias is that with

more pediatric leavening of that loaf, that that wouldn't happen. So, is that happening?

DR. MURPHY: Within the divisions, they don't always go to the pediatrician. That's first. The product hasn't been assigned to the pediatrician, and it may not go to them at all. If it is a written request that has never come before, in other words, a class or a product that has never come before the implementation team, they will come to the implementation team and present their assessment.

But again, the implementation team is a lot like this committee. It does not have everybody who represents all subspecialties, and that's why we need more resources because I think it should have representation from all the different specialties.

So, that initiative was to, one, make sure we just move forward with implementation of this whole massive program in somewhat of a consistent way so we didn't have one group asking industry to do totally different things than another group in a different way. So, it was to ensure regulatory consistency.

Also, we try to make sure that we ask the division certain questions. It's not what the sponsor proposed. What is the public health benefit? What do you think the issues are? What are the ethical issues? We are very dependent upon, if this is not our field, the answers

from the division, and particularly if the division has not participated much in PDIT, it could be an educational effort for them. I can tell you that we do send divisions back and say, try again, come back. We have concerns. We've done this for both scientific and ethical reasons.

So, you're right. If we're going to ensure the highest level of review, we need to have more people with expertise participating within the agency at that level.

Do we get every single written request? The answer is no. Do we get most of them? Yes. If there's a template, we don't get it. In other words, if there's a template like there is for HIV, hypertension, obsessive-compulsive disorder, they don't come to PDIT usually for those.

DR. SANTANA: Yes, I also want to echo what Skip said in terms of recognizing the tremendous amount of work that you and your group have done for this.

I had a different question as it relates to the reality of the rule and what's going to happen in Congress. Can you give us some guidance of what is likely to happen when Congress reviews your report and what would be the ramifications of that for all of us?

DR. MURPHY: I really don't know. All I can tell you is that I heard -- a year or so ago, we really thought that most people felt that exclusivity had a very

good chance of being reauthorized. I think there have been concerns that have arisen since then in two or three main areas.

One of them has been the amount of money on the blockbusters that has been made by some companies. I don't know why that's surprising. In a way, legislation was designed to reward those who did what they were asked to do, and that they're going to make a lot of money is what's driving it. Sorry. I shouldn't say that. It's certainly facilitating the process.

I think that what I've heard is that -- but they're still not looking at what we're calling now the gap drugs, which are the products that don't have any exclusivity or patent. Well, again, it wasn't designed that way.

So, I think the focus now is going to be how could we combine some balance, like we're always doing, of defining if you're going to make a lot of money, is there some additional responsibility you should take. I don't think anybody would have a problem with that. Where it gets into the problem is, how do you define a lot of money? What's the other responsibility? What if that company didn't happen to have a product that was on our list to be developed? Should they go out and buy somebody else's and then come back and develop it? All those issues are very

difficult. Therefore, I have no idea.

There have been suggestions for PhRMA, for the sponsors to contribute to a pool of money, and then there will be a trial entity, either something like the ACTGs or various postulates. But again, those are all just things that you hear people discuss. I have no idea what Congress is going to do about this.

DR. SPIELBERG: I can fill in a few things that Dianne can't because also Dianne can't lobby officially.

In terms of the resources, I think all of us are very concerned about that. Dianne and her crew have done more than a superhuman job. Yet, as she indicated, many of the review divisions don't have pediatricians sitting on them and often struggle. We've seen discussions that really have ended up with protocols that perhaps were not pediatrically optimal.

In response to one of the key features that I think we're getting a lot of backing for in the renewal of the legislation is elevating this whole effort in pediatrics within FDA to an office level. It needs to be recognized for several reasons.

One is continuity. We need to assure that if Dianne gets moved into something else -- and I hope that never happens, but already you're getting filleted into a number of new areas -- that indeed there will be

replacements, that those are real positions that are going to go on in perpetuity to assure that within the agency there is pediatric expertise in the future.

And the second thing is to get adequate numbers of resources because there's just no question. As was pointed out, perhaps there may be 20, 30, 40 compounds coming up for review on the adult side. We're talking 188 drugs coming through the FDAMA process, just to give you an idea. Now, sure, not all of those are the size of a full NDA and require the amount of review of a full NDA, but they require an awful lot of expertise. To a lot of our thinking, the more pediatricians within the agency who, indeed, have a significant amount of their time dedicated to pediatrics, the better.

Regardless of what happens legislation-wise and everything else between the combinations of the rules and incentives and everything else, Lord willing, most drugs in the future are going to be labeled for pediatrics. So, the task is going to get bigger, not smaller, for all the new entities coming down the pike.

I think none of us have a good fix on likelihood of renewal. There are things that are being worked on. There are going to be congressional hearings coming up very soon after the congressional recess, which is just finishing up now, which is, I gather, when they all

go out on the playground and claw each other's eyes out and then they come back and try to be collegial. That's the definition of a recess.

But there are going to be lots of opportunities for input from everybody to try to assure that the process goes forward. There are attempts being made in a number of different realms to deal with some of the off-patent drugs and defining the universe of those drugs and trying to come up with ways of going after at least part of that universe and assuring the compounds that are commonly used, for which there are risks or for which there aren't appropriate formulations, do achieve both labeling for risk, as well as appropriate formulations.

If you look at this piece of legislation, compared to almost any other piece of legislation, the metrics and the report to Congress that Dianne and her group put together I think provide more than adequate support that it worked. If you look at what happened before and what happened now in terms of pediatric clinical investigation, the world has changed fundamentally. And in most therapeutic areas -- and the data are supportive that it's not only blockbusters that have been studied, but a fair number of those 28 drugs weren't even in the top 200 selling drugs in the country and yet made it through the process.

But there are forces that are focusing purely on dollars and not even on the benefit side because if you read the report from FDA carefully, there are estimates of benefit, as well as costs, and people are only looking at the costs, not the dollars saved by kids being kept out of hospital, by improved therapy, by decreased side effects in hospital and out of hospital, by proper dosing and proper formulations. All those things need to be brought forth, and they need to be brought forth both by patients and physicians who understand the issues.

So, it's going to be a battle, one I think more than worthy of engaging in. I think, frankly, the data and metrics are overwhelming that we got the results we wanted and now we need to fix some of the things that remain out there, particularly from my point of view, to deal with many of the issues that remain problems. Many of them can be solved by really providing the FDA the resources and an office level of pediatrics. Compared the Office of Orphan Drugs, this effort is taking infinitely more time and has vastly fewer resources associated with it, and we really need to get that accomplished.

DR. MURPHY: Steve alluded to something. I was just trying to give you an idea of one of the issues that's arisen since we submitted our report. The economic gurus do their modeling and calculations on the first 112

products that we issued written requests for. What happened is that something like 17 of the products -- I'm doing this from memory, so I may be off one or two -- assuming these were just modeling based on what we had asked -- if they got exclusivity, would have accounted for 50 percent of the costs of the program. So, there are a number of companies that are studying products that are not blockbusters, but that's not what's getting the attention. And that's what happens.

DR. SZEFLER: Just a quick comment. I don't know if you've looked at exploring other methods of expanding your expertise. Many of us sit on panels and the topic changes, and it's just a couple of times a year. Is there a way of integrating methods in terms of some consistency or some follow-up with specialists or whatever outside of the FDA on a more continuous basis? You mentioned phone calls periodically, but those tend to be focused and temporary. But is there any kind of level way of expanding expertise that you could maintain some continuity on some of the issues?

For example, you deal with right now in the asthma world the aspect of steroids on growth, and we had a panel on that. But is there a way of keeping some continuity in utilizing expertise out there to enhance the expertise that you have available?

DR. MURPHY: Yes. We're very open to suggestions. I think that we hear from the divisions about what their priority issues are, but it would be very good to hear from this group about what your priorities are concerning the written requests that have been issued.

One of the problems we have is that we can't tell you exactly what we ask for, and that's something I would like to see changed. That's my personal opinion. Let me clarify that. We're not allowed to talk about it. Often what you hear from a sponsor is, to be blunt, not what we asked for, and we can't tell you what we asked for until not only have the trials been conducted, but the studies have been submitted, and we get it labeled. Now, that could be years. And then we could talk about it.

DR. NELSON: One of the issues that will inevitably get caught up probably in the discussion of FDAMA is the complexity and politics that are going on in the world of IRB review. I would expect within the hearings questions of whether children are adequately protected and the like within a system that is gearing up more and more trials.

I have taken, to reflect on whether I'm creating conflicts of interest and perplexity on the part of sponsors, to actually calling directors of research and sponsors and asking them what's in the written request

because sometimes I can't believe what they've put in the protocol and I want to know whether that was true or not. Sometimes they tell me; sometimes they don't. But it makes for an interesting conversation.

But on the IRB side, I think one issue is just the expertise and quality of IRBs. I'm thinking of whether there would be a way to fold in E-11. One of the issues is sufficient pediatric expertise, not only in the performance of the trial, in the review and the design of the trial, but in the review of the trial at the IRB level. Those of us who serve on IRBs or chair IRBs -- I know Rich is, I am; there may be others -- know of the high degree of variability there is in the interpretation and application of Subpart D in a way that some of us would feel is sort of outside the boundaries of what is frankly ethically appropriate.

In some sense, saying that the issue is not only just simply the FDA's process, but the process of the actual conduct and review of these trials, adequate expertise in pediatric investigators -- frankly, I don't think adults should be doing pediatric trials. Period. Pediatricians should be doing pediatric trials. I'll extend that to family practice in certain things. I'm open-minded, but adult physicians should not be doing pediatric trials. That's my own personal opinion. Those

kinds of issues, I think, are also potentially going to get caught up in the discussion of FDAMA, which is not so much an FDA issue, but the FDA is stimulating the process.

DR. MURPHY: And we're very dependent upon the IRBs doing their job. Just so you all know, it's a two-way road. There have been days when I've looked at something and said, did an IRB see this? I've asked the team to go back and call. Are you sure this has gone through an IRB? And the answer has been yes. So, we really are dependent on the IRBs to play a role because as much as we want to have involvement early on, as you know, we don't require them to send in a consent form, much less an assent form.

So, all of these activities -- as you've heard, we're having a hard time keeping up with what we've got on our plate. We certainly don't think it appropriate for us to be taking on those responsibilities. So, there does need to be an additional activity here very much focused on what is going on to ensure IRB expertise when these protocols are coming before them.

DR. NELSON: What would it take to get the kind of crosstalk and communication? You have that question of IRBs. IRBs ask the question of the FDA. The sponsors say the reason the trial looks that way is they blame the FDA for it. But you and I can't talk officially about any of these trials. So, what does it take?

DR. MURPHY: Again, I have to just put disclaimers all around the following statements.

(Laughter.)

DR. MURPHY: I am not a lawyer. I have no ability to tell you the repercussions. There are, apparently, very important repercussions that could result that have to do with secret, confidential trade information. You all know the stock market goes up and down on what a company announces. So, we really aren't allowed to even tell you studies are submitted. Now, that's the usual process.

What I have proposed is that if one has an already marketed product out there and you are voluntarily participating in exclusivity -- we've sent you a written request and you want to participate in it -- that there ought to be a change so that we can talk about these trials. I think that activity alone would allow more open discussion if there were an uproar by the specialists in the field that there's a concern or an IRB has a concern. Then they would know the elements. They would be able to say this is the specific part that's disturbing versus talking in sort of code language or trying to reassure you that that's not what we asked for, that is what we asked for, but we have information about why we asked for that, but we can't tell you about that information either. So,

it really does become a very nonproductive discussion if we can't have the studies that we've asked for under exclusivity available for discussion.

So, that's part of the legislation that we have suggested verbally. We did not put it in the report to Congress, but we have suggested verbally it would benefit this whole process.

DR. SPIELBERG: Invariably you run into proprietary issues, et cetera. But the one way that we can obviate many of those issues is in something that Dianne already alluded to, which is really templates for certain therapeutic areas and certain types of compounds. To the extent that learned groups such as this can contribute to the evolution of templates that will apply to multiple different compounds within a therapeutic area, many of the issues about inappropriate study design, taking an adult protocol, stamping "pediatric" on it, getting beta HCGs on newborns for pregnancy testing, that kind of thing can easily be dealt with.

I think to the extent that we work more on templates and really use this kind of body as a good testing mechanism up and back, with IRB representation and ethics representation, so that we can look at these kinds of designs -- some of the templates that initially were designed in therapeutic areas I think, frankly, did miss

the mark in certain areas of hypertension, which was sort of basically reproduce in kids what you do in adults. Well, that may not really be the right study design. But the best way of looking at that is in therapeutic categories through a body like this.

I hate to increase workloads, but in a sense I think probably one of the best ways would be for this group to meet, if necessary, somewhat more frequently to help out with the evolution of some of those templates in key therapeutic areas because I think that would be the best way in an open, transparent forum where it's not proprietary to a given compound and it's not related to a specific protocol, but it's generic to the development of the key templates. So, when a company comes to you, Skip, with something that you already know what the template should be and it's whacko outside of that template, you don't have to worry about what the specifics of the written request is because basically you understand what the template was.

And the templates go up on the Web. They're transparent. They're open to all and don't provide any individual company a competitive advantage or disadvantage, for that matter.

DR. MURPHY: If we have a template up, it doesn't mean we can't modify it because different drugs

have different levels of information. Believe me, we hear from the sponsors because we require more of one company than we do of another. But that's because their product hasn't been out there as long. We don't have as much safety data or it has a safety issue we're more concerned about. The template is a starting point, but the specifics of the product may mandate changes in that template.

DR. SPIELBERG: What it does for you as an investigator, knowing the template, you can ask the company intelligent questions. Frankly, if you don't get intelligent responses back, you know where the protocol stands. So, it gives you a basis for understanding what the whole picture would be, and then again modify because this compound happens to be unusually metabolized or it's very different than others in the class and therefore this has to be done. Again, the intelligence and the scientific level of the dialogue with the IRB improves.

DR. NELSON: I know it's late, but let me ask one more specific question.

One concern of mine is the ability of one sponsor, for example, to be able to take advantage of the inference of effectiveness or efficacy on the basis of a product that another sponsor has, indeed, already studied. If you look at the FDA guidance on 505, it basically says that the sponsor needs to have permission basically to use

that data or submit that data in a claim for exclusivity.

So, I guess my question is, to the extent to which one would allow for, say, the second compound or the third compound that is within a class where you've already got evidence in hand because you've reviewed it and approved the exclusivity and/or the labeling, in fact, in that compound, why require the sponsor to have permission from another sponsor, because clearly the answer is going to be no, when you've got the data in hand and basically out of fairness to the second or third sponsor, you'll end up putting more kids at risk to an efficacy study when all you really need is the dosing or PK for that different formulation or preparation?

DR. MURPHY: Even though that's in the guidance, it's not used the way you're describing it. If you have product A and B comes along and then C comes along, if you could not extrapolate -- let's just say that -- for whatever reason for A, we then determine that we were wrong. You could extrapolate. We may ask for a different set of information from B because just like the test of hypothesis, it turns out you could. But it wouldn't be that we asked B to get this information from A because, as you said, we know it, so we understand it.

Where it has been used is that you have a product -- I don't know if I can explain this properly.

But it has lost some of its exclusivities and its patents, but it has now been bought by another company and another company now is going to do a trial. So, they'll get three years exclusivity, and they need that data. They can't just send us the reports. So, it's a very different situation than the one you're describing.

It's where if we're going to ask for a study that depends on some other information that was never put in the label but owned by that other company, you can't just tell us that that company -- it was trying to get at the issue we didn't want people just telling us the company allowed them cross reference. That's what it was trying to get at. It was trying to get at the fact that if you're going to ask us to start at building our requests or building the studies you want based on information that somebody else owns, that you need to get that information and let us review it.

But you're right. If it's just product B and C -- different companies with the same indication, we know that information. We don't ask them to purchase it or get it.

I don't think I made that clear, but it's a really different circumstance than what you're describing.

DR. CHESNEY: Thank you, thank you, thank you, Dianne.

We'll gather tomorrow morning at 8 o'clock. Have a good evening.

(Whereupon, at 5:28 p.m., the subcommittee was recessed, to reconvene at 8:00 a.m., Tuesday, April 24, 2001.)

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