

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

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## P R O C E E D I N G S

(8:20 a.m.)

1  
2  
3 DR. CHESNEY: Good morning. Just getting last  
4 minute instructions here. The microphones that you have in  
5 front of you are a little different than we've had before.  
6 Be sure please to push the top button to speak, and also  
7 introduce yourselves. As you know, this is all being  
8 recorded and that makes it easier for the individual  
9 recording.

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

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

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

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

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

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

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

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

4 DR. SZEFLER: Stan Szeffler, Department of  
5 Pediatrics at the University of Colorado.

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. SEEFF: Leonard Seeff, NIDDK/NIH.

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

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

18 DR. REHERMANN: Barbara Rehermann, NIDDK/NIH.

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

21 MS. PETERSON: The following announcement  
22 addresses the issue of conflict of interest with regard to  
23 this meeting and is made a part of the record to preclude  
24 even the appearance of such at this meeting.

25 Since the issues to be discussed by the



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

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

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

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

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

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

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

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

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

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

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

7 Thank you.

8 DR. CHESNEY: Thank you, Jayne.

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

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

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

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

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

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

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

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

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

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

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

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

1 | to your discussion." Thank you.

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

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

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

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

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

1 that will help this committee's discussions.

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

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

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

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

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

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

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

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

25 |           How can pediatric patients whose HCV infection



1 | might warrant treatment be identified?

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

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

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

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

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

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

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

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

1 discuss.

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

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

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

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

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

7           Hepatitis C virus is an RNA virus consisting of  
8 9,000 nucleotides and is translated into a single  
9 polyprotein that consists of several structural and  
10 nonstructural proteins. The structural proteins form the  
11 virus core and envelope, and the nonstructural proteins are  
12 important for viral replication and amplification inside  
13 the cells.

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

25           Hepatitis C virus is present in several

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

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

8 |           Some determinants for the outcome of the  
9 | infection are certainly the virus itself, the genotype that  
10 | infects the patients, the quasispecies distribution, the  
11 | mutation rate, also the viral inoculate size. Then in  
12 | terms of the host, the age at the time of infection is  
13 | important.

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

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

1 | cells may mediate an innate immune response.

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

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

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

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

25 |           There is certainly evidence for the role of

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

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

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

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

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

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

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

20 The study on the single-source outbreak of HCV  
21 in Germany that I mentioned before describes that  
22 antibodies may disappear in recovered patients between 10  
23 and 18 years after infection. This has been shown in up to  
24 40 percent of the recovered patients. So, these patients  
25 cannot be diagnosed as recovered anymore because the

1 | antibody test is the current diagnostic assay.

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 Thank you very much.

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

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

23 Thank you. That was very informative.

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

1 | the adult population.

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

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

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

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

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

14 So, how do you study that?

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

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



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

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

13 | So, a quick summary of the retrospective  
14 | studies, and I've listed just a few at the bottom here, a  
15 | couple from Japan, from the United States, from Germany,  
16 | and another one from the United States. Putting all these  
17 | studies together, the number of patients that were studied  
18 | was somewhere between 70 and 840. The intervals from  
19 | exposure in the retrospective studies were listed as 9 to  
20 | 29 years.

21 | As you can see, there was a very high rate of  
22 | development of cirrhosis; 17 to 55 percent of these studies  
23 | were reported to have developed cirrhosis over a period of  
24 | 20 years. I forgot to mention that in that initial slide  
25 | the usual view that is held is that cirrhosis develops in

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

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

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

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

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

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

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

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

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

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

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

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

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

9 Well, it was followed by a study from Germany,  
10 Dr. Wiese, et al. Again, this was a large number of women,  
11 264 liver biopsies in women who, 20 years earlier, had  
12 been exposed to hepatitis C.

13 Here we use the Ishak Fibrosis Score, 0 to 6.  
14 5 and 6 represent cirrhosis, 3 and 4 represents fibrosis,  
15 and less than that is very little fibrosis.

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

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

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

9                   What was interesting, and it's a point that  
10                  again Dr. Rehermann has made, and I'll come back to that  
11                  later, is that when they followed them up 20 years later,  
12                  45 percent of these youngsters were now RNA negative. They  
13                  had spontaneously lost virus. That was a much higher rate  
14                  of spontaneous loss than we had usually thought to be the  
15                  case, which was about 15 percent.

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

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

1 transplant centers, 29 participating centers since 1995.

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

11 So, now let's go quickly to a series of studies  
12 in transfusion recipients. These are studies that I was  
13 involved with. Blaine Hollinger here has been involved  
14 helping me out with these studies, Harvey Alter, and so on.  
15 These are long-term studies. We reported the first time in  
16 1992, and then we actually have a paper, which I say in  
17 preparation here, that was reported in Hepatology a couple  
18 of months ago.

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

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

5 What's happened to them?

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

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

25 What I think was interesting -- and also it

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

16 Well, we then did the RIBA test on them, the  
17 third generation test, and it turns out that 50 percent  
18 were positive. The others were either indeterminate or  
19 negative. So, we decided to focus our attention on these  
20 17 people. A small number, but this is the earliest, as  
21 far as I know, reported evidence that hepatitis C has been  
22 around, and I believe that hepatitis C was around since the  
23 Second World War, probably in low level. Then when the  
24 drug culture began to flourish, it probably increased, and  
25 that's why we're dealing with a big problem now.

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

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

11                  What's happened to these 17 people? 7 have  
12    died and 10 are alive. Of the 7 who have died, 1 has died  
13    of liver disease, and I'll show you what's happened to the  
14    10.

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

21                  Now what about the people who are living? This  
22    is not an updated slide. But what we have managed, of the  
23    10 people that we know to have been infected and alive, 2  
24    of them we cannot find. That leaves 8. One of those 8 has  
25    had a stroke and the family will not permit us to see that

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

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

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

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

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

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

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

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

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

18 Obviously we've heard about genetics.

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

25 Viral genotype clearly is extremely important,

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

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

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

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

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

1 pure, certainly not Harvey.

2 So, we started off with 100 patients with acute  
3 HCV infection, and we're making the assumption that about  
4 20 percent recover. As I'll show you and as we've already  
5 heard, it may be higher than that in some populations,  
6 leaving 80 patients with persistent infection.

7 We think that if you follow these people out,  
8 30 percent will have stable chronic hepatitis, and by this  
9 we are now talking about histology. That is, if you do  
10 liver biopsies, you're going to see less than 3 out of 6  
11 Ishak fibrosis. 40 percent, variable progression. That  
12 means individuals with bridging fibrosis, and 30 percent of  
13 this group, which is 20 percent of that, with cirrhosis.  
14 Then you treat those people, as we are now doing, and this  
15 was before we have the pegylated interferon, and this may  
16 get better. We say there's a sustained response rate of  
17 about 35 percent, or 20 patients, leading to treatment  
18 failure in 65 percent.

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

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



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

5 So, let me just quickly summarize the data  
6 demonstrating a higher than expected rate of spontaneous  
7 recovery. In our study, 24 percent of individuals who are  
8 transfusion-associated have spontaneously recovered. If  
9 you look at the NHANES data from Miriam Alter, 26 percent  
10 have recovered. Here are the data from leukemic children;  
11 29 percent of her people have recovered. The Kenny-Walsh  
12 and Wiese study, the contaminated Rh immunoglobulin, 45  
13 percent have recovered. The study from Germany, 45 percent  
14 have recovered. And in the paper that I didn't report to  
15 you from Australia, 46 percent have recovered  
16 spontaneously. The question is when and why, and that's  
17 why we pay Barbara to help us find out why they recover.

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

22 DR. CHESNEY: You go ahead, please.

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

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

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

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

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

1 treatment.

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

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

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

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

7                   There was obviously a dramatic difference  
8 between those with genotype 1a and 1b versus genotypes 2  
9 and 3. As you can see, the standard went from 33 to 34 to  
10 42 percent in the genotypes 1b, a dramatic response in  
11 genotypes 2 and 3, 80 percent plus. I think now we're  
12 reaching the point where this is virtually a curable form  
13 of hepatitis C if you have genotypes 2 and 3, and I hope  
14 that that will get better as time goes on and reach 100  
15 percent. In fact, it may have reached that already.

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

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

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

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

11 Let's skip this slide and just go to the final  
12 slide to show you the changes that really have taken place  
13 and are pretty remarkable, I think. We began with  
14 interferon for 6 months, 6 percent. Interferon for 12  
15 months, 16 percent. Interferon plus ribavirin for 6  
16 months, 34 percent. Interferon plus ribavirin for 12  
17 months, up to 42 percent. PEG-interferon about the same,  
18 39 percent. And PEG-interferon with ribavirin, up to 54  
19 percent. So, clearly over the years there has been a  
20 remarkable improvement in the response rate to treatment.  
21 I guess that's where we are likely to be in the very  
22 immediate future as far as treatment is concerned.

23 Now, your problem is to decide what happens to  
24 children who are infected once they reach 20 and move on to  
25 30 and 40 and 50 and 60. There's no answer to that. I

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

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

11 |           Thank you.

12 |           DR. CHESNEY: Thank you very much. Very  
13 | informative.

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

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

24 |           (Laughter.)

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

1 20 minutes is sort of touch on some of the issues you've  
2 heard discussed on hepatitis C in children. Our data are  
3 nowhere near as mature as things you've heard from Dr.  
4 Seeff this morning, unfortunately, but maybe with this  
5 committee's help we can get some direction about how to  
6 pursue your learning what the important topics are at  
7 least.

8           These data I actually extracted from Dr.  
9 Alter's paper and from the NHANES data that you've heard  
10 alluded to earlier, and this is just looking at prevalence  
11 of antibody to hepatitis C by age in the United States.  
12 You can see that most cases are certainly not childhood  
13 cases. The two pediatric age groups are described here,  
14 and the prevalence of this antibody is quite low, less than  
15 .5 percent of the population have been infected or are  
16 infected with hepatitis C.

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

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

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

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

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



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

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

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

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

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

25 |         But basically this is what we found, that

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

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

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

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

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

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

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

13 What these investigators did was look for  
14 hepatitis C RNA at birth by sampling cord blood. 18 of the  
15 266 were positive, indicating that there was already maybe  
16 some viremia at the time of birth, and most were negative.  
17 But if you look at 4 months of age, the vast majority of  
18 these infants had cleared hepatitis C RNA. Were they truly  
19 infected? Was it a transient viremia? It's not really  
20 analogous, for example, to HIV, I think. But 2 remained  
21 positive.

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

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

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

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

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

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

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

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

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

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

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

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

25                 At this point elective cesarean section to

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 C during their pediatric years.

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

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

25 Now what about treatment? What do we want to

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 |           So, what are the therapy considerations for

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

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

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

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

22 Thank you.

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

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

1 now regarding an overview of the FDA initiatives.

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

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

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

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

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

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



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

17                  In 1992 the agency proposed new regulations, or  
18                  revised regulations. These were finalized in December of  
19                  1994, and we refer to this as the 1994 rule. The citations  
20                  for all of these things that I'm going to be speaking about  
21                  are the last two slides in your handout. The intent of the  
22                  1994 rule was to allow a broader basis for inclusion, or to  
23                  clarify a broader basis for inclusion of pediatric data in  
24                  the label. It specifically said that evidence to support  
25                  pediatric claims can include effectiveness data in adults

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1                   Impact of FDAMA. These numbers are constantly  
2 being updated in the Center for Drugs. But as of April 1,  
3 2001, the FDA has issued 188 written requests, which cover  
4 411 studies because each written request, of course, may  
5 include more than one study. The agency has given 28  
6 grants of exclusivity, and 18 products have come along now  
7 with new labeling for pediatric use. The manufacturer will  
8 be able to receive exclusivity for conducting the studies,  
9 even if the studies do not result in changes to labeling,  
10 but that's part of the agreements under FDAMA.

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

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

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

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

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

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



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

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

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

23                   Thank you very much.

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

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

6 | Thank you.

7 | (Recess.)

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

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

19 | (No response.)

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

25 | DR. NELSON: To some extent my questions

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

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

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

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

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

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

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

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

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

4 | DR. CHESNEY: Yes.

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

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

19 | DR. CHESNEY: Yes.

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

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

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

9 | DR. CHESNEY: Dr. Jonas.

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

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

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

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

5 | DR. CHESNEY: Dr. Gorman.

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

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

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

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

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

8 |           DR. CHESNEY: Dr. Edwards.

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

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

19 |           DR. SEEFF: There are conflicting data about  
20 | the value of genotyping in defining outcome. Clearly there  
21 | is a distinct difference with respect to treatment. There  
22 | were some studies that suggested that people with genotype  
23 | 1 were more likely to progress and others that did not  
24 | indicate the case. My sense at the moment is that genotype  
25 | is not a terribly good indicator of what's going to happen



1 to the person, other than the effect of treatment.

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

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

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

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

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

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

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

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

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

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

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

3 DR. CHESNEY: Dr. Hudak.

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

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

25 DR. CHESNEY: Yes.

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

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

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

25 DR. FINK: This is a question about infants.

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

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

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

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

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

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

16 DR. CHESNEY: Yes, Dr. Ramsey.

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

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

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

8 (Laughter.)

9 DR. CHESNEY: Dr. Nelson.

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

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

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

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

19 | DR. CHESNEY: Dr. Luban.

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

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



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

7 DR. BALISTRERI: Yes.

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

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

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

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

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

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

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

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

1 I personally have taken care of many patients.  
2 I started working at the VA before some people here were  
3 born, and I've been seeing the same patients now for over  
4 30 years, some of whom I've got traced back to the time  
5 that they were originally infected. And not all of them  
6 have cirrhosis by any means. So, I think that it's not  
7 just the presence of the virus.

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

12 DR. CHESNEY: Dr. Schwarz.

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

23 DR. CHESNEY: Thank you.

24 Dr. Balistreri.

25 DR. BALISTRERI: If I could just comment on the

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

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

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

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

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

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

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

13 DR. CHESNEY: Yes.

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

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

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

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

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

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

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

3 DR. CHESNEY: Thank you. That was perceptive.  
4 Dr. Gorman.

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

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

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

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

1 relatively small samples, as you can imagine, because 12 to  
2 14 years ago, the numbers of patients who were receiving  
3 alpha interferon for what was then non-A/non-B/C hepatitis  
4 was pretty small.

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

18 DR. CHESNEY: Dr. Fink.

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



1 hepatitis C.

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

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

14 DR. SANTANA: I don't know about that. I was  
15 talking to her earlier, and I don't have the numbers in  
16 front of me. But it's been said many times that there's  
17 probably about a million survivors of child cancer right  
18 now, and if the numbers from the Italian study and the St.  
19 Jude study, which are between 1 to 5 percent prevalence  
20 rates in those survivors -- now, granted, many of those  
21 kids were in the epidemic of the 1980s and 1990s, but that  
22 means that there's probably anywhere between 5,000 to  
23 50,000 kids out there, childhood cancer survivors, that  
24 potentially may be infected and we haven't even screened  
25 them yet.

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

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

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

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

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

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

1           We've done a targeted look-back on a wide  
2           population of children transfused in the decade 1982 to  
3           1992 and have identified a seroprevalence rate of 1.9  
4           percent. That's a mixed group of children, premies, post-  
5           cardiac surgery, a few oncology patients, interestingly  
6           enough, and I think that's perhaps because we lost some to  
7           their primary disease.

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

10           (Laughter.)

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

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

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

23           (Laughter.)

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

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

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

19           DR. CHESNEY: Dr. Edwards.

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

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

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

14 DR. CHESNEY: Dr. Nelson, then Dr. Szeffler.

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

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

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

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

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

17           DR. JONAS: Yes.

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

1 it.

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

9 Do you have any further information on that?

10 DR. REHERMANN: No.

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

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

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

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

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

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

15 DR. NELSON: A combination of both.

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

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

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



1 | if we wait until these children are adults or adolescents?  
2 | 30 percent or 40 percent would definitely recover  
3 | spontaneously within the first or second decade of life,  
4 | and even those that are still viremic wouldn't have much  
5 | liver disease. So, a little bit of fibrosis but probably  
6 | not so much because in all studies it has been described as  
7 | mild hepatitis.

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

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

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

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

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

8 DR. CHESNEY: Dr. Szeffler has been waiting a  
9 long time.

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

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

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

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

9 The next question that we don't have an answer  
10 to is what happens beyond 20 years? Are they going to  
11 assume the rate of progression that occurs in the adult, or  
12 is the fact that the infection took place at an earlier age  
13 likely to set up a different kind of natural history in  
14 which the disease may not progress much beyond that? If  
15 it's 1 percent at 20 years, whereas in the adult it's 15 to  
16 20 percent, do they, in fact, when they get to the adult  
17 age bracket, then begin to go up like this? I don't think  
18 they do, but I don't know the answer to that. And I don't  
19 think anyone does. Blaine may. He's got his hand up  
20 there.

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

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

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

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

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

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

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

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

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

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

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

4 DR. CHESNEY: Dr. Schwarz.

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

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

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

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

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

11 DR. HOLLINGER: No.

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

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

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

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

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

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



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

3 |           The other thing is I think the strategy of  
4 | waiting till 18 -- we know what it's like to try to get  
5 | young adults, older adolescents, in for regular medical  
6 | care and blood tests and this kind of therapy when they  
7 | don't feel ill at all. I actually think that's a very  
8 | difficult population to target specifically the 18-, 19-,  
9 | 20-year-olds that are graduating from high school, that are  
10 | going off to do their life. To say we're going to delay  
11 | your treatment because you're under 18 until your 18 and  
12 | then hit you at that point I think is not a very compelling  
13 | strategy that I would propose to the families in my  
14 | practice.

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

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

3 (Laughter.)

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

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

9 Getting back to some of the things that Bob  
10 Fink was talking about and Dr. Luban as well, the 1982 to  
11 1992 cohorts are 10 to 20 right now. They clearly need  
12 interventions, but by the time we're done with the study,  
13 they're going to be mostly adults. So, the remainder of  
14 that population that's actually not in the study will  
15 functionally be adults by the time we have enough data to  
16 know what to do with that cohort. That doesn't say we  
17 shouldn't do it, but that's just one of the realities.

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

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

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

20 DR. CHESNEY: Dr. Schwarz.

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

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

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

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

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

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

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

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

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

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

10 (Laughter.)

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

18 DR. LUBAN: Most of the transfusion-acquired,  
19 exclusive of the hemophiliacs -- that's another population  
20 that we need to discuss separately -- are now between 7 and  
21 19.

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

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

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

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

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

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

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

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

18 DR. CHESNEY: Dr. Rehermann.

19 DR. REHERMANN: I have two points.

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



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

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

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

21 DR. CHESNEY: Thank you.

22 Dr. Gorman.

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

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

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

11 |           Thank you.

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

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

25 |           DR. GORMAN: Considered or studied? I guess

1 | that's my question."

2 | DR. JONAS: It was not studied.

3 | DR. CHESNEY: Dr. Seeff.

4 | DR. SEEFF: Dr. Rehermann beat me to the punch.

5 | I was about to mention this issue of stigma again. I  
6 | honestly think that this panel, in considering whatever  
7 | report it comes up with, should be talking about the issue  
8 | of stigma associated with the virus, in addition to the  
9 | question of treating the virus. There is enormous panic  
10 | that has been created by this disease, by this infection.  
11 | While I'm not a pediatrician, I happen to have been  
12 | involved with some radio programs in certain circumstances  
13 | in which I've been with parents who talk constantly about  
14 | the stigma of their child being a carrier of the virus and  
15 | that no one else wants to play with the child, that they  
16 | are ostracized from all the various things that they do.

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

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

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

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

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

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

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

10 (Laughter.)

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

13 Dr. Spielberg.

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

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

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

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

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

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

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

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

16 DR. CHESNEY: Dr. Lindsay.

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

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

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

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

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

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



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

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

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

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

4 DR. CHESNEY: That's an interesting concept.

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

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

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

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

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

14 DR. CHESNEY: Dr. Jonas.

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

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

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

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

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

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

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

25

## AFTERNOON SESSION

(1:07 p.m.)

1  
2  
3 DR. CHESNEY: Dr. Murphy is scheduled to talk  
4 to us for half an hour at the end of the day, but in fact  
5 she's going to be here all afternoon. She tells me she has  
6 more than a half hour's worth of information to tell us.  
7 With the renewal coming up and the congressional hearings  
8 next month, I think we all would very much like to hear  
9 what she has to tell us and to again ask her what we can do  
10 to help. I'm sure many of you have questions for her.

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

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

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

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

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

1 of 18 years. Comments. Dr. Schwarz.

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

5 The first is to prevent liver disease.

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

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

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

16 DR. CHESNEY: Thank you.

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

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

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

3 (Laughter.)

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

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

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

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

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

25 There certainly is one group that categorically



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

8 DR. CHESNEY: Dr. Kauffman.

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

1 DR. CHESNEY: Dr. Jonas.

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

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

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

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

9           DR. CHESNEY: Thank you.

10          Dr. Jonas.

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

25          DR. CHESNEY: Dr. Fink.

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

13 DR. CHESNEY: Dr. Gorman.

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

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

1 information necessarily.

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

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

14 DR. BALISTRERI: I agree.

15 DR. CHESNEY: Dr. Lindsay.

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

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

6 I like the idea of using the treatment in a  
7 population where the treatment has been proven to be 70 to  
8 80 effective. That gives you a really good target. I  
9 think that it's important to realize that when we talk  
10 about effectiveness with this treatment, we're talking  
11 about something that's really biologically quite unusual;  
12 that is, that we give a treatment for a fixed length of  
13 time. And from everything that we have available, it  
14 appears that we eradicate a chronic viral infection. Now,  
15 I don't really know that there is really good evidence that  
16 we do that with any other antiviral therapy. Almost all  
17 others are suppressive. So, we're talking about the  
18 potential for eradicating a chronic viral infection and, if  
19 we're successful, providing that individual with long-term  
20 clinical benefit.

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

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

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

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

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

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

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

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

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



1 anything at that point that will predict that.

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

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

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

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

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

1 related but different question.

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

15 DR. CHESNEY: Dr. Lindsay.

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

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

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

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

12 Dr. Hollinger.

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

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

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

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

11 |           DR. CHESNEY: Skip.

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

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

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

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

20           DR. CHESNEY: Dr. O'Fallon.

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

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

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

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

25 | DR. CHESNEY: Talking mainly to the committee,

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

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

21 DR. CHESNEY: Dr. Santana.

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

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

5 DR. NELSON: I was trying to answer question 1  
6 without answering question 2. I agree with you that I'm  
7 more inclined to think the disease is similar enough that I  
8 wouldn't require large cohort sort of efficacy studies and  
9 would look more towards dosing and safety studies  
10 personally. But I was trying to answer 1 without answering  
11 2.

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

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



1                   And I also would say if you're going to exclude  
2 the kids that are going to spontaneously resolve, which  
3 hopefully we could come to some consensus about where we  
4 might choose that to be, I don't know if I would demand a  
5 70 or 80 percent where we might do that.

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

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

19                   DR. SANTANA: I agree with your comment.

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

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

1 DR. CHESNEY: Asymptomatic maybe.

2 Dr. Hollinger.

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

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

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

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

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

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

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

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

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

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

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

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

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

10 |           DR. JONAS: Most of these will be perinatal.

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

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

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

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

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

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

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

11 DR. CHESNEY: Thank you very much.

12 Dr. Jonas.

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

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

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

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

16 DR. CHESNEY: Dr. Schwarz.

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

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



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

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

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

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

1 | general.

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

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

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

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

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

11           (Laughter.)

12           DR. CHESNEY: Go ahead, Skip.

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

1 toxicity.

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

15           DR. CHESNEY: Dr. Szeffler.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 (Laughter.)

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

18 Dr. Kauffman.

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



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

9 DR. CHESNEY: Dr. Balistreri.

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

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

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

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

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

4 | DR. CHESNEY: Dr. Fink.

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

14 | It really strikes me if we need more adult  
15 | data, the adult data we need is either reanalysis of the  
16 | trials or new adult trials to say what in a 4- to 6-week  
17 | time frame with exposure to this therapy predicts good  
18 | response, and then can we use that in pediatrics to limit  
19 | the toxicity, knowing from the adult data that the worst  
20 | patients, in terms of toxicity, will also fall out in that  
21 | 4- to 6-week period, and we don't have to expose large  
22 | numbers of children to a year's treatment that may not be  
23 | beneficial.

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

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

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

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

20 |           DR. CHESNEY: Dr. Nelson.

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

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

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

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

25 Most of us I think believe that the last one is

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

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

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

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

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

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

9 |           I think the liver biopsy is going to be  
10 | rediscussed at this meeting and there are people, as I say,  
11 | who have felt that it's not as important, and we're going  
12 | to have to rethink the whole issue about whether this is  
13 | mandatory. Up until now, it's been mandatory if we use the  
14 | 1997 NIH Consensus Conference data.

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

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

3 DR. CHESNEY: Dr. Hollinger.

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

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

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

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

8 Dr. Danford.

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

20 DR. CHESNEY: Dr. Schwarz.

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

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



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

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

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

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

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

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

19 |           DR. CHESNEY: Dr. Schwarz.

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

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

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

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

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

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

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

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

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

15 DR. CHESNEY: Dr. Gorman.

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

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

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

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

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

20 |           (Laughter.)

21 |           DR. CHESNEY: No standard treatment.

22 |           Dr. Luban.

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

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

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

11 But the other thing is that this is such a  
12 protracted disease that if you had two groups, one that was  
13 treated for a year and one that was not, I don't think it's  
14 going to make a bit of difference to that untreated group  
15 over the course of that one year. If indeed in the treated  
16 group you see real effect, you can then put the people at  
17 the end of the first year onto treatment, and you really  
18 haven't seriously altered the outcome. So, this is not a  
19 disease that is rapid. It takes forever to reach its  
20 endpoint.

21 DR. CHESNEY: Dr. Schwarz.

22 DR. SCHWARZ: We struggled with that issue. I  
23 think that the proponents of the observation group made two  
24 important points.

25 One was what we would learn in a larger number

1 of children than have been studied to date about  
2 spontaneous viral clearance because right now we have  
3 almost no good information.

4 And then the second is, if we're talking about  
5 some form of interferon and then some form of ribavirin, to  
6 look very carefully at the neuropsychological side effects  
7 and growth side effects. So, it may be that the  
8 observation group is more important for the assessment of  
9 toxicity or lack of toxicity than it is for liver disease.

10 DR. CHESNEY: Two excellent points.

11 Dr. Weiss, I think the consensus is that we  
12 can't extrapolate efficacy to children. So, do you want  
13 any more information from us on question 2?

14 DR. WEISS: Let's just go back to this again.  
15 I guess it may be somewhat of a catch 22. We're saying you  
16 can't extrapolate. And if everybody agrees that you can't  
17 because perhaps the responses, et cetera are better, then  
18 that speaks towards trials that are other than just PK and  
19 safety trials. So, what you've talked about doing is  
20 perhaps a delay in treatment, using some type of concurrent  
21 control, whether it's a registry or some other type of  
22 control population, perhaps delaying treatment for a year  
23 in those and then offering them treatment, which are  
24 designs that we've certainly seen and utilized before.

25 This may be a moot issue because oftentimes

1 | when we're talking about extrapolation, it's when it's very  
2 | difficult to do efficacy trials. What you're talking about  
3 | looking at in terms of measuring response rates, sustained  
4 | viral response, similar to what we do with the adult  
5 | settings, you could get those types of information in a  
6 | reasonably short trial. You could probably look at numbers  
7 | that are not very huge numbers. That's part of the second  
8 | set of bullets in question 2.

9 |           I guess the fundamental question about whether  
10 | or not the course of disease is sufficiently similar to  
11 | whether or not you can extrapolate is a fundamental  
12 | question that we address that we have been looking at ever  
13 | since the 1994 rule went into effect. But maybe for this  
14 | disease, it's somewhat of a moot issue because you're going  
15 | to be able to get your efficacy/activity data anyway in the  
16 | course of controlled trials, whether using historical  
17 | controls, a concurrent observational control, a registry  
18 | control. I guess I just want to make sure we clarify that  
19 | particular point because I think it is an important point  
20 | with this disease.

21 |           DR. O'FALLON: Oh, please, let's not talk about  
22 | historical controls. You've already spent the whole  
23 | morning telling us how the face of the disease is changing  
24 | over time. Historical controls are absolutely the wrong  
25 | thing to use in this. We won't be able to interpret the



1 data when we get done.

2 DR. WEISS: But you're saying, though, in this  
3 disease very, very few spontaneous remissions, spontaneous  
4 resolution of the virus, occur. I agree. Historical  
5 control trials are problematic, but in certain settings  
6 where the course of disease is very well documented,  
7 certainly historical controls have been used.

8 DR. O'FALLON: But we're talking about the face  
9 of the disease changing from being the blood transfusion to  
10 the vertical transmission and nobody really knowing how  
11 similar or how different they really are. You're going to  
12 have to have concurrent controls of some variety or  
13 another. Dr. Nelson asked whether we could have the choose  
14 what they wanted to have. Well, that's just fraught with  
15 all kinds of problems, but it's still better than nothing.

16 DR. CHESNEY: Dr. Jay Siegel from the Center  
17 for Biologics.

18 DR. SIEGEL: I just want to clarify this  
19 difference. I feel funny being here as an advocate for  
20 historical controls, and I assure you I'm not. But I think  
21 to follow on Dr. Weiss' points, there's been a lot of  
22 discussion about what you want a control group for, and  
23 there's no question that a control group will get you a lot  
24 of information, and you may not know the spontaneous  
25 remission rate, and you may not be able to determine

1 effects on development and safety endpoints as sensitively  
2 if you don't have a concurrent randomized control group.

3           On the question of efficacy, if you take  
4 sustained virologic response as an endpoint of efficacy,  
5 and if you do a study and you get a 37 or 45 percent  
6 sustained virological response, I don't think there's  
7 anybody here who would say, well, you couldn't conclude  
8 from that that there's a drug effect on sustained  
9 virological response. There's no suspicion that the  
10 control group would have had that level spontaneously. I  
11 think that's what Dr. Weiss was saying so that one can in a  
12 crude sense from historical controls at least determine  
13 that there is an activity which we're equating with  
14 efficacy.

15           There are a lot of other questions like dose  
16 optimization, like sensitive detection of adverse events,  
17 like whether in a combination therapy both elements of the  
18 combination or one element -- that you may well argue for  
19 all sorts of designs other than a simple cohort study.

20           DR. CHESNEY: Dr. Nelson.

21           DR. NELSON: Just to provide a little bit of a  
22 counterpoint, I agree with the comments that Dr. Weiss  
23 made. As I think about the purpose behind trying to  
24 extrapolate efficacy data, it's to try and allow us to  
25 introduce information into pediatric use that doesn't

1 require exposing children to unnecessary risks. So, if we  
2 are willing to construct an efficacy trial that's based on  
3 interventions that are of minimal risk, we're then debating  
4 something that I certainly wouldn't feel strongly about  
5 serving on an institutional review board.

6 But if efficacy was interpreted as requiring  
7 invasive testing in such a way, I'm not convinced that one  
8 couldn't infer from the adult data to at least avoid what  
9 would be considered invasive testing. The devil is in the  
10 details when you get actually down to those kinds of  
11 designs.

12 I agreed with what Ralph said, but not to the  
13 point where I would say let's design a classic adult  
14 efficacy trial and do three liver biopsies and whatever we  
15 can do to adults. I know that's an overstatement.

16 DR. CHESNEY: I agree. I don't think any of us  
17 were thinking to go back to the absolute bottom line  
18 initial therapy.

19 Dr. Hollinger.

20 DR. HOLLINGER: Well, I guess I would have to  
21 disagree that I think that you can't extrapolate the adult  
22 data to the pediatric data. I completely disagree with  
23 that. Monotherapy doesn't do as well as combination  
24 therapy. Genotype 1's don't do as well as genotypes 2's  
25 and 3's. High concentrations of virus don't do as well as

1 low concentrations of virus. I'm not sure what other  
2 extrapolation there is except that it seems like the  
3 sustained virologic response rate may be slightly higher,  
4 and there may be things, as mentioned before. I think,  
5 Bill, you mentioned some things about compliance or other  
6 things.

7 Can you tell me, just for my own information,  
8 what the relative concentrations would be based upon the --  
9 I think, Dr. Jonas, you mentioned also about the dosing on  
10 a per meter squared basis. What would that represent in an  
11 adult? Instead of 3 million three times a week, what would  
12 that represent approximately?

13 DR. JONAS: It would be about 5.

14 DR. HOLLINGER: See, 5 million units. That was  
15 the other thing. The higher the concentration you give,  
16 the longer period of time you give it, the better response  
17 rates. So, that doesn't surprise me. These numbers would  
18 be comparable in what I might expect in an adult receiving  
19 5 million units three times a week. So, I'm not sure what  
20 the issues are about extrapolation between adults and  
21 children. I think they're very comparable.

22 DR. CHESNEY: Go ahead.

23 DR. HUDAK: I'd just like to ask a couple  
24 questions to clarify things because I'm really a bit  
25 confused at this point. I sort of started the day having

1 read the materials here and being fairly persuaded about  
2 the efficacy in adult studies. I'm not exactly sure what  
3 we're trying to decide right now.

4           Clearly, there's been a lot of use of these  
5 agents in the pediatric population. You're doing studies  
6 in Boston. You're doing studies in Baltimore. Other  
7 people are doing studies. We're having all sorts of  
8 editorial comments about we think this therapy is more  
9 effective in children. What does that mean?

10           It seems to me that if you have appendicitis  
11 and you've got an 80 percent death rate if you don't  
12 operate, and you start operating and don't do a controlled  
13 study, and you find out that your death rate is 0, I think  
14 you're pretty safe in concluding that your operative  
15 intervention is very effective.

16           In this situation, I'm fairly persuaded that if  
17 you have a 6-year-old child who comes in who's got HCV and  
18 that child is going to have HCV the next year and the next  
19 year and the next year, I'm willing to grant you that with  
20 98 percent confidence from what I hear.

21           Clearly, there have been children coming in for  
22 treatment who have been treated for some period of time,  
23 and people have been following this for some period of time  
24 and looking at responses. What is the information? Is  
25 this, in fact, effective in eliminating viral load in the

1 | blood? Number one.

2 |           The other issue is in terms of the trial  
3 | design. I think, rightly or wrongly, I sort of look at  
4 | this from the point of-view of if it were my 6-year-old  
5 | child coming in who had HCV in the blood and I was going to  
6 | try to make some decision about enrolling in a trial or  
7 | what to do, I think there are some safety issues that have  
8 | been brought up. I'm not knowledgeable about what all the  
9 | issues are. I've heard a lot of things, but I'm not sure  
10 | how severe they might be, what the incidence is. Clearly  
11 | the spastic diplegia in an infant is a concern. I don't  
12 | think that's operative at 6. But some of the long-term  
13 | psychological issues would worry me.

14 |           So, I'm not sure at this point, having listened  
15 | to everything that everyone has told me, that if my 6-year-  
16 | old child was asymptomatic and was otherwise healthy, with  
17 | incidental or indolent HCV in the blood -- I certainly I  
18 | don't think would go ahead and choose willy-nilly to put  
19 | the child on treatment. I think I'd be much more likely to  
20 | go into a clinical study, which would be placebo controlled  
21 | because, as a professional, I know that the risk of side  
22 | effects is a real issue.

23 |           Certainly in my field, we've done a lot of  
24 | things, most frequently treatment of babies with steroids  
25 | for lung disease where everyone jumped the gun on this, did

1 it for 10 years, and now we're finding out that these kids  
2 have a much increased chance of having cerebral palsy,  
3 which wasn't found out until 10 years after the fact.

4 So, I guess I'm kind of unclear as to which  
5 direction we're going here. I think if there is evidence  
6 that there's efficacy, which I think there must be some, is  
7 a placebo-controlled trial looking at side effects  
8 appropriate? How long are you going to look for side  
9 effects to develop? Is it reasonable, if the placebo group  
10 shows no acute side effects but still has viral load, to  
11 cross them over to treatment only one year later? You may  
12 lose all the information you're going to get about the  
13 long-term side effects, and you don't know that treating at  
14 6 as opposed to 12 is going to make any long-term  
15 difference in the issue you're facing. So, I'm really  
16 quite confused.

17 DR. CHESNEY: Yes, please clarify for us.

18 MR. FLEISCHER: No. Can I add to the  
19 confusion?

20 We've heard a lot today about sustained  
21 virologic response, eradication, cure. But I wonder if we  
22 could just talk a little bit about what the lower limit or  
23 undetectable viral load really means. We have a number of  
24 research-based assays that have various lower limits of  
25 quantification. Those have never really been validated.

1 We don't know what the lower limit of quantification is  
2 with certainty for a lot of these assays. We know with HIV  
3 that just having no measurable virus doesn't mean it's not  
4 there. In HIV we have lots of sanctuary sites, lymph  
5 nodes, CNS, which we don't have good drug penetration into  
6 and good ways of measuring. We don't know whether we have  
7 some sanctuary sites for this. We're only measuring so far  
8 serum HCV RNA. I know there has been some work, but I  
9 don't know very much about it, the work in looking at  
10 actually the viral load in the liver. So, I was wondering  
11 if the experts could talk a little bit about what it really  
12 means to have an "undetectable" viral load.

13 DR. SEEFF: To some extent, the proof is in the  
14 pudding, isn't it? If indeed 10 years later, if we use the  
15 current cutoff -- I guess the lowest level is what? Is it  
16 50? All right, 10 copies. The fact is that if you follow  
17 these patients out using that as the endpoint, 10 years  
18 later and 12 years later and 13 years later, they still  
19 don't have detectable virus. It hasn't come up.

20 Now, it may be in the liver. I think we're  
21 beginning to find that with hepatitis B, by the way. Maybe  
22 we never recover from hepatitis B. Maybe there is  
23 hepatitis B in the liver even though we now even have  
24 antibody in the blood.

25 The fact is, though, what the effect of all of



1 this is. What is the outcome? Maybe 20 years from now it  
2 will change. I don't know, but certainly 10 years later,  
3 in those people who have responded by the criteria that we  
4 have used, they still don't have virus. Their enzymes are  
5 generally normal. They don't have any clinical  
6 manifestations, and their histology is better. So, I can't  
7 deny the possibility that there may still be residual virus  
8 that we can't measure, and what the effect of that will be  
9 over 50 years, no one really knows for sure.

10 We still have to accept the view -- and the  
11 proof is not yet fully in -- that treatment is going to  
12 reduce mortality. I think it makes sense, and at least  
13 there's some preliminary data that would suggest that. I  
14 guess we could do studies looking in the liver and see if  
15 the hepatitis C virus is still there in individuals in whom  
16 it's not in the blood. But after all, as I say, what we're  
17 trying to do is to make the patient who is infected feel  
18 better and remain better as best we're able to determine,  
19 which in liver disease is progression to fibrosis.

20 To me the whole essence of hepatitis C -- and I  
21 know again there's a little discrepancy in this view -- is  
22 progression to fibrosis. If we could cut out progression  
23 to fibrosis, we can use all these instruments and say,  
24 well, in retrospect I didn't feel so good for 25 years.  
25 Most of the time, people just don't feel very good for the

1 last 25 years.

2 (Laughter.)

3 DR. SEEFF: But they don't know about this  
4 until they're told that they have hepatitis C and they've  
5 had it for 25 years.

6 So, it's when they progress to fibrosis and  
7 ultimately to cirrhosis, their portal hypertension begins  
8 to develop, and then you run into trouble that you have an  
9 increased likelihood of development of cancer which in  
10 hepatitis C rarely occurs without significant fibrosis  
11 and/or cirrhosis or that they have hepatocellular failure.  
12 So, that's what we're trying to prevent, and if we can  
13 prevent that, I think we've done the best we possibly can.

14 DR. CHESNEY: Dr. Santana.

15 DR. SANTANA: In my own simple logic, I'm going  
16 to try to summarize what I've heard. I think what I've  
17 heard is that this disease is really no different in  
18 children than it is in adults. It's probably the same  
19 virus. It's the same pathogenesis, probably produces the  
20 same end result if you give it enough time to do what it's  
21 supposed to do. So, I don't think basically the disease is  
22 very different.

23 What I've also heard is that when you intervene  
24 with X treatment, that there is a wide variation of  
25 responses, and if you use the serologic viral response as

1 | your endpoint, some people will respond better than others.  
2 | Well, that's true for many diseases. That's what  
3 | prognostic factors are all about. So, you do get good  
4 | responses in a good number of patients, and when you use  
5 | these treatments in children, you get similar responses.  
6 | You may get some better responses. There may be some  
7 | pharmacokinetic differences. There may be some issues of  
8 | genotype, et cetera that may explain why children may  
9 | respond better. But I haven't heard that children respond  
10 | worse.

11 |           So, the central issue then is not doubting the  
12 | potential efficacy of the intervention, but how can that  
13 | intervention be used in a safe way in children. So, the  
14 | issue to me becomes then what studies do we do with the  
15 | endpoints that we know about, not endpoints that we don't  
16 | know about because we don't know whether these children 30  
17 | years later are going to get hepatocellular carcinoma and  
18 | are going to die. But we do know that we can measure viral  
19 | response. We know that maybe fibrosis is a good indicator  
20 | too. Using those endpoints, how can we design trials to  
21 | maintain that efficacy or improve on the efficacy and then  
22 | try to answer the real question, which is the safety.

23 |           So, maybe we shouldn't be talking about  
24 | randomized studies with placebo controls or observation  
25 | groups. Maybe we should be looking at studies that look at

1 different dosing regimens or different exposure regimens  
2 because ultimately to me that's what would convince me that  
3 the therapy then is both efficacious and safe and not just  
4 efficacious with a lot of safety issues.

5 That's my summary.

6 DR. CHESNEY: Thank you.

7 Dr. Gorman.

8 DR. GORMAN: I think I may have heard the  
9 information this morning slightly differently. I think I  
10 heard that the best prognostic factor you could have when  
11 you develop hepatitis C is being a child. 20 percent of  
12 adults 20 years later have cirrhosis, and less than 1  
13 percent of children have cirrhosis. So, when you were  
14 talking about prognostic factors, the best prognostic  
15 factor that I heard presented was to develop this disease  
16 while you're an infant.

17 I'm sure that it's the same disease virally and  
18 in eventual outcome, but the slope of the progression of  
19 that disease seems to be remarkably different in children.  
20 You can bring in other extraneous factors such as alcohol  
21 consumption that adults have that children don't, but  
22 they're not extraneous. The progression of the disease is  
23 slower in children. So, I think it's the same disease but  
24 the confounders have been eliminated and it doesn't  
25 progress as rapidly and doesn't seem to be as severe as it

1 | is in most adults.

2 |           DR. SANTANA: I'm not sure. I'm beginning to  
3 | think that this is a new disease of kids that happened in  
4 | the last 20 years where it's been a disease in adults  
5 | probably for the last 40 or 50 years. It wasn't until we  
6 | had these "epidemics" in the 1980s and 1990s that it became  
7 | a pediatric disease in terms of children who were exposed  
8 | perinatally -- period -- because how else would kids get  
9 | exposed? It's bloodborne. Or unless it was through  
10 | transfusion. So, we have two groups of patients. We have  
11 | the patients that are now entering their 20's and 30's that  
12 | we cured from other diseases who now have hepatitis C or we  
13 | have the kids who are getting it perinatally. Perinatally  
14 | is a new disease. It only has occurred in the last 20 or  
15 | 25 years.

16 |           DR. GORMAN: But with any new disease, the most  
17 | serious cases percolate to the attention of medical  
18 | providers first. So, you would assume that in our  
19 | particular epidemic -- I agree with you it's new in the  
20 | sense of the incidence, but we should be seeing the more  
21 | severe cases first. They should have percolated to the  
22 | top, and that doesn't appear to be the case. It seems like  
23 | we're getting milder disease even though it's more common.

24 |           DR. CHESNEY: Dr. Weiss, I'm almost embarrassed  
25 | to ask this because it will demonstrate my ignorance, but I

1 | do that all the time anyway, so I don't know why I'm  
2 | worried.

3 | (Laughter.)

4 | DR. CHESNEY: But I interpreted this as that if  
5 | we were going to look at efficacy in children, it would  
6 | take much larger groups of children, that if we just  
7 | extrapolated efficacy from adults to children, that then we  
8 | could just focus on the side effects and the PK/PD  
9 | parameters.

10 | DR. WEISS: It may be just semantics because in  
11 | a lot of settings, you measure efficacy endpoints. There  
12 | are a lot of times, because of the smaller numbers of  
13 | children affected, where the trials that are done -- and my  
14 | colleagues in CDER, maybe Dianne, could speak with respect  
15 | to all those written requests that have been issued over  
16 | the last couple of years with those hundreds of different  
17 | written requests and several hundred studies that have been  
18 | asked for, and many of them have come in. There's been  
19 | sometimes some confusion because they have to, for their  
20 | tracking purposes, identify which trials are efficacy  
21 | trials, which trials are activity trials.

22 | Sometimes you might consider an efficacy trial  
23 | -- if you consider it the same way you might do it for  
24 | adults for the first approval, those trials probably  
25 | wouldn't meet that criteria. But, nevertheless, they do

1 show response rates or whatever it is that's the important  
2 aspect of the disease that you're measuring. Some of them  
3 are controlled. Some of them look at the response rates in  
4 light of what's been documented from the adults. So,  
5 sometimes it maybe gets to be semantics as to what you want  
6 to call it.

7 DR. MURPHY: What Karen has identified I think  
8 and what you're struggling with is what we're all  
9 struggling with, which is it's not just semantics, but it  
10 really gets to are we willing to extrapolate completely or  
11 partially. That's sort of a terrible thing to say because  
12 the way that the 1994 rule is, it's sufficiently similar.

13 We have a category that we've put in your  
14 questions as exposure/response. I'm going to shorten that  
15 to PK/PD, even though it may not always be appropriate.  
16 Because we have felt that there are situations in which you  
17 think the disease and the response are sufficiently similar  
18 that you can extrapolate the efficacy, but you wished a  
19 test of hypothesis, if you will. But it's the same  
20 endpoints. It's the same viral loads. Again, it's a test  
21 of a hypothesis that you can extrapolate. The numbers are  
22 small, so you can't really call them efficacy trials.

23 About 10 percent of our written requests now  
24 are in that category where we think we can extrapolate, but  
25 we want to have this test of hypothesis in addition to dose

1 finding and safety because the safety issues are clearly  
2 different.

3 So, that is what we were trying to get at with  
4 the question. If you think that you can extrapolate, how  
5 would one design this test of hypothesis if you're not  
6 sure, in addition to what safety studies do we need. I  
7 think that's the shortest way to put it.

8 DR. WEISS: You could almost consider it a  
9 little bit of a Bayesian approach. Your priors are going  
10 to be high because you already have adult data and you know  
11 that there is a fair number of similarities. Given the  
12 fact that you have these priors, what additional kinds of  
13 data would it take? It's probably not going to take the  
14 same large numbers and possibly not the same kinds of  
15 controls because you have those priors already.

16 DR. CHESNEY: Dr. Spielberg.

17 DR. SPIELBERG: Sort of drawing on what Bob  
18 Fink talked about earlier on, if you really wanted to look,  
19 say, at dose ranging and PK/PD, what you'd want is an early  
20 marker and having, say, three dose-ranging groups. At 6  
21 weeks, you look at your decrease in viral titers, and you  
22 say, this group is clearly better than that group. You may  
23 want to continue that from a safety point of view because  
24 you may want to work it out another 12 weeks and see if,  
25 indeed, some of the lower doses caught up efficacy-wise.



1 I'm still concerned, even though we talked  
2 about some of the older patients having various behavioral  
3 problems and suicide problems, we have clear evidence of  
4 neurologic damage in the little ones. So, if you have it  
5 in the real little ones and you've got it in the older  
6 ones, my guess is you've got it in the middle ones too. I  
7 don't think we've looked in a structured way at cognitive  
8 function and behavioral outcomes and CNS toxicities. Since  
9 we know nothing about the mechanisms of the CNS toxicity, I  
10 think we're going to have to look very, very carefully.

11 But doing interim analyses, we really don't  
12 have to have an 18-month study and then start another 18-  
13 month study at another dose if, in fact, the data in the  
14 sequential manner allows us to begin with three or four  
15 strata and then drop a stratum very quickly because it's  
16 not doing anything. Now we're down maybe to two strata,  
17 but we want to continue those two strata out another 12  
18 weeks, see where they are, follow safety during that period  
19 of time so that we're getting now more and more about  
20 risk/benefit. We can do that if, in fact, there are enough  
21 adult data to suggest what the time points will be.

22 That's probably the quickest way of getting at  
23 the kinds of PK/PD. We talked about this in ICH E-11 as  
24 well, of bridging data between the adult data and the  
25 pediatric data that increase your confidence that, in fact,

1 | you're getting the same kinds of outcomes that you saw in  
2 | the adults.

3 | DR. CHESNEY: Skip.

4 | DR. NELSON: I think one of the big challenges  
5 | would be to establish some of that neuropsychiatric  
6 | toxicity which would likely require long-term studies and  
7 | likely large scale studies. So, my question is whether  
8 | there could be a registry approach of some kind. All the  
9 | pharmacies I know inform all the pharmaceutical companies  
10 | when I write a prescription for X. So, why couldn't we  
11 | begin to harness some of these databases in a positive  
12 | fashion rather than just a marketing fashion to begin to  
13 | try and generate that kind of data? Would that be received  
14 | well? You know, not holding up approval in marketing but  
15 | having some way that, 20 years down the line, we'll know if  
16 | there has been some subtle neuropsychiatric problems when  
17 | kids hit 7th through 12th grade, having got this as a 2-  
18 | year-old.

19 | DR. SPIELBERG: Absolutely. I think it will be  
20 | probably a combination of the two, intensive examination of  
21 | the kids during the course of a year trial and at their 18-  
22 | month follow-up with intense investigation of cognitive  
23 | function and behavioral testing and attention span. There  
24 | are a number of paradigms for doing this that have come  
25 | primarily from the anticonvulsant literature of looking at

1 cognitive and development effects of anticonvulsants.

2 But then for the long-term kinds of things,  
3 absolutely. I think those kinds of longitudinal, long-term  
4 sorts of examinations are exactly the kinds of things we're  
5 going to have to look at in this and other diseases.

6 DR. CHESNEY: Dr. Weiss.

7 DR. WEISS: That was very helpful. I just want  
8 to point out that that is actually question 4, so if and  
9 when we ever get to that.

10 Actually when we started these discussions at 1  
11 o'clock, I thought we'd have tons of time and be twiddling  
12 our thumbs with all this free time. So, I'm actually  
13 pleased that there's lots of controversy and discussions,  
14 but in an attempt just to try to get through at least  
15 questions 3 and 4 -- we touched a little bit on 4. 3  
16 hopefully may be more straightforward.

17 What I'd like to maybe propose or ask if this  
18 is okay to do, we've heard a lot about the issues of the  
19 need for a control group, and it's ranged from maybe you  
20 don't need a concurrent randomized control to dose-ranging  
21 types of controls to placebo controls to observational  
22 controls. I guess I take away from that there isn't really  
23 one right answer. There are perhaps advantages and  
24 disadvantages to a number of these different options.  
25 That's helpful, I think, as we think about the advice,

1 | which again we could probably debate all day long.

2 |           But one of the points on question 2 that I  
3 | would actually just want to make sure that I personally get  
4 | the information about is the third-to-the-last bullet on  
5 | that first page, which is the identification of those  
6 | children whose HCV infection should be treated and  
7 | therefore could reasonably be included in a clinical trial.  
8 | I know our experts have already discussed some of that. I  
9 | would just like to maybe be able to have a little bit  
10 | clearer criteria of what you would be considering in your  
11 | exclusion and inclusion criteria for putting children in  
12 | trials.

13 |           DR. CHESNEY: Dr. Jonas.

14 |           DR. JONAS: I'll give my opinion for  
15 | discussion. As I sat here and listened to everybody, I was  
16 | scribbling it down myself. I think we're pretty much  
17 | agreed that maybe at this point we're not prepared to just  
18 | say the diagnosis of hepatitis C infection, virus in the  
19 | blood at one point. It's probably not enough.

20 |           Then we've talked a little bit about the  
21 | definition of chronicity. We want to have chronic  
22 | hepatitis C infection. You've heard Dr. Lindsay's several  
23 | definitions of that, but at least I think we want to be  
24 | sure we're not treating anybody who's very, very early in  
25 | infection who may clear the infection on his or her own.

1           So, I propose we can have some sort of  
2 definition, maybe nobody under age 2 or 3 and then have  
3 defined infection, viremic at least 6 months, two separate  
4 points in the preceding period. So, infection, then  
5 chronic infection, and then chronic infection with liver  
6 disease. So, do we want to avoid treating children with no  
7 liver disease from this hepatitis C?

8           This doesn't come up very often in my  
9 experience, but I suppose a cogent argument could be made,  
10 a liver biopsy at that point and have to meet certain  
11 criteria for chronic hepatitis on liver biopsy. So,  
12 infection, then chronic infection, then chronic infection  
13 with liver disease with maybe a cutoff age of 2 or 3 or  
14 something like that is what I'm taking away from all this  
15 to distill it out.

16           I think it gets a little hairier if you start  
17 saying a certain level of liver disease for the reasons  
18 we've discussed.

19           DR. CHESNEY: Dr. Gorman.

20           DR. GORMAN: I'd like to add to your inclusion  
21 list people who have an increased risk of liver disease for  
22 other etiologies. Dr. Luban talked about frequent  
23 transfusers, children who are receiving multiple  
24 transfusions. Comorbid viral infections such as hepatitis  
25 B might also be reasons to include people in studies

1 earlier.

2 DR. JONAS: Actually we usually use those for  
3 exclusion criteria.

4 (Laughter.)

5 DR. JONAS: You're sort of defining our list of  
6 exclusion criteria there.

7 DR. GORMAN: Knowing the desire for clean data  
8 by the industry and the FDA, I can understand those being  
9 used for exclusion criteria. However, we have difficulty  
10 treating basically healthy children otherwise. Even liver  
11 disease, depending on how you define it, may be perceived  
12 as basically healthy children. If you're talking about a  
13 minor elevation of the AST or the ALT or GGT, or whatever  
14 liver enzyme you wish to say, if you're going to talk about  
15 phase 2 cirrhosis or fibrosis without bridging, I think  
16 people will get a little antsy about that as a diseased  
17 child.

18 DR. JONAS: Just note that I didn't say  
19 anything about transaminases.

20 DR. GORMAN: I noticed.

21 But people who have other risk factors for  
22 progression of their hepatic disease I would consider even  
23 if the agency and the pharmaceutical industry would be less  
24 than enthusiastic about those.

25 DR. CHESNEY: Dr. Fink.

1 DR. FINK: I don't disagree with anything that  
2 was said, but I would probably add to that that I would  
3 look at least a two-tiered approach saying 12 and above  
4 first. Even for antibiotics and many other drugs that are  
5 less toxic, we look at 12 and above first and then we look  
6 at 6 to 12. In this disease where I haven't heard any real  
7 compelling argument that waiting to look at 12 and above  
8 first would impair the 6- to 12-year-olds, I would think it  
9 would just be the wise thing to stick to 12 and above first  
10 and then, as a second tier, look at the 6- to 12-year-old  
11 age group particularly since there are neurologic  
12 toxicities that are of concern.

13 DR. JONAS: Can I just make a comment to that?  
14 I just want to remind you that interferon is approved for  
15 chronic hepatitis B in children down to the age of 1, and  
16 it's double the dose.

17 DR. SCHWARZ: 2.

18 DR. JONAS: The studies were done to the age of  
19 1. It says 1 on the label, and the dose is double of what  
20 we're discussing here, and it's a 6-month course of  
21 therapy, just so you know.

22 DR. CHESNEY: Are there other issues on  
23 question 2 you want us to -- shall we go through all the  
24 bullets?

25 DR. WITSS: I was just looking at the clock and

1 the fact that we want to try to finish up within the next  
2 hour. That's fine. We can go through the bullets and make  
3 sure that we've covered them. A lot of them we somewhat  
4 covered in the discussions, but it would probably be  
5 helpful to go through them, and if there is no more  
6 discussion, that would be fine.

7 DR. CHESNEY: In addition, should it be  
8 determined that extrapolation may be appropriate, comment  
9 on the following. The first one, the identification of  
10 subgroups whose disease may be sufficiently different that  
11 extrapolation would not be appropriate.

12 DR. SANTANA: I think the only group that I can  
13 think of would be the transfusion patients because they  
14 have so much other comorbidity that potentially they could  
15 be different both in terms of their efficacy and safety.  
16 So, rather than including them, I would probably do it as a  
17 separate stratum or something. I don't know. Some study  
18 design. But I think those may be sufficiently different  
19 clinically that they should be treated in my view, but they  
20 should be separate from the others in terms of the analysis  
21 of the endpoints.

22 DR. CHESNEY: That's a good point.

23 What other groups do you exclude, Dr. Jonas?

24 DR. JONAS: Typically we exclude other viral  
25 infections, HIV infection, hepatitis B co-infection. We



1 | certainly look for other causes of chronic liver disease in  
2 | patients with chronic hepatitis. So, we look for Wilson's  
3 | disease and alpha-1-antitrypsin deficiency. We look for  
4 | autoimmune hepatitis because there is a danger if we  
5 | misdiagnose someone, just as in adults with autoimmune  
6 | hepatitis, as having hepatitis C because they have a  
7 | positive test and if we use interferon, we may worsen their  
8 | condition. We exclude people who have other autoimmune  
9 | diseases that might be worse, and then anyone who has an  
10 | obvious contraindication such as pre-existing serious  
11 | depression, substance abuse, unwillingness to use birth  
12 | control. We talked about that before. So, we have to do  
13 | pregnancy monitoring monthly and a birth control  
14 | questionnaire.

15 |           DR. SCHWARZ: Active malignancy. Hemophilia is  
16 | probably different biologically. It's certainly different  
17 | when it comes to the liver biopsy. And then some young age  
18 | of exclusion.

19 |           DR. JONAS: Decompensated liver disease was the  
20 | other big one. If anyone is very ill, starting to have a  
21 | lower albumin or prolonged prothrombin time or has had  
22 | bleeding varices or jaundice or anything. So, anyone who  
23 | has very advanced liver disease. They respond very  
24 | differently and they're at much greater risk with these  
25 | therapies.

1 DR. CHESNEY: Yes.

2 DR. O'FALLON: I interpreted that question a  
3 little differently when I saw it. I thought which children  
4 are not like the adults. And there were the vertical  
5 transmission. That's obvious. And then to a great extent  
6 the cancer survivors, all those pediatric cancer survivors  
7 who are now young people who are at high risk. So, I just  
8 wonder if you can truly extrapolate from the adults to  
9 those groups. They might have a different variety.

10 DR. CHESNEY: I think Dr. Schwarz did mention  
11 active malignant disease, not cured though.

12 DR. SCHWARZ: Right.

13 And then of course, if we're talking about  
14 extrapolation from adult efficacy data and if the existing  
15 data suggests that young children might have a better  
16 response, then I think that the age should be open for  
17 discussion. I personally think it's wrong to look at a  
18 cohort of young children with a low viral load and pre-  
19 cirrhotic liver disease and a short duration of disease and  
20 then extrapolate from the adult experience to them. I  
21 don't think that's correct.

22 DR. CHESNEY: Dr. Luban.

23 DR. LUBAN: I'd just like to add that there  
24 will be and is ongoing data collection on hemophilia and  
25 hepatitis C from any number of different studies. So,

1 | you'll have a subgroup to compare to another subgroup.

2 |           DR. WEISS: What I'm taking away from this too  
3 | is that there are a number of different groups, if you're  
4 | going to treat and you've defined your parameters to treat,  
5 | many of them appropriate to treat. But like most analyses  
6 | that are done, you would look at certain important  
7 | subgroups after the fact. If you're doing a randomized  
8 | controlled trial, you might want to stratify, but if you're  
9 | not doing that, if you're doing a single-arm type of trial,  
10 | it's probably less important for stratification, but you  
11 | certainly want to be able to define up front those  
12 | subgroups and be able to look at them afterwards and  
13 | determine whether or not you can come up with some types of  
14 | conclusions regarding their responses or similarities or  
15 | not. Does that make sense?

16 |           DR. CHESNEY: Study designs that may provide  
17 | for the optimal collection of safety, pharmacokinetic, and  
18 | activity data.

19 |           DR. SPIELBERG: Again, I'd need to really see  
20 | what the chronicity data looked like in the adults because  
21 | if you want to set up things in a relatively clean  
22 | population to get an idea of dose-ranging, you want the  
23 | shortest-term study you can do, if you will, a phase I.  
24 | It's not really a phase I study, but basically it's a PK/PD  
25 | viral clearing study to get an idea of dose-ranging.

1           The one thing we've learned from this whole  
2    FDAMA experience is in some of the younger kids, the  
3    clearance of their drugs may be even vastly greater on a  
4    milligram per kilogram-basis, and we may in fact be  
5    underdosing drugs such as ribavirin. I have no idea how  
6    that applies to biologics. I don't think we have any real  
7    data on clearance of biologics in the middle age toddler  
8    population who just chews up small molecular entities at  
9    two to three times the rate of many of the older kids.

10           But we need those data first, and I hope we  
11    would be able to do that kind of an initial study in a  
12    relatively short study looking at a relatively short  
13    endpoint so that at least when we start the longer-term  
14    studies, we're in better shape dose-wise.

15           We'll only get acute safety out of that. We  
16    already have acute safety because of the exposures we have.

17           Then the idea is designing the longer-term  
18    study for safety, having recognized already that we've  
19    begun optimizing the doses in those populations.

20           But we are going to have to be careful. Again,  
21    around the time of puberty, we know again there are going  
22    to be fairly significant pharmacokinetic shifts for many  
23    drugs. I have no idea how that applies to a drug like  
24    ribavirin, but we've got to establish that. Otherwise,  
25    again, we're going to be doing what we laughed at our

1 | internists friends for doing, treating a ballerina and a  
2 | sumo wrestler with the same dose of drug.

3 | DR. CHESNEY: Skip.

4 | DR. NELSON: Just to be clear, Steve, you'd do  
5 | that as a population pharmacokinetic and with adjustments  
6 | so that everyone in the trial would hopefully over a  
7 | reasonable period of time end up on an optimum dose so you  
8 | could see it as a therapeutic trial at the same time?

9 | DR. SPIELBERG: You could actually do it in  
10 | that way so that you would fold your initial dose-ranging,  
11 | if you had rapid enough feedback, which sometimes doesn't  
12 | happen because of the amount of time it takes to get the  
13 | levels back and everything else. But if you did have a  
14 | rapid enough feedback -- and maybe that could be built in  
15 | -- you would start off again with several different strata,  
16 | following the viral titers, and then fold the patients into  
17 | the longer-term observational study once you had determined  
18 | the dosing.

19 | But also don't forget you're also going to need  
20 | different endpoints for cognitive effects in different  
21 | kids. So, it gets very difficult. You're not going to  
22 | have 2-year-olds read Shakespeare back to you, and the  
23 | kinds of attention span issues and the kinds of assays that  
24 | you're going to be using for looking at CNS effects are  
25 | going to also have to be age-stratified. So, it gets a

1 little complicated around the edges, but it can be done.

2 DR. NELSON: I only ask because I think  
3 designing trials that favor the possibility of benefit for  
4 an individual participant I think is always a good thing  
5 and having that kind of population approach with an ability  
6 to adjust dose for the individual as opposed to the "you're  
7 in this cohort for the next 3 months, come hell or high  
8 water" approach.

9 DR. SPIELBERG: Yes. Again, remember, we don't  
10 have something where, if you're not at the right dose in  
11 the first 2 days, you die. This isn't a meningitis trial.  
12 This is a long-term kind of thing so that we're in a very  
13 different kind of situation in terms of dose-finding, and  
14 individuals can dose-find into the right range. That's  
15 actually maybe a nice design for this.

16 DR. WEISS: The biologics are a little bit  
17 tricky in terms of pharmacokinetics. It might be a little  
18 bit clearer with the ribavirin or other compounds coming  
19 down the pike, but traditionally with a lot of our  
20 biologicals, especially if we're talking about a pegylated  
21 molecule, the paradigms may be a little bit more difficult  
22 in terms of trying to determine optimal dose  
23 response/exposure.

24 MR. FLEISCHER: I'll just tell you that  
25 basically was the design of the first Rebetrone study:

1 three doses, then rollover into the one at 4 weeks based on  
2 antiviral response and actually hemoglobin response for the  
3 ribavirin patients.

4 DR. CHESNEY: I sense that we need to start  
5 thinking seriously about taking a break. Shall we discuss  
6 the choice of control groups before the break and then come  
7 back to tackle the other three questions?

8 DR. WEISS: I think we already did choice of  
9 control. We beat that horse into the ground. Hopefully it  
10 will be brief before we break. Maybe we could talk about  
11 what are appropriate endpoints, particularly liver biopsy.  
12 A number of people have talked about the role of liver  
13 biopsy. It's controversial in adults as well, but more so  
14 in children. I don't think anybody probably has an issue  
15 with looking at other types of -- the HCV RNA assays  
16 perhaps, but maybe we could just focus on liver biopsy as a  
17 measurement.

18 DR. LINDSAY: It would seem, given all the  
19 concerns that we all have about long-term effects of the  
20 disease, long-term natural history of the disease, that a  
21 baseline liver biopsy is important in terms of the design.  
22 But I think it would be extremely reasonable to extrapolate  
23 the adult data on histologic effects of a sustained  
24 virologic response to the pediatric population, and instead  
25 of doing liver biopsies as an endpoint of efficacy in the

1 short run, enroll these SVR pediatric patients into long-  
2 term follow-up studies where the liver biopsy would be  
3 planned for year 5 or some distant point just to  
4 demonstrate that the histologic benefit is there.

5 DR. CHESNEY: Dr. Schwarz.

6 DR. SCHWARZ: I'd just like to second that  
7 because, as Maureen said, the histologic changes in  
8 children, even those referred to a referral center, are  
9 fairly minimal. So, I think we're just not likely to see a  
10 change 12 months down the road. So, for both the safety  
11 and the lack of utility of the liver biopsy, I would agree  
12 we shouldn't do it as a short-term endpoint.

13 I might also share our disappointing experience  
14 in trying to come up with a serum marker of liver fibrosis  
15 as a surrogate endpoint for liver disease in hepatitis C.  
16 We looked at plasma transforming growth factor beta and  
17 serum procollagen peptide 3. And there were data in adults  
18 with hepatitis C that these were useful noninvasive markers  
19 of liver fibrosis. What we found out was that the growing  
20 normal child has so much TGF-beta and so much procollagen  
21 peptide 3 that until we got to the 15-year-old with  
22 hepatitis C, we couldn't tell a difference between our  
23 hepatitis C-infected children and the controls.

24 DR. CHESNEY: Thank you. I was wondering if  
25 there wasn't some kind of collagen marker that could be



1 followed.

2 Dr. Danford.

3 DR. DANFORD: Am I to conclude that because  
4 nobody has mentioned them, that MRI or other imaging  
5 modalities that are noninvasive are not useful in this  
6 setting?

7 DR. SCHWARZ: Yes.

8 DR. NELSON: Will that always be true, or do  
9 you think the imaging could improve to where it might  
10 become useful? Is there anybody working to extend the  
11 envelope in that direction? Because it would certainly be  
12 helpful.

13 DR. SCHWARZ: It would be wonderful, but I  
14 think that with those few exceptions of the young children  
15 with severe liver disease in whom the imaging techniques  
16 are useful, that the differences are just too subtle.

17 DR. CHESNEY: Let's take a break and plan to be  
18 back at 25 after 3:00 to tackle our last three questions.

19 (Recess.)

20 DR. CHESNEY: I guess we can go ahead and get  
21 started with question 3. I particularly wanted to thank  
22 all of you who are still so incredibly energized. I think  
23 I need to go and have my hepatitis C test done to see why  
24 I've been tired for all my life.

25 (Laughter.)

1 DR. CHESNEY: Question number 3. The marketed  
2 treatments for hepatitis C infection in adults include  
3 polyethylene glycol conjugated to interferon, various non-  
4 PEG interferons, and combination therapy consisting of  
5 Intron A, interferon A, and ribavirin. The data to support  
6 an indication for PEG-interferon plus ribavirin in adults  
7 have recently been submitted to the agency; preliminary  
8 results suggest marginally higher response rates, but  
9 possibly more safety concerns such as more severe  
10 neuropsychiatric events, bone marrow suppression, thyroid  
11 disorders, and cardiovascular events.

12 No products are currently approved for the  
13 treatment of hepatitis C infection in children. Studies  
14 with the interferon A/ribavirin combination are underway.  
15 Interim pharmacokinetic and safety data have recently been  
16 submitted to the agency. The interferon manufacturers are  
17 interested in studying the combination of PEG-interferon  
18 and ribavirin but not PEG-interferon alone in children.

19 Two questions. First of all, are additional  
20 studies of interferon-based therapies in pediatric patients  
21 warranted at this time? And I interpret that to be  
22 interferon alone or interferon plus ribavirin. If the  
23 answer is yes, then should only combination therapy be  
24 studied or is it appropriate to also evaluate PEG-  
25 interferon monotherapy in pediatric patients?

1                   So, the first question, are additional studies  
2 of interferon-based therapies in children warranted at this  
3 time? Dr. Nelson. . .

4                   DR. NELSON: Can one infer that the increased  
5 safety concerns are from the PEG-interferon, and if so, is  
6 there any evidence of dose response in terms of those  
7 safety issues?

8                   DR. WEISS: We have marketed PEG-interferon  
9 monotherapy. It's the first approval that came along, and  
10 that was I think in January of this year, just a few months  
11 ago. In that study, there were three dose arms. There was  
12 definitely a dose response with respect to toxicity of the  
13 PEG-interferon. If that was your question.

14                  DR. NELSON: Most of the toxicities we're  
15 worried about are in the long-term issues, neuropsychiatric  
16 and the like. So, to pick something that has a higher rate  
17 of those when we don't have good ways of studying them just  
18 strikes me as risky.

19                  Then I was trying to ask myself, well, under  
20 what circumstances would I do that? And that's if maybe I  
21 could get away with a lower dose that would not have those  
22 safety issues and maintain efficacy and perhaps have other  
23 tradeoffs that would make it worthwhile. So, I was trying  
24 to wrap my mind around that question.

25                  DR. WEISS: Actually in the controlled trials

1 that led to the approval of PEG-interferon monotherapy, it  
2 was a head-to-head comparison of three different doses of  
3 PEG-interferon versus Intron A. So, it wasn't really a  
4 comparison to Rebetrone, which is interferon plus ribavirin,  
5 which is probably a more important question because most  
6 people do not use Intron A monotherapy. Response rates  
7 were probably about doubled when using the PEG-interferon,  
8 especially the two higher doses of PEG-interferon, but the  
9 toxicities were also somewhat higher.

10 A lot of this is theoretical because there  
11 isn't a large, large database with PEG-interferon right  
12 now, but given the longer half-life, the longer that these  
13 levels last, there's certainly a concern about toxicities,  
14 the fact that a main way to treat toxicities of interferon  
15 are to either dose reduce or take drug holidays if  
16 something lasts for quite a long period of time. It may be  
17 that the actual toxicities themselves are not different,  
18 but they last longer and so they may be harder to treat.  
19 So, those are the kinds of concerns.

20 A lot of this is theoretical, and in a sense it  
21 may not be a terribly fair question to ask this committee  
22 because we don't have the data analyzed thus far in adults  
23 on PEG-interferon plus ribavirin. It's a little bit  
24 premature. And we don't have the full data set in  
25 pediatric patients being treated with Rebetrone yet to ask

1 that particular question. So, realizing that it may be  
2 somewhat of a difficult question to ask, given the database  
3 that we have right now, nevertheless we decided to ask it.

4 DR. CHESNEY: Three hands went up instantly  
5 over here.

6 (Laughter.)

7 DR. CHESNEY: I'm not sure who was first, but  
8 let me start with Dr. Schwarz who's our guest.

9 DR. SCHWARZ: Addressing the question as to  
10 whether additional studies of interferon-based therapies in  
11 pediatric patients are warranted, I'd like to respond to  
12 both Dr. Nelson and something Dr. Spielberg said having to  
13 do with both the safety and the way the safety is measured.  
14 I want to address particularly the neuropsychiatric side  
15 effects because I think that's something we're all  
16 concerned about.

17 I believe that if we're going to treat  
18 hepatitis C in children, we have to use interferon-based  
19 therapies because all the therapies to date have some  
20 interferon basis.

21 The neuropsychiatric side effects may be quite  
22 different in newborns, growing children, and adults. I did  
23 want to comment on this spastic diplegia business because  
24 it is very frightening. The spastic diplegia that was  
25 observed was in newborns treated for cavernous hemangioma.

1 I believe it was 1 million units of alpha interferon subQ  
2 daily for 4 to 6 months. That is I think probably  
3 biologically quite different than using interferon in older  
4 children. So, none of us want to get into that in newborns  
5 with hepatitis C.

6 But very cautiously studying the cognitive,  
7 neuropsychiatric endpoints of the use of interferon in  
8 growing children and interferon plus/minus ribavirin has  
9 not been done. We're not going to know anything more about  
10 it with the Rebetrone trial because that's combination.  
11 It's not a controlled trial. And it may also be quite  
12 different than the neuropsychiatric effects of interferon  
13 in adults which are primarily depression.

14 So, I personally think we really have a  
15 responsibility to look very carefully at these cognitive  
16 endpoints with validated testing instruments in the young  
17 population.

18 DR. CHESNEY: With interferon alone.

19 DR. SCHWARZ: And with different doses.

20 Well, my bias is that there should be  
21 interferon plus placebo, interferon plus ribavirin, and  
22 then some observation group, again primarily so we can  
23 compare neuropsychiatric endpoints at least during, let's  
24 say, a year of therapy before a crossover.

25 DR. CHESNEY: Great, very helpful.

1 Dr. Spielberg.

2 DR. SPIELBERG: Karen, what do we know about  
3 pegylated proteins in kids? I know there are some products  
4 out there that are a replacement in various enzymopathies  
5 where there are pegylated versions. Do you get similar  
6 increased durations of exposure? Do we have any way of  
7 guesstimating before we actually start putting such a  
8 pegylated compound into, say, a 2-year-old, whether once-a-  
9 week therapy is going to be adequate or whether we're going  
10 to need twice-a-week therapy? Is there any basis at this  
11 point for us to make any judgments?

12 DR. WEISS: In terms of pediatric patients,  
13 relative to the adult experience, I don't know if there is.  
14 There is experience with other PEG proteins, PEG-ADA for  
15 instance, approved on the basis of, I think, 10 or 6  
16 children. It was one of the smallest clinical trials ever  
17 that led to approval. PEG-asparaginase, which is now used  
18 in the oncology setting, primarily in children with ALL  
19 that have hypersensitivity to native asparaginase.

20 But I certainly can't, off the cuff, tell you  
21 that we have enough priors already with our experience with  
22 PEG to know. Victor, you've probably have had more  
23 experience in dealing with the PEG-asparigenases maybe.  
24 But even that's a different molecule, and there we're  
25 talking about the antibodies that affect the clearance of

1 the half-life of the molecule. It's probably a little bit  
2 different.

3 But even so, even in interferons, there is an  
4 issue of neutralizing antibody developing with the native  
5 interferons. Thus far we don't have any evidence that that  
6 impacts on efficacy responses, and pegylation is supposed  
7 to actually minimize that.

8 DR. SPIELBERG: So, we are breaking new ground  
9 then. Clearly, in terms of understanding PK, we're going  
10 to really need to look at it very carefully.

11 DR. CHESNEY: Dr. Gorman.

12 DR. GORMAN: Is one of the mechanisms of action  
13 of interferon, in terms of its toxicity, considered the  
14 interruption of angiogenesis? And if so, do we have any  
15 evidence that that is going to cause irreversible deficits  
16 in the brain? Spastic is clearly one, but my concern would  
17 be during the development. At different phases there may  
18 be very critical times during childhood where brain blood  
19 vessel growth might be fairly important.

20 I was surprised. I'm often surprised because,  
21 unlike Dr. Chesney, my areas of ignorance are immense.

22 (Laughter.)

23 DR. GORMAN: I was surprised to hear that  
24 interferon had already been approved for hepatitis B. So,  
25 we have data now that we are interfering with the cognitive



1 development of an entire group of children?

2 DR. JONAS: I don't know that anyone has looked  
3 at the angiogenesis part outside of antitumor therapy and  
4 experimental models in animals. I'm sorry. I just don't  
5 know anything about it.

6 DR. GORMAN: But it seems to me the reason we  
7 try it on cavernous hemangiomas is --

8 DR. JONAS: Oh, yes, it is an anti-angiogenic  
9 substance. Yes, for sure.

10 DR. GORMAN: And with the doses that are lower  
11 than we're treating hepatitis B but still substantial --  
12 pharmacologically active I think might be an appropriate  
13 word -- we may be interrupting the blood vessel development  
14 in the brain.

15 DR. CHESNEY: Well, that's that.

16 Dr. Lindsay.

17 DR. LINDSAY: I just wanted to comment a little  
18 bit on the frequency of reporting of neuropsychiatric  
19 events in the PEG-interferon versus standard interferon  
20 trials. As I mentioned this morning, I think that the  
21 instruments that we use to measure, quantitate, understand,  
22 define these events are very crude, and we're just now  
23 doing the first full extensive cognitive testing on  
24 patients receiving interferon. I think it's the first  
25 extensive study that's being done in adults.

1                   But when you look at the frequency of reporting  
2 symptoms in the instruments that were used, in one of the  
3 studies, both depression and impaired concentration --  
4 impaired concentration-is a very common complaint of  
5 patients -- were numerically higher in the standard  
6 interferon recipients and lower in the PEG-interferon  
7 groups, but not statistically different. The frequency of  
8 irritability and insomnia were not statistically different  
9 comparing standard to pegylated interferon. So, at least  
10 in adults, numerically there's no statistical difference.

11                   What's interesting I think -- many of us think  
12 -- because of the sustained, relatively constant levels of  
13 alpha interferon in the pegylated interferon product  
14 therapy, the patients don't have what they describe as a  
15 constant up and down kind of difficulty with thinking and  
16 sleeping and irritability and so forth. So, it may  
17 actually be that when we do these formalized cognitive  
18 evaluations, there will be a difference in favor of the  
19 pegylated compounds. We'll have to see what we find.

20                   DR. CHESNEY: I'm getting very uncomfortable  
21 with interferons. What do we know about interferons in  
22 infants? I was already to go with it, but now that I hear  
23 about angiogenesis and subtle cognitive things that  
24 children aren't going to tell you, or you really have to go  
25 looking for them. What do we actually know about

1 | interferons and neuropsychiatric side effects in children?

2 |           DR. WEISS: We do not have a lot of experience  
3 | with neuropsychiatric adverse events. I'm not sure how  
4 | good our assessment tools are for them. I think that's a  
5 | big question mark, and I think that's something that needs  
6 | to be kept in mind when you consider potential benefits and  
7 | potential risks of these therapies. It may be harder to  
8 | identify subtle changes in certain age ranges. You have  
9 | the confounding factor of adolescence, for instance, where  
10 | there could be behavioral changes and other events  
11 | happening. Those are just all things that have to be taken  
12 | into consideration.

13 |           DR. SPIELBERG: Karen, following up on what  
14 | Skip had asked a few moments ago, is there a registry set  
15 | up for the hepatitis B indication and do we know how many  
16 | kids have been treated for hepatitis B at this point?

17 |           DR. WEISS: We did not ask, as I recall, for a  
18 | phase IV commitment for a registry. The actual trial  
19 | itself was an observational controlled trial, children  
20 | ranging in age, I believe, from 1 up to 18. There were  
21 | approximately 150 children randomized, 70 to treatment and  
22 | 70 with observation. It was a 6-month dosing and then a  
23 | follow-up period of an additional 6 months. We did not ask  
24 | at that time -- and that was perhaps an oversight -- for  
25 | specific long-term follow-up with respect to the

1 | neuropsychiatric or developmental types of issues. There  
2 | were very, very few children at the younger age range, as I  
3 | recall, in that trial.

4 |           The big factor that we were looking at was  
5 | sustained response rates. From my discussions way back  
6 | when with some of the pediatric gastroenterologists, I  
7 | think everybody was very interested in treating and having  
8 | things available on the label for hepatitis B. It was  
9 | hepatitis C that was more of a question mark about whether  
10 | or not treatment was actually indicated.

11 |           DR. CHESNEY: Dr. Luban.

12 |           DR. LUBAN: I don't know, Karen, if this will  
13 | help you or not, but I believe Dr. Folkman at Boston  
14 | Children's does have a registry of the hemangioma  
15 | interferon-treated infants and perhaps some data can be  
16 | abstracted from that.

17 |           DR. WEISS: This is jumping ahead to question  
18 | 4, but I think it's clear from the discussions thus far  
19 | that we're going to need, no matter what we do, to follow  
20 | up children for long periods of time and to discuss what  
21 | kinds of sensitive tools should be used to evaluate them.  
22 | My colleagues in the Center for Drugs can mention probably  
23 | what's being done or is going to be considered perhaps for  
24 | the Rebetrone trial. But that's an important question that  
25 | I hope we get to today.

1 DR. CHESNEY: Dr. Fink.

2 DR. FINK: Two comments. One, I think again as  
3 we look at the young infant, as we look at the PEG-  
4 ribavirin combination, we also have to keep in mind that  
5 besides the ribavirin toxicity, you're dealing with  
6 immunomodulatory drugs in a group, at least if you go below  
7 age 6 where the immune system is really maturing. To say  
8 that we can safely extrapolate adult data on ribavirin to  
9 the under 6-year-old I think is extraordinarily dangerous  
10 with systemic ribavirin because its use as an aerosol in  
11 RSV infection showed immunomodulatory effects when it was  
12 only aerosolized, not systemically administered. So, if we  
13 go to the young child with this without any clear-cut way  
14 of studying it, I think we're just asking for trouble.

15 On the registry end of things, the one comment  
16 I would like to make is I think registries are great. They  
17 teach you things in retrospect, but in today's environment  
18 I'm not sure I see what the utility of a registry is that  
19 goes beyond maybe 5 or 10 years of data collection in that  
20 it's hard for me to imagine, in the rapid evolution of  
21 treatments we have today, that PEG-interferon/ribavirin  
22 will be the treatment of choice of hepatitis C in 5 or 6  
23 years. So, I have a feeling these registries are going to  
24 tell us the long-term consequences of therapies we no  
25 longer use. They're probably not going to contribute much

1 data to current therapy.

2 DR. CHESNEY: Dr. Jonas, am I right that you've  
3 already entered some patients into the Rebetrone study? Is  
4 that correct? And did you have anxieties about interferon  
5 and angiogenesis?

6 DR. JONAS: The angiogenesis part, actually no,  
7 because these are short-term and we treated for hepatitis  
8 B. We had a fair amount of experience with hepatitis B and  
9 interferon at higher doses. People do report behavioral  
10 disturbances in adolescents, and in the large studies,  
11 there are always one or two where you hear about the  
12 question of suicide ideation. But we don't have all kinds  
13 of children with learning disabilities and failure to  
14 develop in terms of the study.

15 First of all, I can't think of any that are  
16 below that we entered. They're pretty much school-aged  
17 children, 7, 8, 9, 10, and so forth. As I said, they  
18 attend school. They participate in gym. They're tired.  
19 You get a history that they may be tired or they don't eat  
20 very well, those kinds of things. Some of them have no  
21 symptoms whatsoever, no side effects.

22 I guess you may be getting the wrong impression  
23 of this group of children who are stumbling all over  
24 themselves and then can't speak anymore. It really isn't  
25 like that. I don't mean to trivialize the concern. I'm

1 | saying that it's not something that is easily apparent.

2 |           Actually all of my children are off therapy for  
3 | a year. They're in the follow-up phase on the Rebetron.

4 |           DR. GORMAN: Have you done pre- and post-IQ  
5 | testing?

6 |           DR. JONAS: No.

7 |           DR. GORMAN: Have their grades in school  
8 | fallen?

9 |           DR. JONAS: The grades are an issue. Some of  
10 | them actually are better, but you don't know if it's  
11 | because people are paying more attention to their grades  
12 | and their study habits and their sleeping and things. In  
13 | the teenagers, I've seen volatility. When you stop and  
14 | they're worse, the parents go, can you put them back on.

15 |           (Laughter.)

16 |           DR. JONAS: I don't mean to trivialize it  
17 | because I think your concern is very real, but it's not  
18 | like we have all kinds of suicide attempts or children who  
19 | are not functioning in their daily lives in the activities  
20 | of daily living and relationship disorders. The older  
21 | children on the higher doses -- because if you dose the 17-  
22 | and 16-year-olds like a kid and give them the 5 million and  
23 | 6 million units, sometimes you notice the problems there,  
24 | and I've actually dose-reduced to an adult type dose for  
25 | the really older teenagers.

1 My experience is limited.

2 DR. SCHWARZ: I would agree. I think that  
3 without doing the detailed cognitive function that I  
4 personally think should be done, the general impression is  
5 that the children tolerate interferon quite well and they  
6 do attend school and their grades don't suffer. So, I  
7 think the neurotoxicity -- this business of very high dose  
8 daily interferon in newborns -- while it's very sobering  
9 and should be considered, is probably the very worst  
10 toxicity of interferon. So, in the growing child, it  
11 should be studied carefully, but I don't think we should be  
12 too alarmist about it. We should just recognize it and  
13 study it appropriately.

14 DR. LINDSAY: Just from a design perspective,  
15 this might be an area where during a lead-in evaluation  
16 screening phase, during which time viral testing can be  
17 determined to demonstrate chronic infection, 3, 6 months  
18 serial cognitive testing could be done to determine  
19 baseline in the children. It may be very useful.

20 DR. CHESNEY: Dr. Fink.

21 DR. FINK: The neurocognitive testing and  
22 evaluation obviously is something we're all concerned  
23 about, but it also strikes me that if we're talking about  
24 patients who have received blood transfusions for treatment  
25 of leukemia or particularly in the in utero drug-exposed



1 infants, how are we possibly going to separate  
2 neurocognitive differences due to this treatment of  
3 hepatitis C from the whole issue of in utero drug exposure?

4 DR. SCHWARZ: I think you have to use each  
5 patient as his own control for that. I agree with you.

6 DR. SANTANA: I certainly don't like to quote  
7 anecdotal data either, being a scientist, but we did  
8 conduct a study at St. Jude of very high doses of  
9 interferon alpha in children with neuroblastoma who were in  
10 remission. It was an immunomodulatory phase of therapy  
11 after they had had standard induction and bone marrow  
12 transplantation. It was very high dose interferon alpha.  
13 It was a dose-finding kind of study too. It was up to  
14 doses of 32 million units three times a week for an initial  
15 phase of a month and then alternate weeks for a total of 16  
16 weeks of therapy. Although the study prospectively did not  
17 look at cognitive issues, neuropsychiatric behavioral  
18 issues, I took care of many of those patients. In general,  
19 it was very well tolerated.

20 I was thinking of the data as I heard the  
21 discussion. I don't remember any major issues. Obviously,  
22 they were not prospectively being looked at. These are  
23 kids between the years of 4 and 8 years of age. So, it was  
24 rewarding that we were giving such very high doses of  
25 Intron A and we were not seeing a lot of issues.

1           The only toxicity we did see, which was very  
2 surprising and actually we did report it to the FDA, was a  
3 kid who developed a myocarditis and became quite ill, and  
4 it was totally unassociated to anything else. This was one  
5 of the kids who had gotten the very high doses, up to 32  
6 million units. And that had not previously been reported,  
7 so it may have just been a spurious adverse event. The kid  
8 did eventually recover from it, but it was kind of scary.

9           So, that's the only data I have in very high  
10 dose alpha interferon.

11           DR. CHESNEY: Maybe the quick answer to the  
12 first bullet is yes, we do think, and unless you want us to  
13 define that further, the next question, should only  
14 combination therapy be studied, or is it appropriate to  
15 also evaluate PEG-interferon monotherapy? Is it all right  
16 to move on to that?

17           DR. WEISS: Yes.

18           DR. CHESNEY: Skip.

19           DR. NELSON: As I recall, there was a  
20 suggestion -- it might have been, Steven's or Ralph's --  
21 that given the potential improved response in infants, for  
22 example, that monotherapy might still be a justified  
23 question. So, I guess I raise that. I think that came up  
24 earlier just in passing in the discussion. I mention it to  
25 see if people still think that that's the case. I don't

1 have the expertise to comment one way or the other.

2 DR. CHESNEY: Dr. Schwarz.

3 DR. SCHWARZ: I think it is very important to  
4 do a prospective controlled trial. One of the reasons for  
5 the importance is the effect of the predictable anemia from  
6 ribavirin on intellectual functioning. Frank Oski did  
7 very, very careful studies in Baltimore showing the impact  
8 of iron deficiency of anemia on intellectual functioning.  
9 So, I think that we really need to understand how the  
10 combination affects that versus PEG alone. As we said, we  
11 may see fairly high response rates to PEG monotherapy.

12 DR. CHESNEY: Dr. Fink.

13 DR. FINK: It would strike me that could also  
14 be built into the study design in a single trial, that you  
15 start out with PEG monotherapy and in those patients who  
16 don't reduce their viral load, you then consider adding  
17 ribavirin in. You don't have to even do it as two separate  
18 trials. The ribavirin could sort of be the poor responder  
19 add-on.

20 DR. CHESNEY: Naomi.

21 DR. LUBAN: I just have a question for the  
22 group. What do you do about immunization during the length  
23 of time that the kids are being treated? How does one  
24 handle that?

25 DR. JONAS: Immunizations are very early

1 childhood, and so we're not talking about treating in the  
2 primary immunization series. You mean just a general flu  
3 shot or something preschool?

4 DR. LUBAN:- Well, that plus H-flu at a later  
5 point in time. If you look at the whole schema, there are  
6 the early immunizations. Rich can go over these probably  
7 in about one microsecond. But there certainly are serial  
8 immunizations preschool, H-flu, boosters, and whatnot.

9 DR. JONAS: We haven't taken that into separate  
10 consideration and we give them as recommended mostly.

11 DR. WEISS: Have you administered immunizations  
12 while people have been on interferon therapies? I'm just  
13 curious to know if you looked at that.

14 DR. JONAS: Again, back to anecdotes again, but  
15 I'm sure I have. I'm sure that it has come up and we have  
16 just kept them in their general scheme of immunizations.

17 DR. WEISS: It's a very good question, Dr.  
18 Luban, because we've been actually asking that more and  
19 more with some of our newer immunomodulatory therapies that  
20 we've approved for chronic use, like the anti-TNFs for RA  
21 that are being used for years, beta interferons for  
22 multiple sclerosis that are being administered for several  
23 years, actually a lifelong type of treatment. Again, we're  
24 talking there more in adults where you might be giving the  
25 annual flu shots and whatever. There are phase IV studies

1 that we've been asking, and so that's something that can be  
2 built into phase IV commitments to look at responses to  
3 various types of immunizations.

4 On the other hand, too you could just, I  
5 suppose, delay an immunization because this is a year  
6 therapy, and I guess if the time frame isn't so critical,  
7 if there's a concern about not being able to mount an  
8 immune response, you could delay the immunization.

9 DR. SANTANA: We delay the cancer kids for a  
10 whole year and really, with few exceptions, don't have that  
11 much problem. They catch up when they're done.

12 DR. JONAS: Excuse me. But it's my  
13 understanding this is more immunostimulatory. Is there a  
14 concern that they wouldn't respond as well to  
15 immunizations, or that it would interfere with their  
16 therapy?

17 DR. CHESNEY: One of the ways you get better  
18 from a live virus is to generate interferon. So, maybe it  
19 wouldn't be as --

20 DR. JONAS: Yes. I was just wondering if there  
21 was a specific concern that the committee had about that.

22 DR. GORMAN: I have none about the dead  
23 vaccines. I guess there is some concern about hyper-  
24 response maybe even more so for live vaccines.

25 DR. CHESNEY: Just one thing. You didn't ask

1 us if we're comfortable giving ribavirin. That's an  
2 assumption here. Should we use only combination or the  
3 interferon alone?

4 DR. WEISS:- I'm going to refer that to my  
5 colleagues in the Center for Drugs.

6 DR. CHESNEY: Can we leave that alone? I'm  
7 happy to leave it alone, but I actually have more anxiety  
8 about the ribavirin.

9 MR. FLEISCHER: We've done it. We'll know  
10 better probably in the next six months to a year whether we  
11 did anything bad. I think one of the things that was  
12 interesting is how fast the trials were enrolled and the  
13 comfort level of the investigators who are following those  
14 kids in the Rebetrone trials, and some of those kids are now  
15 out after receiving the drug for 48 weeks. So, we'll maybe  
16 have some information once the final results come in, once  
17 the trials are completed.

18 DR. CHESNEY: Dr. Weiss, did you want to say  
19 something before we went on?

20 DR. WEISS: No. I think that answers our  
21 question that we have regarding the PEG-interferon  
22 monotherapy. It was put down because one of the arguments  
23 was, given the smaller numbers of children, if truly PEG-  
24 interferon plus ribavirin is really a much more optimal  
25 combination, is it appropriate to expose kids to a less

1 effective therapy. That's the whole issue, whether or not  
2 one should actually study PEG-interferon as monotherapy or  
3 should you just ditch that as a regimen and just wait and  
4 use the combination treatment with the idea that you want  
5 to optimize treatment as much as possible. But I think we  
6 got some good answers, so I'm happy with moving on.

7 DR. LINDSAY: Could I just ask a question?  
8 Certainly a major indication potentially for PEG-interferon  
9 monotherapy would be anemic patients. So, are there  
10 sizeable numbers of children who have anemia in whom just  
11 PEG-interferon monotherapy might be a reasonable study?  
12 Chronic anemia?

13 DR. JONAS: I personally think that if the  
14 anemia is the issue, it's actually very dose-dependent,  
15 monitorable, and I think that our children tolerate a  
16 couple drops in hemoglobin better than adults. The risk in  
17 adults is cardiovascular disease, coronary artery disease.  
18 Children don't have those kinds of risks, and they will  
19 tolerate. So, the patients who are being transfused are a  
20 separate issue altogether. I think the issue is more the  
21 teratogenicity and immunogenicity of ribavirin exposure. I  
22 don't know if that's your major concern. The anemia is a  
23 problem but can be watched with good safety monitoring and  
24 dose reduced.

25 DR. LINDSAY: The issue that I was thinking

1 about was among children who have chronic anemias and  
2 require transfusions. Would it be better to do a trial  
3 using PEG monotherapy rather than PEG plus ribavirin?

4 DR. JONAS: I think that should be separate  
5 from this trial. I think those considerations should be  
6 made, but not what we're discussing today.

7 DR. LUBAN: That's actually the easiest group  
8 to take care of because you just increase their transfusion  
9 during the next transfusion. So, that group I wouldn't  
10 worry about.

11 I think the little ones who have a natural  
12 nadir of hemoglobin which is age-dependent and growth-  
13 dependent are the more critical ones, but they may not  
14 become part of this trial because those are usually the 6-  
15 month to 2-yearers.

16 DR. CHESNEY: Issue 4 has to do with the long-  
17 term follow-up of both adult and pediatric patients who  
18 have received treatment. Information is needed to address  
19 the impact of therapy on the clinical endpoints of  
20 cirrhosis, carcinoma, and mortality. Please discuss  
21 approaches to maximize the collection of long-term follow-  
22 up data in pediatric patients who have been enrolled. Who  
23 should receive follow-up? How long should the follow-up  
24 be, and what parameters should be followed?

25 DR. WEISS: And this doesn't need to be limited



1 just to the efficacy outcomes that are outlined in the  
2 lead-in. Obviously, we're also very interested in the  
3 long-term safety as well.

4 DR. CHESNEY: Everybody should be followed up  
5 forever.

6 (Laughter.)

7 DR. CHESNEY: And what parameters? I don't  
8 mean to trivialize it either, but it seems to me that there  
9 is going to be such a small number that we really need  
10 every bit of data we can get from those that we can follow.

11 Dr. Fink.

12 DR. FINK: I would think until there is some  
13 agreement from Congress on a national medical data bank,  
14 that that undertaking is relatively impossible because  
15 unless you bank this data someplace by Social Security  
16 number at a national level, there are some surprising  
17 studies that I'm aware of in asthma that about 60 percent  
18 of adults don't recall that they had significant childhood  
19 asthma with hospitalizations. Are they going to remember  
20 their hepatitis C history?

21 DR. CHESNEY: Kathy.

22 DR. EDWARDS: I don't want to belabor the  
23 point, but I do think that there is an opportunity,  
24 actually at least coming up in the next week, where large  
25 numbers of pediatric subspecialists congregate. This may

1 | be something where you might want to discuss this.  
2 | Certainly the NIH in other situations has been interested  
3 | in large databases of common diseases, or investigators  
4 | such as Jerry Winkelstein at Hopkins who has done the  
5 | patients with CGD. So, I think this may be something that  
6 | people want to discuss and how follow-ups both of kids with  
7 | various types of disease processes with hepatitis C might  
8 | be followed and funds could be garnered for that.

9 | DR. CHESNEY: Is this something, Dr. Schwarz --  
10 | is it called the Gut Club? Am I correct? Is that  
11 | something that they could pull together?

12 | DR. SCHWARZ: Well, we don't call ourselves the  
13 | Gut Club anymore. We have graduated to the North American  
14 | Society of Pediatric Gastroenterology, Hepatology, and  
15 | Nutrition, NASPGHN.

16 | DR. CHESNEY: I'm sure something you all have  
17 | talked about a lot is how to -- these children are all  
18 | going to be in the care of a hepatologist, surely.

19 | DR. SCHWARZ: It is a concern, although I share  
20 | Dr. Fink's conservatism about the kind of information we're  
21 | going to get from a registry versus prospective controlled  
22 | neuropsychiatric function studies.

23 | I can share our experience with our liver  
24 | transplant program. We're trying to look at ways to  
25 | improve neuropsychologic outcome following pediatric liver

1 | transplantation. So, we're now doing those very detailed  
2 | neurocognitive function studies. We're learning so much,  
3 | not necessarily cheerful news, about our neuropsych outcome  
4 | in our transplant patients that we really would not have  
5 | known from just the casual clinic visit or even school  
6 | performance. So, I have my doubts as to the amount of  
7 | quality information we can get from a registry.

8 |           The other thing that I would like to comment on  
9 | because there may be folks here that have influence with  
10 | the CDC. One of the important long-term questions about  
11 | hepatitis C morbidity and mortality is does the virus cause  
12 | cancer. We are just completing a study with the CDC  
13 | looking at primary hepatic malignancies in children in the  
14 | U.S. in the last 25 years, cross referenced with the SEER  
15 | database.

16 |           It was very sobering because I think we found  
17 | 927 cases of primary hepatic malignancy. CDC doesn't have  
18 | histologic bases, so we had to cross reference with SEER,  
19 | which is histologically based. About a third of these  
20 | children, we think, have hepatocellular carcinoma, the  
21 | adult disease, not hepatoblastoma. Of the 927 cases, 17  
22 | had an associated etiology, 14 of which were hepatitis B.

23 |           So, I think getting much better quality  
24 | information from the CDC mortality data bank will be  
25 | important in the future to find out if children do get

1 hepatocellular carcinoma from hepatitis C.

2 DR. CHESNEY: Naomi.

3 DR. LUBAN: I guess you heard me use this  
4 reference to hemophilia quite a bit today, and I'll use it  
5 again along these lines. Certainly the Maternal and Child  
6 Health/CDC initiative in growth and development of  
7 hemophilia and the serial follow-up of those initially  
8 children now young adult and adults for virologic disease  
9 has been one of the most successful programs, at least from  
10 a hematologic perspective. I think it really could be a  
11 model for hepatitis C. It is not just a registry. It is  
12 actually involved in looking at growth and development. It  
13 follows the children at least yearly. It monitors the  
14 children serially with a wide spectrum of viral serology,  
15 and because it's organized and it's a multi-institutional  
16 kind of data collection, it can provide for clinical  
17 trials. It's expensive but so are many things in life.

18 I think that a model like that would be really  
19 superb for this setting. That way you would have a data  
20 collection set that would be serial, that would be managed  
21 by CDC which has got those capabilities, and you have a  
22 group of investigators that are pulled together that can  
23 respond to clinical trial initiatives.

24 DR. CHESNEY: Any other comments on who should  
25 receive follow-up, duration, and parameters to be followed?

1 DR. WEISS: Just a follow-up to what Dr. Luban  
2 was saying. Currently, though, our mechanism at the FDA --  
3 it would be very nice if there was a government-funded  
4 organization that could undertake to encompass all the  
5 children that had been not only treated but infected and to  
6 do these kinds of follow-up. But what we have available to  
7 us right now to any company that's coming along and doing  
8 pediatric studies, our mechanism is basically phase IV  
9 commitments, to ask these companies to continue to follow  
10 up the patients that have been in trials longer term. That  
11 could be a couple years. It could be 5 years. It could be  
12 10 years, whatever it is. But that's all spelled out  
13 carefully as we go towards approval for the pediatric  
14 indication as we discuss how long studies should be, what  
15 kinds of measurements to evaluate, something sometimes  
16 about how it's going to be reported to the FDA annually or  
17 whatever, and those kinds of things.

18 In the absence of some other more centralized  
19 organization to do this, that's what we have and that's  
20 what we would need advice on I think for right now, as of  
21 2001, if we're going to be discussing with our  
22 manufacturers -- these are going to be pharmaceutical  
23 companies -- their pediatric studies and what kinds of  
24 commitments that we would want from them once something is  
25 indicated for pediatric use.

1 I could use some practical advice on how long  
2 children should be studied, what kinds of things to look  
3 for. Should it be a questionnaire after X number of years  
4 to be sent out to the parents? Check for significant  
5 psychiatric problems or whatever. It could be anything.  
6 These are very difficult questions and they're not,  
7 obviously, unique to this particular situation. We've been  
8 struggling with that very issue in a number of other areas.  
9 So, if the committee has any advice or any experience with  
10 those kinds of longer-term follow-up, we'd really love to  
11 hear it.

12 DR. CHESNEY: You don't have any control over  
13 that, though, do you?

14 DR. WEISS: We're getting a little bit better  
15 able to control it in the sense that under FDAMA there have  
16 been new requirements not so much to force companies to do  
17 studies if they don't do them, but the information about  
18 the phase IV commitments is now going to be publicly  
19 available. They're going to be put up on a website. The  
20 companies have to actually provide us, on at least an  
21 annual basis, with the status of their phase IV studies and  
22 the progress, whether or not they're delayed and the  
23 reasons why. That information is going to be publicly  
24 available. So, there is that incentive, the public  
25 pressure to comply with these commitments, but there's no

1 other disincentive. You're not going to, obviously,  
2 withdraw approval or other types of things.

3 DR. CHESNEY: Dianne.

4 DR. MURPHY: There is, as Karen noted, the  
5 increased attention that will be paid as far as phase IV.  
6 Under the exclusivity, under FDAMA, section 111,  
7 exclusivity, we have a couple of trials -- and I think  
8 we've mentioned this to some members of the committee  
9 before -- where we have issued a written request which has  
10 in it a long-term follow-up for 10 years in which we have  
11 said that part of the construct is that you must bring in  
12 5-year data plus the evidence that you have developed an  
13 infrastructure for the longer-term follow-up because of the  
14 numbers that are involved sometimes, and that you would get  
15 your exclusivity when you bring that interim data in. So,  
16 we do have some experience with that.

17 These are more than large, simple trials, some  
18 of them. They get to some of the endpoints that are not  
19 terribly complicated, but still they are endpoints that you  
20 are measuring along the way. So, that has been one  
21 approach, but that's very difficult.

22 In addition, we recently had an NICHD meeting  
23 on adverse event reporting in which we were trying to get  
24 some idea of what long-term follow-up was. As you all  
25 realize, most of our studies are weeks. Long-term follow-

1 up is months. We clearly got the message that one year was  
2 not long-term follow-up, which for us has really been long-  
3 term follow-up.

4 So, it's a-whole new universe for us to be  
5 stepping into, and that's why we keep bringing this issue  
6 to the committee because we know it's an evolving field and  
7 there will be different, I'm sure, paradigms, depending on  
8 the disease and the safety profiles, et cetera. But we do  
9 see it as a very important issue.

10 DR. CHESNEY: Skip.

11 DR. NELSON: My question relates to whether  
12 there's authority to require, within whatever mechanism,  
13 long-term follow-up of any child who receives the product.  
14 Often studies are powered on efficacy endpoints and not  
15 safety endpoints. You don't see serious safety concerns  
16 until you have a large population who is administered a  
17 medication. Can you require data collected on kids that  
18 were not in the studies as opposed to the kids that get  
19 that particular product after it's marketed?

20 DR. MURPHY: First of all, as far as requiring,  
21 that word means we have regulations that say, yes, we're  
22 approving your product with the following phase IV  
23 commitments. But as Karen has indicated, we and the  
24 industry don't have a very good record in this area, and  
25 there are efforts to try to improve that process.



1                   For the agency to do anything about somebody  
2                   who's not meeting their phase IV commitments, basically we  
3                   have limited tools. This is what the lawyers tell me, so  
4                   I'm stepping way beyond my expertise here. The tools are:  
5                   an imminent hazard, misbranded, take it off the market.  
6                   You can imagine what level of evidence we'd have to have to  
7                   be able to do that. So, we can require it as part of the  
8                   approval process, but the tools that we have presently are  
9                   really often humiliation, bully pulpit. As we've seen in  
10                  pediatrics, it really hasn't worked too well. So, these  
11                  are the kind of quandaries that we're in.

12                  One of the reasons we like exclusivity is they  
13                  don't get it until they bring in some of that information  
14                  that you need. But that means that we have to have the  
15                  ability to construct a trial that can last for more than a  
16                  year and still have the potential for benefiting from  
17                  exclusivity, which we hope to have as we move into more  
18                  products that haven't been marketed before because one of  
19                  the issues has been so much of what we're doing right now  
20                  is the older products that have been on the market.

21                  DR. NELSON: But to follow up, I would assume  
22                  if you design a trial for exclusivity, you wouldn't design  
23                  a trial that would include everyone who would be receiving  
24                  that medication regardless of whether they were in that  
25                  initial trial.

1 DR. MURPHY: That was the part of your question  
2 I was selectively disremembering.

3 (Laughter.)

4 DR. MURPHY: To require them to study every  
5 child who took the product is not within our purview at  
6 this point. I think you need a nationally funded study  
7 that would look at something like that. We often refer to  
8 things as putting on the table this pediatric Framingham  
9 type of follow-up or studies. What are the big public  
10 health issues and where do you want to put your tax dollars  
11 to work for some of these long-term follow-ups?

12 DR. WEISS: You can also ask, though -- and  
13 we've done this before. People may like the word  
14 "registry" and maybe there's a better way to call it. In  
15 addition to longer-term follow-up -- it's a little  
16 different with hepatitis C than, for instance, with JRA  
17 where our anti-TNF therapies are going to be used for long  
18 periods of time on these children. But we ask for not only  
19 longer-term follow-up of the children that were in the  
20 original trials, just to continue them out -- they were no  
21 longer controlled trials at that point -- but also for an  
22 additional registry to be established. You could limit it  
23 to, say, the first X hundred people that come in will be  
24 enrolled in a registry.

25 I don't remember all the details. I don't

1 know, Bill, if you remember the details more about it, but  
2 we asked for that to happen with additional patients coming  
3 on to look at various aspects of disease treatment and  
4 confounding medications and other types of conditions. So,  
5 it's something that we actually can ask for as a phase IV  
6 commitment.

7 DR. GORMAN: Knowing how focused pediatricians  
8 sometimes are on labeling, I don't think we ever read the  
9 label, but we really like to have stuff on it. If I was  
10 trying to design a phase IV follow-up study for the  
11 experimental group, leaving the registry out, especially in  
12 this particular disease where we don't expect to see  
13 anything in the first 20 years other than cirrhosis, things  
14 such as hospitalizations, if there's a difference between  
15 the treatment and control group, would be very suggestive.  
16 If diseases and their incidences were dramatically  
17 different from that of the general population. Again, the  
18 neuropsychiatric effects.

19 Dr. Oski in his iron studies was looking for  
20 the ability of teenage girls to pay attention and noticed  
21 that there was a 6-second difference in their ability to  
22 pay attention, which in my normal clinical exam I would not  
23 have noticed. But with iron deficiency, it appears to be 6  
24 seconds longer, and it affected their academic performance.  
25 Maybe high school graduation rate might be a reasonable

1 surrogate, perhaps not. Maybe their SAT scores, things  
2 that would be relatively painless for the company to  
3 gather.

4 I think their adult heights and weights might  
5 be awful interesting, especially since we heard about the  
6 fall-off and we hear that they rebound, but do they get  
7 back to their original growth curves, their growth  
8 velocities, or is it lost forever?

9 DR. SANTANA: Karen, what are you really asking  
10 for? It may be an unsurmountable task to ask the drug  
11 companies to do this. They'll do it for the first couple  
12 years, and then after that, they won't do it. It costs a  
13 lot of money. Paediatric patients move when their parents  
14 move. This is not a disease that they may remember 10 or  
15 15 years later. If they're cured from their hepatitis C,  
16 nobody will ever know. And we may be putting the companies  
17 here in a position of something they just can't do.

18 So, are we really asking that you want some  
19 long-term safety data on these patients that were treated  
20 with X and you define a reasonable interval for that?  
21 Because you're not going to be able to identify the  
22 hepatocellular carcinomas 30 years later. That's  
23 impossible to do unless you have a national registry, which  
24 is what you're asking for.

25 So, I think we've got to be careful because I

1 think we're confusing national registries for long-term  
2 follow-up information of patients versus a very limited  
3 focus of a patient got drug X and I want to make sure that  
4 I can identify that patient forever in case something  
5 happens to that patient. To me those are two different  
6 models, and I think you're probably talking about the  
7 latter, not the former. Am I correct?

8 DR. WEISS: You're right, Victor. There are  
9 two separate areas. One is knowing better information  
10 about natural history and long-term sequelae regardless of  
11 treatment, which is a very important issue and one that I  
12 think is still probably a real need. But then the  
13 responsibility of our pharmaceutical manufacturers who want  
14 to come in and have these obligations -- you're right.  
15 It's the latter.

16 It's really more looking at what is a  
17 reasonable request to ask for -- and we want to be  
18 reasonable here -- in terms of duration, in terms of the  
19 kinds of follow-up, in terms of the kinds of information we  
20 want to get collected that would be important for  
21 pediatricians to know about, to be able to update the  
22 labeling several years down the road or 5 years down the  
23 road, or whatever it is with outcome data of both kinds  
24 really. Durability of response probably isn't as critical  
25 because we think if we're extrapolating from the adult

1 | experience, there are very few people that lose their  
2 | response after a certain period of time. But there are  
3 | these long-term safety issues and the effects of  
4 | interferons, in particular, on children.

5 | DR. SANTANA: I guess you guys have the best  
6 | models. Don't you do that for devices when some of these  
7 | experimental devices like pacemakers or subQ ports, which I  
8 | have experience with --

9 | DR. WEISS: We don't have the device people  
10 | here.

11 | DR. SANTANA: Those get identified up front,  
12 | and that's prospectively monitored.

13 | DR. SPIELBERG: The issues of follow-up are  
14 | obviously critical, and the practical aspects are very,  
15 | very difficult. Things that increase long-term follow-up  
16 | is if you have a chronic disease and there are very few  
17 | subspecialists and you keep going back to their  
18 | subspecialists and your third party payor allows you to  
19 | keep going back to that same subspecialist, and falls off  
20 | dramatically if you don't have a defined chronic process  
21 | with a parent support group and all the other things that  
22 | keep you going back.

23 | Rates of attrition for intercurrent illness.  
24 | You're going to lose 50 percent in six months. You're  
25 | going to lose another 25 percent at a year, and then

1 they're all going to disappear into the woodwork, and it  
2 becomes harder and harder to get long-term follow-up.

3 For a process like this where you're on a drug  
4 for a year and it requires going back to the same  
5 specialist for a year, you might do a little bit better.  
6 But once you are "cured," you want to disappear into the  
7 woodwork as fast as you can, and your third party payor  
8 wants you to disappear into the woodwork as fast as you  
9 can, being now a healthy person who can go to the GP once  
10 every other year for well child care.

11 Because of the mobility of American society, as  
12 well, people don't stay in the same jobs. They don't stay  
13 in the same cities. They move around a great deal. In an  
14 interesting way, having spent a large portion of my  
15 academic life in Canada, it's a little bit easier on the  
16 Canadian scene because people tend to not move as much and  
17 because you have a single third party payor. So, at least  
18 if you stay within the province, you have a single third  
19 party payor. If you move provinces, your third party payor  
20 changes, but at least the national system allows for  
21 longer-term follow-up.

22 So, I think we do have to be a little bit  
23 careful in terms of long-term promissory notes. It's  
24 extremely hard to do and it's extremely hard to keep  
25 cohorts together for long periods of time.

1 DR. FINK: Even when you have an ideal  
2 situation -- I've dealt with the Cystic Fibrosis Foundation  
3 registry for close to 30 years now. There's a twofold  
4 difference across the United States on what is the upper  
5 limits of normal for liver enzymes for AST and ALT from  
6 different labs.

7 (Laughter.)

8 DR. FINK: There's a fivefold difference in IgE  
9 levels, and trying to get reliable height and weights with  
10 a stadiometer with the shoes off and only socks has  
11 required yearly reeducation and site visits.

12 (Laughter.)

13 DR. FINK: And that's probably an ideal disease  
14 where you've got good capture.

15 I think the answer is a registry is never going  
16 to have research quality data that will allow you to  
17 decipher small changes. If you're talking about neuropsych  
18 testing, I can't even believe that a registry can begin to  
19 address those issues.

20 DR. WEISS: So, what shall we do?

21 DR. FINK: I think you do short-term  
22 prospective data collection and you live with it.

23 DR. CHESNEY: Dr. Schwarz.

24 DR. SCHWARZ: My question is going to reveal my  
25 ignorance about the regulatory process. But it seems to me



1 that we don't have enough information right now to make a  
2 wise recommendation about long-term follow-up. In other  
3 words, we haven't done those carefully controlled  
4 neurocognitive function tests during and immediately after  
5 therapy. To me, since the long-term follow-up is so very  
6 difficult, particularly in the maternal/fetal population  
7 where we're talking about homeless individuals and so on,  
8 the importance of the long-term follow-up would be very  
9 different if there were intellectual defects discovered  
10 during interferon therapy that persisted 6 months after  
11 therapy. Then I think it really would be important to try  
12 very hard to get some longer-term follow-up. If, on the  
13 other hand -- and I think Maureen and I might guess that we  
14 wouldn't see too much deficit at 12 months, at the  
15 endpoint, and 6 months afterwards. Then it would probably  
16 not be fair to the pharmaceutical companies to demand very  
17 long-term follow-up.

18 DR. CHESNEY: Judith.

19 DR. O'FALLON: We haven't talked about ethical  
20 issues. This is all very practical, whether it can be  
21 done, which is of course important. Ultimately it's the  
22 bottom line. But if you have a disease that the patients  
23 are not going to die from -- it's not like cancer where  
24 they're likely to be dying soon. Here is something that  
25 they're likely to live with for many decades and some

1 fairly substantial percentage of them never will suffer any  
2 major sequelae, according to those numbers that we saw,  
3 really bad stuff.

4 If we treat a whole lot of people that are  
5 really not going to have all that much trouble from the  
6 disease and we cause them trouble that will stop them from  
7 having the kinds of jobs that they could have had, have the  
8 education that they could have had, where they're going to  
9 be limited, I think there's a problem here. It's one thing  
10 to treat the life-threatening diseases. It's another one  
11 to be treating ones that are smoldering and actually may  
12 never cause major problems to the sufferers.

13 DR. SANTANA: But that's the whole point. The  
14 serious stuff you should be able to identify early on in  
15 the first year or two years of the therapy. Those you will  
16 identify, and then that serves as a baseline for you to  
17 define how much more aggressive your follow-up should be  
18 for everybody.

19 The counterpoint to that is you also have to  
20 have a mechanism, as we learned in cancer, to identify  
21 patients so even those that do not have early issues can  
22 still have issues 10 or 15 years later. So, you can  
23 capture those. But those you don't capture by being very  
24 stringent on the pharmaceutical company to follow them very  
25 closely. There has to be another way to explore that.

1 I would be more concerned that if you do a  
2 trial and early on in the first couple of years you do  
3 identify that there are serious issues, then you have the  
4 information you need to define your long-term follow-up.

5 DR. CHESNEY: Do you need any more input?

6 DR. WEISS: No. I think we need to digest our  
7 input that we have. This has been very, very helpful. For  
8 the sake of time, I think we've decided that we do not need  
9 to -- the last question was an optional question, and I  
10 think we actually touched upon a lot of those issues  
11 already in our discussions.

12 So, I want to thank everybody on this committee  
13 for their enthusiasm and their discussion, and we will be  
14 anxiously awaiting the transcript to review what you all  
15 said and take it back with us. Thank you.

16 DR. CHESNEY: Well, let me thank you and  
17 Russell for setting this whole day up and for finding our  
18 invaluable experts for us and for providing us with very  
19 difficult questions, difficult issues, which we've all  
20 learned from. So, let me thank you both because I think  
21 we've all learned a tremendous amount here too.

22 Dianne Murphy is going to give us an overview  
23 of what's going on at the Center now. Dr. Rehermann, Dr.  
24 Schwarz, Dr. Jonas, and Dr. Lindsay, if you all want to  
25 stay, that's fine, but if you feel like it's time for you

1 to go, we all thank you tremendously. You've been a wealth  
2 of information today, and we could not have done any of  
3 this without you. So, thank you very much for your time  
4 and expertise.

5 DR. MURPHY: I'm going to go through this  
6 pretty quickly because you have a handout. Hopefully that  
7 is really all that you would need.

8 I'm going to talk about the response to  
9 exclusivity, the health impact of the new labels -- and  
10 that's really the bottom line of what we want you all to  
11 know what we're seeing already with only 18 new labels. I  
12 could also comment on the things that I know that are  
13 coming. We really are seeing important changes that are  
14 being made to labels.

15 I am really not going to spend time on our  
16 report to Congress, because we don't have it and it gets  
17 very complicated. If you want to ask me some questions  
18 about it, that's fine.

19 And then a quick update on the Pediatric Rule,  
20 again remembering that we could not require studies under  
21 the rule until this past December, but to give you an idea  
22 of the number of deferrals and waivers.

23 The stats that you've become very familiar with  
24 at this point are that we now have received over 200  
25 proposals from industry to study products. We have issued

1 over 188 written requests and over 40-some other letters to  
2 sponsors about incompleteness or what else, that we can't  
3 issue a written request. So, well over 200 responses.

4 Products that have gone through the entire  
5 process, meaning they have received a written request, they  
6 have conducted the studies, they've analyzed the studies,  
7 and they submitted them, are 34. Again, it takes a while.  
8 Even though exclusivity by law is required to be denied or  
9 granted within 90 days, it takes a while after the  
10 submission of the studies to get the label written. Our  
11 usual is up to a year.

12 So, of those 34, we now have 28 that have been  
13 granted exclusivity. We have 18 new labels. I'm going to  
14 quickly talk about the 13, just to give you the breadth of  
15 the diseases for which we now have an extended age group or  
16 an extended safety profile, but mostly talk about the 5  
17 where we think we have important dosing changes out of  
18 these 18.

19 These, very quickly, are the ones which we've  
20 extended the age or they have additional information that  
21 is either similar or some specific comment we can make  
22 about pediatrics in these indications which include not  
23 only fever but HIV, gastroesophageal reflux, diabetes,  
24 conjunctivitis, hay fever, ichthyosis, rhinitis, urticaria,  
25 type 2 diabetes, hypertension, and anesthesia.

1                   Now, these five products we think have  
2 particularly significant changes in them as far as  
3 pediatrics is concerned: midazolam, which is used for  
4 sedation in conjunction with anesthesia; etodolac for  
5 treatment of JRA, fluvoxamine for treatment of obsessive-  
6 compulsive disorder, gabapentin as adjunctive therapy in  
7 the treatment of partial seizures, and propofol for  
8 induction and/or maintenance of anesthesia.

9                   Because I thought the committee might want to  
10 have some idea of the numbers involved, we've tried to  
11 include on this slide a synopsis of the moiety that was  
12 studied, the studies we asked for, the age ranges that were  
13 included and the number of patients.

14                   As you can see, in midazolam, we asked for  
15 single-dose PK/PD study comparing at least three dosage  
16 levels. We asked for a controlled dose response study in  
17 the age group 6 months to 16 years involving about 500  
18 patients.

19                   What we found is with midazolam we were able to  
20 get an effective dose at which they should start from the  
21 dose-ranging studies, defined the volume of distribution,  
22 and its similarity to adult protein binding elimination,  
23 the additional information on AEs and warnings about  
24 concomitant medications, and particularly important,  
25 identified a subpopulation of children with congenital



1 heart disease and pulmonary hypertension who are at very  
2 high risk for having severe respiratory problems if you  
3 didn't start at the very, very lowest end of the dosing  
4 regimen and go slowly up. Importantly, we had a new oral  
5 liquid formulation.

6 Etodolac. This product had an osteoarthritis  
7 indication in adults. We asked for a 12-week open-label  
8 study, a PK/PD study really, to look at can we extrapolate  
9 one of those tests of hypothesis type of things using  
10 endpoints that you would for arthritis. 6 to 16-year-olds,  
11 68 patients. I don't think you could all these efficacy  
12 trials.

13 This basically did pass muster, if you will, by  
14 feeling that there was an appropriate dose response.  
15 However, what was interesting was that there was a higher  
16 dose on a per kilogram basis in the younger children.  
17 We're finding that this 5 and 6-year-old group -- we're  
18 finding very different clearances in children in this age  
19 group in some products. It was approximately two times the  
20 lower dose recommended for adults. Not always depending on  
21 the product and how it's eliminated, but again, these are  
22 our first 18 labels.

23 This is fluvoxamine. This study was asked for  
24 because we were getting information about concerns that  
25 adolescents were being underdosed, that there seemed to be



1 out there some concerns that the adolescents -- apparently  
2 for reasons people were looking at them -- were not  
3 reaching the levels you would have expected. So, we  
4 actually had an open-label PK study in 7-year-olds to 17-  
5 year-olds and a long-term open-label safety study in 8-  
6 year-olds to 17-year-olds.

7 It always kills me. We get all this good  
8 information and we end up synthesizing it down to a  
9 sentence or two. I think there's actually been an abstract  
10 published on this. Maybe Dr. Kauffman can comment later,  
11 if he knows, on what was actually found, which is in  
12 essence, yes, the adolescents were being underdosed, but  
13 not only were the adolescents potentially being underdosed,  
14 but girls between the years of 8 and 11, again in limited  
15 numbers, but in disproportionate numbers, would have  
16 sometimes up to two times the AUC levels. So, we found  
17 this very different distribution of serum levels by  
18 physiologic state.

19 Gabapentin. We asked for quite a bit for this  
20 product, a double-blind, randomized, placebo-controlled,  
21 parallel group efficacy and safety study as an add-on  
22 therapy. Patients 3- to 12-years-old. Then we asked for a  
23 double-blind, randomized, placebo-controlled efficacy study  
24 in the next age group. So, we had about 250 and 75  
25 patients here.

1           The third study was a PK performed on a subset  
2 of the efficacy because we try to be efficient, if at all  
3 possible, in these studies. Four, an open-label extension  
4 study, and five, a single-dose PK study in the 1-month to  
5 12-year-olds. You can see the numbers are getting up  
6 there, over 1,000 patients.

7           These studies were able to establish  
8 effectiveness down to 3 years of age. Because we were  
9 looking, they were able to identify neuropsychiatric events  
10 in the 3- to 12-year-old group that were not present in the  
11 control group. It had to do with hostility and aggression,  
12 poor school performance, et cetera. Again, even though  
13 these had hundreds of kids, still when you're finding it in  
14 studies that are relatively small with hundreds of kids,  
15 you're concerned that it definitely is occurring.

16           Oral clearance was normalized per body weight,  
17 was increased in children less than 5, and a higher dose of  
18 gabapentin was required in the children less than 5. And  
19 we had a new oral liquid formulation.

20           The last of our five products, propofol. A  
21 randomized, double-blind, comparative dose-ranging trial to  
22 evaluate the efficacy and safety in 0- to 16-year-olds,  
23 over 300 children. Study two, randomized open-label  
24 comparative parallel group to evaluate safety in the 0- to  
25 3-year-olds, 157 patients.

1           This was a very interesting result. They were  
2     able to extend the age down to 2 months for the indication  
3     of for maintenance of anesthesia. For induction of  
4     anesthesia, it remained at 3 years of age. We're going to  
5     get to the PICU aspects of this.

6           They identified concomitant administration with  
7     fentanyl may result in serious bradycardia, and the abrupt  
8     discontinuation following prolonged infusion may result in  
9     flushing of hands and feet, agitation, tremulousness, and  
10    hyperirritability, sort of emersion effects that you may  
11    see coming out of anesthesia.

12           Data we put in the label. We felt it very  
13    important to get out there because we know these studies in  
14    the pediatric ICU are ongoing, and we don't know the  
15    reason. We could spend hours talking about the analyses  
16    that were done, looking at this is a chelating agent,  
17    magnesiums, numerous studies done, multi-center. Was it  
18    center-driven? It did seem to be one center more than  
19    another. But what we put in the label is that propofol is  
20    not indicated for pediatric ICU sedation as safety has not  
21    been established. In a single multi-center trial of  
22    critically ill ICU patients, there was an increased  
23    mortality, causality not established, of 9 percent in the  
24    propofol arm versus 4 percent in the standard sedative arm.

25           So, you can see with the first 18 labels we

1 think there is very important information being generated  
2 at this time.

3 Our report to Congress, as I said, was  
4 submitted in January. It addressed the effectiveness in  
5 obtaining pediatric information, the adequacy of the  
6 incentive, the economic impact, and suggestions for  
7 modification. You can ask me questions about that. It's  
8 up on the Web.

9 The Pediatric Rule. Very quickly, to give you  
10 some follow-up on what's been happening with that. Again,  
11 we can require studies for certain new and marketed drugs  
12 and biologic products. The important part about the rule  
13 is that it makes thinking about pediatric studies a part of  
14 the drug trial development process.

15 Again, if anybody thinks that FDA just sits  
16 here and waits for the truckloads to unload, you don't  
17 understand what we do. It is very important that we're  
18 involved in drug trial development in the early stages and  
19 that we can ask the questions: is this product going to be  
20 used in children, what do you know about the safety, what  
21 do you know about the pharmacokinetics of it, do we want to  
22 consider developing it for children, when do you want to  
23 consider developing it for children? All of that goes on  
24 pre-IND into phase II and pre-NDA discussions.

25 Again, we could not require studies to be

1 submitted up until December of this past year. As of right  
2 now, we have deferred 114 products, which means that we  
3 have not said you don't need to study them. We have said  
4 we need more safety information. We need more phase IV  
5 information in adults. Or we've said this is what you need  
6 to do, bring it in later, and we've set a date. But they  
7 didn't have them at the time of the approval.

8 We have waived 149, and I knew some people were  
9 going to say, what? 149? You don't think it's important  
10 to study 149 products? So, I thought we would give you an  
11 idea of what those were.

12 I think you will agree that most of us don't  
13 want to go out and start studying facial wrinkles in  
14 children or some of the acne vulgaris. We can extrapolate  
15 at certain pubertal stages we feel for certain things.  
16 Age-related macular degeneration, osteoporosis, again  
17 mostly diseases that are related to age in onset at a later  
18 time in life.

19 One of these, however, you all had this  
20 discussion on sleep disorder for which there is an  
21 indication -- the sleep disorder that is labeled presently  
22 for adults is different and not the same at all for sleep  
23 disorders that may occur in children. So, that's why that  
24 is on there.

25 Post-menopausal breast cancer, et cetera.

1                   This is just a few more: fertility,  
2                   contraception, abortifacients, and chronic obstructive  
3                   pulmonary disease. `

4                   Important points just to remind everybody. We  
5                   cannot delay the approval of an adult indication. That's  
6                   why, as we move through this process, we do have a number  
7                   of deferrals, and we expected that. Unlike exclusivity,  
8                   the rules limit it to the indication that is under review  
9                   or in development. It doesn't permit us to ask for off-  
10                  label development. And promotes early consideration, as I  
11                  said, of pediatric use and drug development plans.

12                  You all should have this handout of the  
13                  announcement about the interim rule that was published on  
14                  the Web this past week about additional safeguards for  
15                  children in clinical investigations of FDA-regulated  
16                  products. This is in response, as you heard from Karen, to  
17                  the Children's Health Act, but I also think that the  
18                  committee deserves some credit for saying, we think this is  
19                  important and this needs to be carried forward and, working  
20                  with the Academy and other interested parties, to make it  
21                  clear to people that Subpart D did not apply to regulated  
22                  products. And it does now as an interim rule. It is still  
23                  open for additional comment.

24                  Now, I'm not up here to discuss the revised  
25                  consensus bullet points. It should have "draft" on here.

1 I hope you all have "draft" on your copies because it is  
2 not final, and it was supposed to have "draft" on there.  
3 This is in response to the meeting we had on placebo-  
4 controlled trials and the ethical issues.

5 We have a pediatrics ethics working group  
6 internally. They met. They tried to reconstruct that we  
7 thought would be points that were a consensus. We sent  
8 this to the committee. We received a number of comments  
9 back. We revised it again.

10 I think at this point why I'm bringing it back  
11 to you is because so much has happened. Unless we go back  
12 and look at an all-day videotape, we're finding it hard to  
13 determine what was actually discussed at the meeting versus  
14 everything that has intervened in the meantime. So, we're  
15 asking you again, not today, but we really would like you  
16 to look at these points in brackets because we're not sure  
17 that this was fully discussed. It may have been mentioned,  
18 but because of increasing discussions with Helsinki and  
19 other issues, we wanted to make sure that we hadn't passed  
20 over our thoughts into what really should be a consensus  
21 statement from the committee. So, that's why we're asking  
22 you one more time to please look at this.

23 We did put it in a slightly different order,  
24 talking about placebo-controlled trials in general, and  
25 then add-on trials, and then withdrawal trials.

1           We think we're at a watershed -- this is my  
2           concept of a watershed -- event right here which is  
3           reauthorization of FDAMA, section 111. We know even if it  
4           is not reauthorized, there's a huge amount of work that is  
5           in the pipeline right now for pediatrics, and this  
6           committee is contributing tremendously to that scientific  
7           and ethical base. But we do feel that you are going to be  
8           here for a while, contributing to many of our questions  
9           both science-based and ethically driven, as we go through  
10          this process.

11                 Tomorrow we enter again another arena, which is  
12           how does one study a product which I think will be for  
13           discussion, but we certainly hear people think is needed in  
14           a population which may have difficulty communicating their  
15           concerns to us, and certainly the ethical issues.

16                 I always end with this one of my daughter  
17           overlooking the mountains because we look forward to the  
18           future and being able to keep this arena moving forward  
19           because I think it's just tremendously exciting to us about  
20           the number of scientific issues that are being looked at  
21           and thought about, not that we wouldn't do it anyway, but  
22           it always helps to have a lot of other players, who can  
23           fund some of these studies, participate in the field too.

24                         Any questions?

25                         DR. CHESNEY: Can I just make one comment? In



1 | the folder are the three bullet points that Dianne has  
2 | asked us specifically to comment on. So, I just wanted to  
3 | be sure you recognized they were there and not just in the  
4 | slides.

5 | Skip.

6 | DR. NELSON: First of all, a phenomenal effort.  
7 | I think it's amazing, given how many pediatricians there  
8 | are within the FDA, that in fact you've been able to  
9 | accomplish as much as you've accomplished.

10 | So, my questions are as much to ask how do we  
11 | take it to the next level, which is related to the extent  
12 | to which there's pediatric input within the various  
13 | divisions as they begin to generate written requests, as  
14 | they begin to discuss with various sponsors the design of  
15 | particular trials, whether you feel there's adequate  
16 | pediatric input at that stage so that when sponsors are  
17 | designing trials or receiving requests and then they're  
18 | being brought to IRBs, which is where I see them, that  
19 | they're felt to be pediatric-appropriate.

20 | And then a follow-up question to that would be  
21 | the extent to which this committee could do more than it's  
22 | currently doing, whether you feel it could be used more  
23 | effectively in different ways to facilitate the design of  
24 | appropriate pediatric trials.

25 | DR. MURPHY: Clearly there's not enough in the

1 way of resources at FDA right now. We refer to it as the  
2 thin line. It's really very thin for the volume, if you  
3 consider the number of NDA's that we approve in a year, 30  
4 or 40, and we're cranking out 188 written requests. It  
5 gives you an idea of the disproportionate number of  
6 activities. So, yes, we need more resources, and we made  
7 that very clear I think to everybody. We just can't  
8 continue the way we are right now.

9           That relates also to the people within the  
10 division, because the people within the division are not  
11 assigned to pediatrics, even if they're a pediatrician.  
12 It's sort of like what happens in industry. They're  
13 assigned to do drug development for certain diseases, and  
14 it's very seldom just a pediatric disease. So, all of this  
15 activity is carved out on top of their additional efforts.  
16 We know that most of the pediatricians do not have time to  
17 participate at the level we wished they could because this  
18 regulatory history, this scientific history, this ethical  
19 discussion is really being limited to very few of us, and  
20 it's impossible for us to be able to disperse all of this  
21 information in an effective way and a timely way.

22           So, clearly what we're looking for is more  
23 resources so that we can assign people, at least 50  
24 percent, to pediatrics because we don't want them to leave  
25 their divisions because they leave their science. It's

1 sort of like having a faculty member who doesn't see  
2 patients anymore. They sort of lose their credibility. If  
3 you're not in your science division you tend to lose some  
4 of your credibility. So, we really do want to be able to  
5 target people maintaining their division activities while  
6 being clearly identified for pediatrics.

7 As to what could this committee do, I think one  
8 of the things that we're always struggling with is  
9 timeliness versus efficiency versus when does the issue  
10 cross to the point where you really can't move forward.  
11 When we don't think we can move forward without additional  
12 external discussion -- now, sometimes that external  
13 discussion will be that we can call up people and say,  
14 we've searched the literature; we need a clarification. We  
15 do a lot of that. We do a lot of talking to investigators,  
16 a lot of talking to NIH and CDC. It's when we need more  
17 information like that, like the discussion here today, that  
18 we do bring it forward.

19 Do I think that we will look back and wish we  
20 had done a better job on some of our requests? Absolutely.  
21 I don't think you can put a program in place with this many  
22 written requests and say that you're sure that every one of  
23 those written requests were stellar. I think they are the  
24 best evidence that we had, the best science that we had.

25 Do we want to improve upon that? Yes, but

1 that's where the resource issue comes in because if we can  
2 bring enough people into an active discussion, then I think  
3 you have more consistency. You have more communication and  
4 therefore better consistency in the way that some of the  
5 trials are requested.

6 One of the reasons we have so many different  
7 divisions is that each product -- it depends on the stage  
8 of information that we have, or as Karen was saying, how  
9 many priors we have. Is it already approved in adults?  
10 What's the safety profile of the product? What are the  
11 needs in kids? All those things have to be addressed. I  
12 don't think any committee could address 188 of those. So,  
13 it has to be those which we have difficulty with.

14 DR. NELSON: Just a quick follow-up. Are you,  
15 as a representative I guess of the pediatric initiative  
16 within the FDA, seeing all the written requests? Part of  
17 the reason I ask is my impression is that there's a  
18 different willingness on the part of pediatricians to have  
19 an appreciation for the risks of trials and whether you  
20 need to subject children to those risks to get certain  
21 information. It is a different kind of risk-benefit  
22 calculus than someone who is an adult physician in adult  
23 trials would consider. Often some of what would be  
24 considered an inappropriate trial design by a pediatric IRB  
25 would look more like an adult study. My bias is that with

1 | more pediatric leavening of that loaf, that that wouldn't  
2 | happen. So, is that happening?

3 |           DR. MURPHY: Within the divisions, they don't  
4 | always go to the pediatrician. That's first. The product  
5 | hasn't been assigned to the pediatrician, and it may not go  
6 | to them at all. If it is a written request that has never  
7 | come before, in other words, a class or a product that has  
8 | never come before the implementation team, they will come  
9 | to the implementation team and present their assessment.

10 |           But again, the implementation team is a lot  
11 | like this committee. It does not have everybody who  
12 | represents all subspecialties, and that's why we need more  
13 | resources because I think it should have representation  
14 | from all the different specialties.

15 |           So, that initiative was to, one, make sure we  
16 | just move forward with implementation of this whole massive  
17 | program in somewhat of a consistent way so we didn't have  
18 | one group asking industry to do totally different things  
19 | than another group in a different way. So, it was to  
20 | ensure regulatory consistency.

21 |           Also, we try to make sure that we ask the  
22 | division certain questions. It's not what the sponsor  
23 | proposed. What is the public health benefit? What do you  
24 | think the issues are? What are the ethical issues? We are  
25 | very dependent upon, if this is not our field, the answers

1 from the division, and particularly if the division has not  
2 participated much in PDIT, it could be an educational  
3 effort for them. I can tell you that we do send divisions  
4 back and say, try again, come back. We have concerns.  
5 We've done this for both scientific and ethical reasons.

6 So, you're right. If we're going to ensure the  
7 highest level of review, we need to have more people with  
8 expertise participating within the agency at that level.

9 Do we get every single written request? The  
10 answer is no. Do we get most of them? Yes. If there's a  
11 template, we don't get it. In other words, if there's a  
12 template like there is for HIV, hypertension, obsessive-  
13 compulsive disorder, they don't come to PDIT usually for  
14 those.

15 DR. SANTANA: Yes, I also want to echo what  
16 Skip said in terms of recognizing the tremendous amount of  
17 work that you and your group have done for this.

18 I had a different question as it relates to the  
19 reality of the rule and what's going to happen in Congress.  
20 Can you give us some guidance of what is likely to happen  
21 when Congress reviews your report and what would be the  
22 ramifications of that for all of us?

23 DR. MURPHY: I really don't know. All I can  
24 tell you is that I heard -- a year or so ago, we really  
25 thought that most people felt that exclusivity had a very

1 | good chance of being reauthorized. I think there have been  
2 | concerns that have arisen since then in two or three main  
3 | areas.

4 |           One of them has been the amount of money on the  
5 | blockbusters that has been made by some companies. I don't  
6 | know why that's surprising. In a way, legislation was  
7 | designed to reward those who did what they were asked to  
8 | do, and that they're going to make a lot of money is what's  
9 | driving it. Sorry. I shouldn't say that. It's certainly  
10 | facilitating the process.

11 |           I think that what I've heard is that -- but  
12 | they're still not looking at what we're calling now the gap  
13 | drugs, which are the products that don't have any  
14 | exclusivity or patent. Well, again, it wasn't designed  
15 | that way.

16 |           So, I think the focus now is going to be how  
17 | could we combine some balance, like we're always doing, of  
18 | defining if you're going to make a lot of money, is there  
19 | some additional responsibility you should take. I don't  
20 | think anybody would have a problem with that. Where it  
21 | gets into the problem is, how do you define a lot of money?  
22 | What's the other responsibility? What if that company  
23 | didn't happen to have a product that was on our list to be  
24 | developed? Should they go out and buy somebody else's and  
25 | then come back and develop it? All those issues are very

1 | difficult. Therefore, I have no idea.

2 |           There have been suggestions for PhRMA, for the  
3 | sponsors to contribute to a pool of money, and then there  
4 | will be a trial entity, either something like the ACTGs or  
5 | various postulates. But again, those are all just things  
6 | that you hear people discuss. I have no idea what Congress  
7 | is going to do about this.

8 |           DR. SPIELBERG: I can fill in a few things that  
9 | Dianne can't because also Dianne can't lobby officially.

10 |           In terms of the resources, I think all of us  
11 | are very concerned about that. Dianne and her crew have  
12 | done more than a superhuman job. Yet, as she indicated,  
13 | many of the review divisions don't have pediatricians  
14 | sitting on them and often struggle. We've seen discussions  
15 | that really have ended up with protocols that perhaps were  
16 | not pediatrically optimal.

17 |           In response to one of the key features that I  
18 | think we're getting a lot of backing for in the renewal of  
19 | the legislation is elevating this whole effort in  
20 | pediatrics within FDA to an office level. It needs to be  
21 | recognized for several reasons.

22 |           One is continuity. We need to assure that if  
23 | Dianne gets moved into something else -- and I hope that  
24 | never happens, but already you're getting filleted into a  
25 | number of new areas -- that indeed there will be



1 replacements, that those are real positions that are going  
2 to go on in perpetuity to assure that within the agency  
3 there is pediatric expertise in the future.

4 And the second thing is to get adequate numbers  
5 of resources because there's just no question. As was  
6 pointed out, perhaps there may be 20, 30, 40 compounds  
7 coming up for review on the adult side. We're talking 188  
8 drugs coming through the FDAMA process, just to give you an  
9 idea. Now, sure, not all of those are the size of a full  
10 NDA and require the amount of review of a full NDA, but  
11 they require an awful lot of expertise. To a lot of our  
12 thinking, the more pediatricians within the agency who,  
13 indeed, have a significant amount of their time dedicated  
14 to pediatrics, the better.

15 Regardless of what happens legislation-wise and  
16 everything else between the combinations of the rules and  
17 incentives and everything else, Lord willing, most drugs in  
18 the future are going to be labeled for pediatrics. So, the  
19 task is going to get bigger, not smaller, for all the new  
20 entities coming down the pike.

21 I think none of us have a good fix on  
22 likelihood of renewal. There are things that are being  
23 worked on. There are going to be congressional hearings  
24 coming up very soon after the congressional recess, which  
25 is just finishing up now, which is, I gather, when they all

1 go out on the playground and claw each other's eyes out and  
2 then they come back and try to be collegial. That's the  
3 definition of a recess.

4 But there are going to be lots of opportunities  
5 for input from everybody to try to assure that the process  
6 goes forward. There are attempts being made in a number of  
7 different realms to deal with some of the off-patent drugs  
8 and defining the universe of those drugs and trying to come  
9 up with ways of going after at least part of that universe  
10 and assuring the compounds that are commonly used, for  
11 which there are risks or for which there aren't appropriate  
12 formulations, do achieve both labeling for risk, as well as  
13 appropriate formulations.

14 If you look at this piece of legislation,  
15 compared to almost any other piece of legislation, the  
16 metrics and the report to Congress that Dianne and her  
17 group put together I think provide more than adequate  
18 support that it worked. If you look at what happened  
19 before and what happened now in terms of pediatric clinical  
20 investigation, the world has changed fundamentally. And in  
21 most therapeutic areas -- and the data are supportive that  
22 it's not only blockbusters that have been studied, but a  
23 fair number of those 28 drugs weren't even in the top 200  
24 selling drugs in the country and yet made it through the  
25 process.

1           But there are forces that are focusing purely  
2           on dollars and not even on the benefit side because if you  
3           read the report from FDA carefully, there are estimates of  
4           benefit, as well as costs, and people are only looking at  
5           the costs, not the dollars saved by kids being kept out of  
6           hospital, by improved therapy, by decreased side effects in  
7           hospital and out of hospital, by proper dosing and proper  
8           formulations. All those things need to be brought forth,  
9           and they need to be brought forth both by patients and  
10          physicians who understand the issues.

11                 So, it's going to be a battle, one I think more  
12          than worthy of engaging in. I think, frankly, the data and  
13          metrics are overwhelming that we got the results we wanted  
14          and now we need to fix some of the things that remain out  
15          there, particularly from my point of view, to deal with  
16          many of the issues that remain problems. Many of them can  
17          be solved by really providing the FDA the resources and an  
18          office level of pediatrics. Compared the Office of Orphan  
19          Drugs, this effort is taking infinitely more time and has  
20          vastly fewer resources associated with it, and we really  
21          need to get that accomplished.

22                 DR. MURPHY: Steve alluded to something. I was  
23          just trying to give you an idea of one of the issues that's  
24          arisen since we submitted our report. The economic gurus  
25          do their modeling and calculations on the first 112

1 products that we issued written requests for. What  
2 happened is that something like 17 of the products -- I'm  
3 doing this from memory, so I may be off one or two --  
4 assuming these were just modeling based on what we had  
5 asked -- if they got exclusivity, would have accounted for  
6 50 percent of the costs of the program. So, there are a  
7 number of companies that are studying products that are not  
8 blockbusters, but that's not what's getting the attention.  
9 And that's what happens.

10 DR. SZEFLER: Just a quick comment. I don't  
11 know if you've looked at exploring other methods of  
12 expanding your expertise. Many of us sit on panels and the  
13 topic changes, and it's just a couple of times a year. Is  
14 there a way of integrating methods in terms of some  
15 consistency or some follow-up with specialists or whatever  
16 outside of the FDA on a more continuous basis? You  
17 mentioned phone calls periodically, but those tend to be  
18 focused and temporary. But is there any kind of level way  
19 of expanding expertise that you could maintain some  
20 continuity on some of the issues?

21 For example, you deal with right now in the  
22 asthma world the aspect of steroids on growth, and we had a  
23 panel on that. But is there a way of keeping some  
24 continuity in utilizing expertise out there to enhance the  
25 expertise that you have available?

1 DR. MURPHY: Yes. We're very open to  
2 suggestions. I think that we hear from the divisions about  
3 what their priority issues are, but it would be very good  
4 to hear from this group about what your priorities are  
5 concerning the written requests that have been issued.

6 One of the problems we have is that we can't  
7 tell you exactly what we ask for, and that's something I  
8 would like to see changed. That's my personal opinion.  
9 Let me clarify that. We're not allowed to talk about it.  
10 Often what you hear from a sponsor is, to be blunt, not  
11 what we asked for, and we can't tell you what we asked for  
12 until not only have the trials been conducted, but the  
13 studies have been submitted, and we get it labeled. Now,  
14 that could be years. And then we could talk about it.

15 DR. NELSON: One of the issues that will  
16 inevitably get caught up probably in the discussion of  
17 FDAMA is the complexity and politics that are going on in  
18 the world of IRB review. I would expect within the  
19 hearings questions of whether children are adequately  
20 protected and the like within a system that is gearing up  
21 more and more trials.

22 I have taken, to reflect on whether I'm  
23 creating conflicts of interest and perplexity on the part  
24 of sponsors, to actually calling directors of research and  
25 sponsors and asking them what's in the written request

1 | because sometimes I can't believe what they've put in the  
2 | protocol and I want to know whether that was true or not.  
3 | Sometimes they tell me; sometimes they don't. But it makes  
4 | for an interesting conversation.

5 |           But on the IRB side, I think one issue is just  
6 | the expertise and quality of IRBs. I'm thinking of whether  
7 | there would be a way to fold in E-11. One of the issues is  
8 | sufficient pediatric expertise, not only in the performance  
9 | of the trial, in the review and the design of the trial,  
10 | but in the review of the trial at the IRB level. Those of  
11 | us who serve on IRBs or chair IRBs -- I know Rich is, I am;  
12 | there may be others -- know of the high degree of  
13 | variability there is in the interpretation and application  
14 | of Subpart D in a way that some of us would feel is sort of  
15 | outside the boundaries of what is frankly ethically  
16 | appropriate.

17 |           In some sense, saying that the issue is not  
18 | only just simply the FDA's process, but the process of the  
19 | actual conduct and review of these trials, adequate  
20 | expertise in pediatric investigators -- frankly, I don't  
21 | think adults should be doing pediatric trials. Period.  
22 | Pediatricians should be doing pediatric trials. I'll  
23 | extend that to family practice in certain things. I'm  
24 | open-minded, but adult physicians should not be doing  
25 | pediatric trials. That's my own personal opinion. Those

1 kinds of issues, I think, are also potentially going to get  
2 caught up in the discussion of FDAMA, which is not so much  
3 an FDA issue, but the FDA is stimulating the process.

4 DR. MURPHY: And we're very dependent upon the  
5 IRBs doing their job. Just so you all know, it's a two-way  
6 road. There have been days when I've looked at something  
7 and said, did an IRB see this? I've asked the team to go  
8 back and call. Are you sure this has gone through an IRB?  
9 And the answer has been yes. So, we really are dependent  
10 on the IRBs to play a role because as much as we want to  
11 have involvement early on, as you know, we don't require  
12 them to send in a consent form, much less an assent form.

13 So, all of these activities -- as you've heard,  
14 we're having a hard time keeping up with what we've got on  
15 our plate. We certainly don't think it appropriate for us  
16 to be taking on those responsibilities. So, there does  
17 need to be an additional activity here very much focused on  
18 what is going on to ensure IRB expertise when these  
19 protocols are coming before them.

20 DR. NELSON: What would it take to get the kind  
21 of crosstalk and communication? You have that question of  
22 IRBs. IRBs ask the question of the FDA. The sponsors say  
23 the reason the trial looks that way is they blame the FDA  
24 for it. But you and I can't talk officially about any of  
25 these trials. So, what does it take?

1 DR. MURPHY: Again, I have to just put  
2 disclaimers all around the following statements.

3 (Laughter.)

4 DR. MURPHY: I am not a lawyer. I have no  
5 ability to tell you the repercussions. There are,  
6 apparently, very important repercussions that could result  
7 that have to do with secret, confidential trade  
8 information. You all know the stock market goes up and  
9 down on what a company announces. So, we really aren't  
10 allowed to even tell you studies are submitted. Now,  
11 that's the usual process.

12 What I have proposed is that if one has an  
13 already marketed product out there and you are voluntarily  
14 participating in exclusivity -- we've sent you a written  
15 request and you want to participate in it -- that there  
16 ought to be a change so that we can talk about these  
17 trials. I think that activity alone would allow more open  
18 discussion if there were an uproar by the specialists in  
19 the field that there's a concern or an IRB has a concern.  
20 Then they would know the elements. They would be able to  
21 say this is the specific part that's disturbing versus  
22 talking in sort of code language or trying to reassure you  
23 that that's not what we asked for, that is what we asked  
24 for, but we have information about why we asked for that,  
25 but we can't tell you about that information either. So,



1 | it really does become a very nonproductive discussion if we  
2 | can't have the studies that we've asked for under  
3 | exclusivity available for discussion.

4 |           So, that's part of the legislation that we have  
5 | suggested verbally. We did not put it in the report to  
6 | Congress, but we have suggested verbally it would benefit  
7 | this whole process.

8 |           DR. SPIELBERG: Invariably you run into  
9 | proprietary issues, et cetera. But the one way that we can  
10 | obviate many of those issues is in something that Dianne  
11 | already alluded to, which is really templates for certain  
12 | therapeutic areas and certain types of compounds. To the  
13 | extent that learned groups such as this can contribute to  
14 | the evolution of templates that will apply to multiple  
15 | different compounds within a therapeutic area, many of the  
16 | issues about inappropriate study design, taking an adult  
17 | protocol, stamping "pediatric" on it, getting beta HCGs on  
18 | newborns for pregnancy testing, that kind of thing can  
19 | easily be dealt with.

20 |           I think to the extent that we work more on  
21 | templates and really use this kind of body as a good  
22 | testing mechanism up and back, with IRB representation and  
23 | ethics representation, so that we can look at these kinds  
24 | of designs -- some of the templates that initially were  
25 | designed in therapeutic areas I think, frankly, did miss

1 the mark in certain areas of hypertension, which was sort  
2 of basically reproduce in kids what you do in adults.  
3 Well, that may not really be the right study design. But  
4 the best way of looking at that is in therapeutic  
5 categories through a body like this.

6 I hate to increase workloads, but in a sense I  
7 think probably one of the best ways would be for this group  
8 to meet, if necessary, somewhat more frequently to help out  
9 with the evolution of some of those templates in key  
10 therapeutic areas because I think that would be the best  
11 way in an open, transparent forum where it's not  
12 proprietary to a given compound and it's not related to a  
13 specific protocol, but it's generic to the development of  
14 the key templates. So, when a company comes to you, Skip,  
15 with something that you already know what the template  
16 should be and it's whacko outside of that template, you  
17 don't have to worry about what the specifics of the written  
18 request is because basically you understand what the  
19 template was.

20 And the templates go up on the Web. They're  
21 transparent. They're open to all and don't provide any  
22 individual company a competitive advantage or disadvantage,  
23 for that matter.

24 DR. MURPHY: If we have a template up, it  
25 doesn't mean we can't modify it because different drugs

1 have different levels of information. Believe me, we hear  
2 from the sponsors because we require more of one company  
3 than we do of another. But that's because their product  
4 hasn't been out there as long. We don't have as much  
5 safety data or it has a safety issue we're more concerned  
6 about. The template is a starting point, but the specifics  
7 of the product may mandate changes in that template.

8 DR. SPIELBERG: What it does for you as an  
9 investigator, knowing the template, you can ask the company  
10 intelligent questions. Frankly, if you don't get  
11 intelligent responses back, you know where the protocol  
12 stands. So, it gives you a basis for understanding what  
13 the whole picture would be, and then again modify because  
14 this compound happens to be unusually metabolized or it's  
15 very different than others in the class and therefore this  
16 has to be done. Again, the intelligence and the scientific  
17 level of the dialogue with the IRB improves.

18 DR. NELSON: I know it's late, but let me ask  
19 one more specific question.

20 One concern of mine is the ability of one  
21 sponsor, for example, to be able to take advantage of the  
22 inference of effectiveness or efficacy on the basis of a  
23 product that another sponsor has, indeed, already studied.  
24 If you look at the FDA guidance on 505, it basically says  
25 that the sponsor needs to have permission basically to use

1 | that data or submit that data in a claim for exclusivity.

2 |           So, I guess my question is, to the extent to  
3 | which one would allow for, say, the second compound or the  
4 | third compound that is within a class where you've already  
5 | got evidence in hand because you've reviewed it and  
6 | approved the exclusivity and/or the labeling, in fact, in  
7 | that compound, why require the sponsor to have permission  
8 | from another sponsor, because clearly the answer is going  
9 | to be no, when you've got the data in hand and basically  
10 | out of fairness to the second or third sponsor, you'll end  
11 | up putting more kids at risk to an efficacy study when all  
12 | you really need is the dosing or PK for that different  
13 | formulation or preparation?

14 |           DR. MURPHY: Even though that's in the  
15 | guidance, it's not used the way you're describing it. If  
16 | you have product A and B comes along and then C comes  
17 | along, if you could not extrapolate -- let's just say that  
18 | -- for whatever reason for A, we then determine that we  
19 | were wrong. You could extrapolate. We may ask for a  
20 | different set of information from B because just like the  
21 | test of hypothesis, it turns out you could. But it  
22 | wouldn't be that we asked B to get this information from A  
23 | because, as you said, we know it, so we understand it.

24 |           Where it has been used is that you have a  
25 | product -- I don't know if I can explain this properly.

1 But it has lost some of its exclusivities and its patents,  
2 but it has now been bought by another company and another  
3 company now is going to do a trial. So, they'll get three  
4 years exclusivity, and they need that data. They can't  
5 just send us the reports. So, it's a very different  
6 situation than the one you're describing.

7 It's where if we're going to ask for a study  
8 that depends on some other information that was never put  
9 in the label but owned by that other company, you can't  
10 just tell us that that company -- it was trying to get at  
11 the issue we didn't want people just telling us the company  
12 allowed them cross reference. That's what it was trying to  
13 get at. It was trying to get at the fact that if you're  
14 going to ask us to start at building our requests or  
15 building the studies you want based on information that  
16 somebody else owns, that you need to get that information  
17 and let us review it.

18 But you're right. If it's just product B and C  
19 -- different companies with the same indication, we know  
20 that information. We don't ask them to purchase it or get  
21 it.

22 I don't think I made that clear, but it's a  
23 really different circumstance than what you're describing.

24 DR. CHESNEY: Thank you, thank you, thank you,  
25 Dianne.

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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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