

# TRANSCRIPT OF PROCEEDINGS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGIC HEALTH

MICROBIOLOGY DEVICES PANEL

MEDICAL DEVICES ADVISORY COMMITTEE

Volume II

This transcript has not  
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Pages 1 thru 223

Rockville, Maryland  
January 21, 2000

MILLER REPORTING COMPANY, INC.

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PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGIC HEALTH

MICROBIOLOGY DEVICES PANEL  
MEDICAL DEVICES ADVISORY COMMITTEE

VOLUME II

Friday, January 21, 2000

8:20 a.m.

9200 Corporate Boulevard  
Rockville, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

Microbiology Panel Members Present:

Patricia Charache, M.D., Chair

Natalie L. Sanders, M.D., M.P.H.

Carmelita U. Tuazon, M.D.

Michael L. Wilson, M.D.

David W. Gates, Ph.D., Industry Representative

Stanley M. Reynolds, Consumer Representative

Consultants:

Paul H. Edelstein, M.D., Temporary  
Voting Member

L. Barth Reller, M.D.

Leonard B. Seeff, M.D.

Steven C. Specter, Ph.D.

John A. Stewart, M.D.

Lauri D. Thrupp, M.D.

Panel Discussant:

Miriam Alter, Ph.D.

Guest:

Frederick C. Nolte, Ph.D.

FDA Staff:

Freddie M. Poole, Executive Secretary

Steven I. Gutman, M.D., M.B.A.,

Division Director

Woody R. Dubois, Ph.D., Branch Chief

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P R O C E E D I N G S

1 MS. POOLE: Good morning. Welcome to the next  
2 session of the Microbiology Devices Advisory Panel Meeting.

3 Just a few housekeeping items. If you have cell  
4 phones, could you please switch them off now? If you have  
5 pagers, could you turn them on "vibrate" so that our  
6 advisory committee and speakers won't be disturbed? Thank  
7 you.  
8

9 For today's meeting, we also have a Conflict of  
10 Interest Statement to Read.

11 The following announcement address conflict of  
12 interest issues associated with this meeting and is made  
13 part of the record to preclude even the appearance of an  
14 impropriety. To determine if any conflict existed, the  
15 agency reviewed the submitted agenda for this meeting and  
16 all financial interests reported by committee participants.  
17 The conflict of interest statutes prohibit special  
18 Government employees from participating in matters that  
19 could affect their or their employers' financial interest.  
20 However, the agency has determined that participation of  
21 certain members and consultants, the need for whose services  
22 outweighs the potential conflict of interest involved, is in  
23 the best interest of the Government. Therefore, a waiver  
24 has been granted for Dr. Lauri Thrupp for his interest in a  
25 firm that could potentially be affected by the panel's

1 recommendations. Copies of this waiver may be obtained from  
2 the agency's Freedom of Information Office, Room 12-A-15 of  
3 the Parklawn Building. We would like to note for the record  
4 that the agency took into consideration other matters  
5 regarding Drs. Melvin Weinstein, Paul Edelstein, and Barth  
6 Reller. Each of these panelists reported interests in firms  
7 at issue, but in matters that are not related to today's  
8 agenda. The agency has determined therefore that they may  
9 participate fully in all discussions."

10 "The agency would also like to note for the record  
11 that Frederick Nolte, who is a guest today, has identified  
12 himself as having a professional relationship with one or  
13 more of the firms at issue. In the event that the  
14 discussions involve any other products or firms not already  
15 on the agenda for which an FDA participant has a financial  
16 interest, the participant should excuse himself or herself  
17 from such involvement, and the exclusion will be noted for  
18 the record."

19 "With respect to all other participants, we ask  
20 that in the interest of fairness, all persons making  
21 statements or presentations disclose any current or previous  
22 financial involvement with any firm whose products they may  
23 wish to comment upon."

24 Dr. Charache?

25 DR. CHARACHE: We would like to begin by

1 reintroducing today's panel, and we'll ask each panel member  
2 to introduce himself or herself as we go around.

3 My name is Dr. Patricia Charache. I am a  
4 Professor of Pathology, Medicine and Oncology at Johns  
5 Hopkins, and my current title is Program Director, Quality  
6 Assurance and Outcomes Research.

7 DR. SANDERS: Natalie Sanders, Assistant Clinical  
8 Professor of Medicine at University of Southern California,  
9 and I am also the Medical Director for EBIOCARE.com, which  
10 is a specialty pharmacy with an internet platform.

11 DR. EDELSTEIN: Paul Edelstein, University of  
12 Pennsylvania. I am Professor of Pathology and Laboratory  
13 Medicine. I am Director of the Clinical Microbiology  
14 Laboratory at the University Hospital.

15 DR. TUAZON: I am Carmelita Tuazon, Professor of  
16 Medicine at the George Washington University Medical Center.

17 DR. RELLER: Barth Reller, Director of Clinical of  
18 Microbiology, Duke University Medical Center, Professor of  
19 Medicine and Pathology.

20 DR. SPECTER: Steven Specter, University of South  
21 Florida College of Medicine. I am Professor of Medical  
22 Microbiology and Immunology and Associate Dean for  
23 Preclinical Education.

24 DR. GUTMAN: I am Steve Gutman, Director of the  
25 Division of Clinical Laboratory Devices.

1 MR. REYNOLDS: Stanley Reynolds. I am the  
2 Consumer Representative, with Pennsylvania Department of  
3 Health, Bureau of Laboratories.

4 DR. GATES: David Gates, Becton Dickinson. I am  
5 Director of Quality and Compliance, and I am the Industrial  
6 Rep.

7 DR. NOLTE: Rick Nolte, Associate Professor of  
8 Pathology and Lab Medicine at Emory University, and I am  
9 Laboratory Director of Clinical Microbiology and Molecular  
10 Diagnostics at Emory University Hospital.

11 DR. STEWART: John Stewart, Center for Disease  
12 Control, Division of Viral Diseases. I am in charge of the  
13 Clinical Virology Lab.

14 DR. THRUPP: Lauri Thrupp, Professor in the  
15 Infectious Disease Division, University of California  
16 Irvine, Chief of Infection Control and a consultant to the  
17 Clinical Microbiology Lab at UCI Medical Center.

18 DR. WILSON: Mike Wilson, Director of the  
19 Department of Pathology and Laboratory Services at Denver  
20 Health; Associate Professor of Pathology at the University  
21 of Colorado School of Medicine.

22 DR. SEEFF: Leonard Seeff, NIDDK, NIH, and a take  
23 care of the garbage on the third and the ninth floor of  
24 Building 31; at your disposal.

25 [Laughter.]

1 DR. CHARACHE: I will thank the panel for  
2 enlightening us on their occupations.

3 We will now continue with New Business. I will  
4 remind the panel that we have one item of business leftover  
5 from yesterday to complete at the end of the day today to  
6 address some issues that we had been asked to address then  
7 and ran out of time. So we will try to remain more on time  
8 if we can possibly do so today to meet the travel times that  
9 people have.

10 Our first order of New Business is presentations,  
11 Division Director.

12 DR. GUTMAN: Good morning. I'd like to welcome  
13 you all again. It's colder today, but there is less snow.

14 As mentioned yesterday, the test under review  
15 today is a new version of a type of product previously  
16 reviewed and licensed by the Center for Biologics. The FDA  
17 has worked interactively with the sponsor to develop methods  
18 for evaluating the data gathered and for establishing  
19 appropriate claims.

20 The central issue is the same as that posed  
21 yesterday--what general or what specific claims are  
22 supported by the data sets and what labeling is appropriate.

23 As a result of interactions with the company, FDA  
24 has very recently suggested several rather late  
25 modifications in the criteria used to characterize patient

1 subgroups, and the data you will be seeing today isn't  
2 different from the data that has already been provided you,  
3 although there are some modifications in the criteria, and  
4 we apologize for any confusion that that may cause, and the  
5 company is certainly willing and the agency is willing to  
6 answer questions if that does in fact cause confusion.

7           The modified criteria make a number of assumptions  
8 when critical details were not available from the records to  
9 the clinical and laboratory data. We anticipate discussion  
10 of these in the course of analysis by the panel, and during  
11 his presentation this morning, or in fact at any time, Dr.  
12 Ticehurst is prepared to answer questions about the nature  
13 of these, at least from the agency's point of view.

14           The sponsor has been quite receptive to FDA's  
15 suggestions and has with remarkable alacrity modified its  
16 presentation as a result of our interactions, and in so  
17 doing, some of the wind has been taken out of the agency's  
18 sails in terms of its planned presentations this morning, so  
19 we will either be uncharacteristically or mercifully brief.

20           In the course of deliberations, we will be asking  
21 for whether the criteria we are suggesting in conjunction  
22 with the sponsor are appropriate and how the data, design  
23 and criteria impact intended use and proposed labeling.

24           As was true yesterday, at issue is the quality of  
25 data being drawn from largely archived or retrospective

1 samples, and I will put on the table right up front the same  
2 question raised yesterday: Is the data pristine enough to  
3 support the sponsor's claims, and if not, what additional  
4 data, what additional information, or what changes in claims  
5 may be warranted. And as was true yesterday, your input is  
6 sought in the context of what is known about hepatitis C and  
7 with an eye to the FDA Modernization Act mandate of seeking  
8 the least burdensome routes to product approval.

9 Thank you.

10 [Pause.]

11 They have caught me off guard. We actually have  
12 two certificates of appreciation for two people who have  
13 been with our committee for four years and have done  
14 yeoman's service and will both be sorely missed.

15 David Gates, who has been a wonderful Industry Rep  
16 and has provided the perspective that we truly covet in our  
17 panel deliberations--it has been four years, my gosh--and I  
18 have here a plaque from our Center Director and a letter of  
19 appreciation from our Commission.

20 [Presentation to Dr. Gates; applause.]

21 DR. GUTMAN: I wondered why the agenda said  
22 "Presentations."

23 Then, also, an amazing and cherished member for  
24 many years, Dr. Charache, who has been with us for four  
25 years, receives the same two accolades.

1 [Presentation to Dr. Charache; applause.]

2 DR. GUTMAN: I now turn it over to the sponsor.

3 DR. CHARACHE: Yes. Our next order of business is  
4 the premarket approval application, Abbott AxSYM HCV  
5 Microparticle Enzyme Immunoassay for the qualitative  
6 detection of anti-HCV in human sera or plasma, to aid in the  
7 diagnosis of HCV infection. These tests are not intended  
8 for blood donor screening.

9 The first presentation will be by Sue Sanborn,  
10 introducing the presentation as a whole.

11 MS. SANBORN: Good morning and thank you.

12 My name is Sue Sanborn. I am Manager of  
13 Regulatory Affairs at Abbott Diagnostics Division. I'd like  
14 to thank the FDA for enabling Abbott to present before the  
15 Microbiology Panel, and I'd like to thank the panel members  
16 for their participation in today's discussion.

17 [Slide.]

18 We will be presenting the Abbott AxSYM HCV in  
19 vitro diagnostic assay. The intended use and indications  
20 for use are on this foil.

21 This assay is a microparticle enzyme immunoassay  
22 for the qualitative detection of antibody to hepatitis C  
23 virus in human serum or plasma.

24 The detection of anti-HCV is evidence of HCV  
25 infection. Although not indicative of a particular HCV-

1 associated disease state, antibodies to HCV are detected in  
2 HCV-infected individuals with asymptomatic, acute, and  
3 chronic hepatitis. An HCV antibody result, the patient's  
4 clinical presentation, history, and other laboratory results  
5 are used to diagnose HCV-associated disease.

6 [Slide.]

7 In our proposed package insert in both the  
8 limitations of the procedure and the intended use, the  
9 following warning would be indicated: "The effectiveness of  
10 this assay for use in screening blood or plasma for donors  
11 has not been established, and it is for in vitro diagnostic  
12 use only and is not for use in blood or donor plasma  
13 screening."

14 [Slide.]

15 The AxSYM HCV PMA was submitted to the FDA in June  
16 of 1997. The data from the clinical study takes into  
17 consideration ongoing discussions between CDRH and Abbott.  
18 The clinical information in your original packets was based  
19 on suggestions for the specimen categories with discussions  
20 with CDRH as late as September of 1999. However, as Dr.  
21 Gutman mentioned, we took a different look at the specimen  
22 categories based on discussions with CDRH as late as last  
23 week, and the clinical data being presented today reflect a  
24 change in those specimen categories.

25 Further explanation of the specimen categories

1 will be discussed in the clinical presentation summary, and  
2 I apologize for this inconvenience. I know Freddie Poole  
3 provided you a new set of the clinical data slides.

4 The agenda presenters and invited speakers for  
5 today's presentation are as follows. Following my  
6 introduction, Dr. James Stewart, Director of Hepatitis and  
7 Retrovirus Assay Development, will provide an overview of  
8 the in vitro diagnostic reagent system this assay uses and  
9 the AxSYM HCV assay format.

10 Dr. Jules Dienstag, Associate Professor of  
11 Medicine at Harvard Medical School and on the staff at  
12 Massachusetts General Hospital, is one of Abbott's speakers  
13 and our consultant. He will discuss the natural history of  
14 the hepatitis disease with reference to clinical and  
15 diagnostic utility of anti-HCV testing.

16 Dr. Sally Hojvat, Director of Clinical Research at  
17 Abbott, will follow with a summary of the AxSYM HCV  
18 clinical studies that support the intended use of the AxSYM  
19 HCV assay.

20 Also with us this morning as an invited guest of  
21 Abbott is Dr. Duane Thiele, Professor of Internal Medicine  
22 and Chief of Hepatology at the University of Texas  
23 Southwestern Medical Center in Dallas. Several of the  
24 specimens from the acute HCV infection category in our  
25 clinical study were obtained from Dr. Thiele. He will be

1 available for any questions you have on these specimens.

2 At this time, I'd like to turn the presentation  
3 over to Dr. Stewart.

4 DR. STEWART: Good morning.

5 [Slide.]

6 My name is Jim Stewart. I am the Director of  
7 Hepatitis and Retrovirus Assay Development with the Abbott  
8 Diagnostics Division.

9 I will present a very brief overview of the AxSYM  
10 system and the technology that is employed in the AxSYM HCV  
11 immunoassay.

12 As you know, testing for antibodies to hepatitis C  
13 has been in place for over 10 years. The reagents utilized  
14 for this testing have been in standard use for many years,  
15 with accepted performance in both diagnostic laboratories  
16 and blood banks.

17 Abbott's major focus over the last few years has  
18 been to move this tested antibody detection technology onto  
19 more automated systems to significantly improve laboratory  
20 throughput and work flow.

21 [Slide.]

22 AxSYM HCV is a microparticle-based immunoassay  
23 designed specifically to run on the AxSYM instrument system.  
24 AxSYM is a fully-automated immunoassay analyzer to perform a  
25 variety of immunoassays for viral markers and other specific

1 analytes.

2 AxSYM was introduced outside the United States in  
3 1993. It was initially 510(k) cleared as a Class I devices  
4 in May of 1995. There are now over 15,000 AxSYM instruments  
5 placed worldwide, including over 4,000 in the United States.

6 [Slide.]

7 This is a picture of the AxSYM instrument. All  
8 sample processing steps, from pipetting of the sample to  
9 assay processing to data reduction and result reporting are  
10 performed automatically by the AxSYM instrument. The user  
11 loads the selected reagents and samples and initiates the  
12 run. The instrument then automatically schedules and  
13 controls the sample processing to give the optimal release  
14 of test results.

15 In your package as well is a slide that describe  
16 some of the other key features of the AxSYM instrument; I  
17 won't go into that in detail this morning but rather will  
18 move to the next slide and talk specifically about the AxSYM  
19 HCV assay.

20 [Slide.]

21 AxSYM technology represents microparticle  
22 fluorescence-based enzyme immunoassays, or MEIAs.  
23 Fundamentally, the AxSYM HCV assay is designed to detect  
24 anti-HCV in human serum or plasma. These antibodies are  
25 produced in response to exposure to or infection with the

1 hepatitis C virus. AxSYM HCV is designed to detect  
2 antibodies against multiple HCV gene products, including  
3 both structural and nonstructural proteins of the HCV  
4 genome.

5 [Slide.]

6 This schematic shows the format of the AxSYM HCV  
7 assay. Anti-HCV indicative of infection with the hepatitis  
8 C virus is captured by a solid-phase microparticle which is  
9 coated with recombinant antigens representing the multiple  
10 areas of the HCV genome. These antigens have been used  
11 extensively in HCV test kits that are licensed outside the  
12 United States and within the United States.

13 Antibody which is bound to the microparticle is  
14 then detected in a second step using an alkaline phosphatase  
15 labeled "goat anti-human conjugate." This sandwich  
16 generates a fluorescent emission when incubated with the  
17 substrate 4-methyl-umbalipheral [ph.] phosphate. The  
18 fluorescence is then measured and compared to a cutoff value  
19 based on internal calibrators. Fluorescent rate counts  
20 above that established cutoff are considered positive for  
21 anti-HCV antibodies.

22 [Slide.]

23 The AxSYM HCV assay we are reviewing today has  
24 been available outside the United States since 1995. It has  
25 been recognized as a standard of care in numerous countries

1 as evidenced by its approval and widespread use. It has  
2 been approved by a number of the major regulatory agencies  
3 outside the U.S., including the Paul Ehrlich Institut in  
4 Germany, the Agence de Medicement [ph.] in France, and  
5 COSESHO [ph.] in Japan. Worldwide, over 21 million AxSYM  
6 HCV tests were used in 1999.

7 As I mentioned, the recombinant antigens utilized  
8 in the European test kit are the same as those we will be  
9 reviewing today and are common to those used in other widely  
10 available HCV products.

11 In 1999, AxSYM HCV ranked first in the Paul  
12 Ehrlich Institut evaluation of licensed HCV test kits, based  
13 primarily on an enhanced ability to detect anti-HCV in  
14 established seroconversion panels. Panels like these will  
15 be represented in the U.S. clinical data that we will be  
16 discussing shortly.

17 [Slide.]

18 In summary, AxSYM HCV is a microparticle enzyme  
19 immunoassay for the qualitative detection of anti-HCV in  
20 human serum or plasma. The presentations following me will  
21 expand on the utility of this assay by providing supporting  
22 data that, first, the presence of anti-HCV is indicative of  
23 HCV infection and that anti-HCV in combination with the  
24 patient's clinical presentation, medical history and other  
25 laboratory tests can lead to diagnosis of HCV-associated

1 disease.

2           The next presenter is Dr. Jules Dienstag,  
3 Associate Professor of Medicine, Harvard Medical School, and  
4 Gastrointestinal Unit, Massachusetts General Hospital. Dr.  
5 Dienstag will elaborate on the clinical and diagnostic  
6 utility of the anti-HCV testing.

7           Dr. Dienstag?

8           DR. DIENSTAG: Good morning. I need to tell you  
9 that I am serving as a consultant for Abbott, but I am not a  
10 regular consultant. This is an ad hoc activity on my part,  
11 and I have agreed to do this for two reasons. One is that  
12 Abbott has played an enormously helpful role to academic and  
13 Government scientists over the last 25 years in providing  
14 assays that are used for research purposes and ultimately  
15 became clinically beneficial. So I wouldn't have done this--  
16 --we are all busy and have other things to do--but I thought  
17 it was very important to support this application.

18           The other reason I decided to come here is that I  
19 figured in January, it would be good to get away from the  
20 cold and the snow in Boston.

21           [Laughter.]

22           I have been asked to talk about the natural  
23 history of hepatitis C or the clinical utility of hepatitis  
24 C antibody testing, and it is difficult to cover this in a  
25 short period, and especially with some of the experts in the

1 room, I feel sort of silly doing this. But I want to say  
2 enough so there is a context that you can rely upon as you  
3 hear the data presented about the new diagnostic approach,  
4 or I should say, the new instrument for an old diagnostic  
5 approach. So if we could turn on the slides, I'm afraid  
6 I'll use the old technology.

7 [Slide.]

8 This is the hepatitis C genome, and the proteins  
9 shown in blue are the antigens that are used in the  
10 immunoassay to detect hepatitis C antibodies. And you will  
11 hear these names, so I thought you should at least see what  
12 they are.

13 C100-3 is the earliest protein, a product of the  
14 nonstructural Gene 4. It was the original antibody in the  
15 first-generation tests, and it has now been supplanted, or I  
16 should say supplemented, by an adjacent area of the  
17 nonstructural three-area gene of C33-C, and you can see  
18 over on C22-3 part of the nucleocapsid core. Some of the  
19 later-generation immunoassays also include NS-5 protein, and  
20 you'll hear a little more about this.

21 Let's go to the next slide, please.

22 [Slide.]

23 These are data from Miriam Alter, who happens to  
24 be in the audience. I'd like to show you that using  
25 hepatitis C antibody testing, you can do sero surveys in the

1 population, and based on these tests, about 1.8 percent of  
2 the population, or just short of 4 million people have  
3 antibodies. This is a study that was published just  
4 recently in The New England Journal representing the  
5 epidemiology of hepatitis C in the United States in recent  
6 years, and of these people with hepatitis C antibodies,  
7 about two-thirds or so have viremia and are thought to have  
8 infection. So some people have antibodies without infection,  
9 and we'll talk a little bit more about this. But 1.8  
10 percent.

11 [Slide.]

12 Of patients who present with acute and chronic  
13 liver disease in the United States, hepatitis C accounts for  
14 about 17 percent of the acute cases of hepatitis and for  
15 about 45 percent of the chronic liver disease that occurs in  
16 the United States.

17 [Slide.]

18 And if you look at all patients with acute  
19 hepatitis C infection--and we have to keep in mind that we  
20 don't see very many of these anymore, and I'll talk about  
21 that--but when we had an opportunity to identify many  
22 patients with acute hepatitis C, the data suggested early on  
23 that about 50 or 60 percent would have ongoing liver injury  
24 and would be labelled as having chronic hepatitis. But we  
25 now know by looking at viremia that even among those people

1 who improve clinically and in whom liver enzyme tests,  
2 biochemical markers of inflammation, improve and return to  
3 normal, a substantial proportion remain viremic. So our  
4 current conclusion is that about 85 percent of all patients  
5 infected acutely will remain chronically infected. About  
6 two-thirds of these will remain chronically infected with  
7 liver injury, and maybe one-third or 20 percent will remain  
8 chronically infected without demonstrable liver injury. In  
9 a small proportion, the very fortunate few recover  
10 completely.

11 [Slide.]

12 I'll show you an idealized serologic pattern of  
13 what we identified during acute and chronic hepatitis. In a  
14 patient exposed to acute hepatitis at time zero, we begin to  
15 see the first clinical signs of liver injury at a median or  
16 mean of about 7 weeks, and this is the aminotransferase.  
17 Alanine aminotransferase goes up first. Antibody is  
18 evolving as this occurs, but we really don't begin to see  
19 antibody until about the time of acute hepatitis represented  
20 biochemically.

21 The earliest indicator that we can identify  
22 nowadays are amplification techniques for hepatitis C RNA.

23 [Slide.]

24 The next slide shows you a patient with chronic  
25 hepatitis. In that last panel, the patient recovered, but

1 in this case, the ALT elevations didn't go away, and  
2 although they may over time flatten out, they remain  
3 abnormal. Hepatitis C antibody is present throughout, and  
4 usually, hepatitis C RNA is detectable as well.

5 [Slide.]

6 In the next slide, just to add one little wrinkle  
7 to this, when the first immunoassays were introduced,  
8 relying on c100 as the primary probe for antibody, this  
9 antibody usually didn't appear for several weeks to several  
10 months after the onset of acute hepatitis. With the  
11 introduction of second-generation assays incorporating c22  
12 and c33, the appearance of antibody is much earlier.  
13 Sometimes, there is a slight delay, but in almost all cases  
14 of acute hepatitis seen clinically or recognized clinically,  
15 by the time that happens, antibody to hepatitis C can be  
16 detected, so it is a very useful test for acute diagnosis.  
17 And again, the gold standard is considered hepatitis C RNA,  
18 which appears even before biochemical liver injury.

19 [Slide.]

20 So one of the things that I was asked to do is  
21 tell you how a clinician--a hepatologist, which is what I  
22 am--uses hepatitis C antibody testing. The fact of the  
23 matter is that when a patient is identified who has acute or  
24 chronic liver disease, the first test we do, the initial,  
25 the primary test is an enzyme immunoassay test for hepatitis

1 C antibody. In certain situations, we supplement this or  
2 confirm this with an immunoblot assay which I'll discuss,  
3 and then later, a subsequent test that we'll do is a test  
4 for hepatitis C RNA, again done by amplification, and this  
5 can be done for a variety of reasons. Often, it is done in  
6 anticipation of antiviral therapy, and we like to look at  
7 viral load. Not shown on this slide is that currently, in  
8 anticipation of antiviral therapy, we also look at genotype  
9 given that certain genotypes require longer-term therapy and  
10 more benign genotypes require shorter-duration therapy.

11 [Slide.]

12 If you look at the next slide, I just want to make  
13 a point about the sensitivity, specificity, predicted value  
14 of these tests. I am not going to show you data on this,  
15 and maybe Miriam will discuss this later. But if you are  
16 using a test for hepatitis C antibody in a screening  
17 situation such as in the blood bank--and again, that's not  
18 what we're discussing today--but in a blood bank, if you are  
19 using a test where the frequency of the disease or the  
20 infection in the population is about one percent, and if you  
21 have a 99 percent specificity, and you are dealing with a  
22 group like this with a low probability of true infection, if  
23 you study 1,000 patients, you will identify 10 true  
24 positives, and you will identify 10 false positives--99  
25 percent specificity, one out of every 100 will be false

1 positive; out of 1,000, you'll find 10 people. So when you  
2 are doing screening in blood banks or among people with a  
3 low prior probability of infection, normal random  
4 population, potentially one out of every two will be a false  
5 positive. And for that setting, we use confirmatory or  
6 supplementary tests, a blotting assay, which identify the  
7 specific antigens against which there is immunoreactivity.

8           On the other hand, if you are dealing with a  
9 population such as drug users or somebody who has had a  
10 transfusion and then ended up with hepatitis, there, the  
11 prior probability of infection is so high that the  
12 likelihood of false positive is so low that in clinical  
13 practice, we don't bother to do supplementary testing in  
14 such situations.

15           [Slide.]

16           Now, how do we identify hepatitis C nowadays?  
17 Because of a variety of things that have happened over the  
18 last couple of decades, we don't see very much acute  
19 hepatitis anymore. And as a clinician who sees patients  
20 with liver disease, most of the patients I identify  
21 currently have had this disease for 20 or 30 years, and  
22 these are what I call "hippie-yuppies." These are people  
23 who in the sixties and seventies experimented with drugs,  
24 maybe even once or twice--maybe during a college party, they  
25 were inebriated, and somebody talked them into this. And

1 they felt fine, they grew up in society and became respected  
2 members of our communities, our bankers, our lawyers, our  
3 teachers, our physicians, our government workers.

4 [Laughter.] And now they come in, they have insurance  
5 physicals, they have yearly physicals, they attempt to  
6 donate blood, and some of them are found to have abnormal  
7 liver tests. Many insurance companies are now testing  
8 everyone for hepatitis C antibody, and lo and behold, they  
9 have hepatitis C.

10 In the old days when we had a patient with  
11 hepatitis, we would often say, okay, we have to decide  
12 whether this is acute or chronic, and then we would follow a  
13 patient for six months, and if the patient fulfilled that  
14 six-month landmark, we would say chronic hepatitis. But  
15 nowadays, almost everybody we see with hepatitis C has  
16 chronic hepatitis, and this notion of waiting six months to  
17 make a diagnosis of chronic liver disease is really not  
18 necessary.

19 So just to put this in perspective, most  
20 hepatologists who see hepatitis C--and every one of us does,  
21 and we see quite a bit of it--almost every case we see is  
22 chronic. The only cases that I ever see of acute hepatitis  
23 nowadays are in health workers who sustain accidental  
24 exposures, percutaneous exposures. So in our hospital  
25 system, which includes the Massachusetts General Hospital

1 and the Brigham and Women's Hospital, we had five acute  
2 cases of hepatitis C in the last year, all in nurses who  
3 stuck themselves, but no other cases of acute hepatitis.

4 Next slide, please.

5 [Slide.]

6 So when you have these tests, when you see a  
7 patient de novo, you can use hepatitis C antibody testing to  
8 establish a diagnosis. And usually what happens is the  
9 patient has antibody to hepatitis C and hepatitis C RNA, and  
10 that doesn't tell you whether the patient has acute or  
11 chronic infection; it tells you that the patient has  
12 infection. But in almost all cases, the distinction between  
13 acute and chronic is made on clinical and epidemiologic  
14 grounds.

15 I won't go through all of these, because it will  
16 just bore you. Why don't we go to the next slide?

17 [Slide.]

18 Just a few words about the natural history of  
19 disease. Leonard Seeff has been a pioneer in defining this,  
20 and Miriam Alter has collected data through the CDC, and  
21 these data are a reflection of both of their work. The  
22 important point is that there is still a substantial number  
23 of cases of acute hepatitis C occurring each year, abut they-  
24 are few and far between, and the numbers have declined by 80  
25 percent between the last decade and this decade. Almost all

1 patients with acute hepatitis C will end up with chronic  
2 liver disease, and the problem with chronic liver disease  
3 associated with hepatitis C is that in many cases, it is a  
4 relatively nonprogressive, slowly progressive, insidiously  
5 progressive disease that may take decades to evolve, but in  
6 a proportion, maybe 10 to 20 percent, evolution to cirrhosis  
7 can occur within 10 to 20 years, and this is a group that is  
8 at risk for liver failure and within increasing and alarming  
9 frequency, hepatocellular carcinoma.

10 [Slide.]

11 These are data among patients. This is a  
12 collection of what we know from long-term natural history  
13 studies. Among patients with chronic hepatitis which you  
14 might say might be identified 10 to 20 years after acute  
15 infection; cirrhosis might be present after 20 years or so,  
16 and hepatocellular carcinoma begins to appear at about 30  
17 years. The frequency, based on retrospective analysis, of  
18 cirrhosis is about somewhere between one-tenth of a percent  
19 and 7 percent per year among patients with chronic  
20 hepatitis, and among those with well-compensated cirrhosis,  
21 the likelihood of evolving to hepatocellular carcinoma is  
22 somewhere in the vicinity of one to 4 percent per year.

23 [Slide.]

24 This is a slide that Leonard Seeff gave me that  
25 was made by Harvey Alter, and it is designed to show you

1 what happens when blind men evaluate or examine an elephant.  
2 This is an old proverb. The blind man examining the tail  
3 things he is examining a rope; the blind man sitting on the  
4 hump thinks he is sitting on a whale; the blind man at the  
5 trunk thinks that he is examining a tree branch or some such  
6 thing.

7 The important point is that the same thing is true  
8 in terms of different perspectives for the people who  
9 encounter hepatitis C. If you are in a blood bank, and the  
10 people who come to blood bank to donate blood are healthy  
11 people with no clinical disease, if you follow the people  
12 you identify with hepatitis C antibody, most of those people  
13 will do very well for many years, if not decades. Even if  
14 you identify people who become infected with hepatitis C  
15 that is acquired after blood transfusion, and you follow  
16 that subset of patients for 10, 20, or 30 years, most of  
17 them will do very well and have very limited consequences of  
18 their hepatitis C.

19 If, on the other hand, you are a transplant  
20 hepatologist or surgeon, or you are a hepatologist, you are  
21 going to be referred to the other end of the bell-shaped  
22 curve--the patients who have progressed; the ones who have  
23 ended up with cirrhosis and its complications. And then, if  
24 you are somewhere in the middle, if you are a primary care  
25 physician or an internist, you might see more of a spectrum-

1 -some people with very limited disease, some people with  
2 very serious disease.

3           We see many patients who have this infection who  
4 live an entirely unchanged life, except for the fact that we  
5 ask them to keep coming back to see us, and there are no  
6 clinical consequences. Dr. Seeff has done studies of long-  
7 term follow-up--40, 50 years or so now--and the clinical  
8 consequences are really not that substantial. So when we  
9 see patients with severe liver disease, we are looking at  
10 the end of the spectrum. A lot more needs to be done to  
11 help us identify who is going to progress and who is not  
12 going to progress, and because we don't have good handles on  
13 this, we tend to overtreat, trying to get everybody to  
14 improve with antiviral therapy when in fact many of the  
15 patients we treat probably would not have progressed even  
16 without our intervention. So the natural history is  
17 confusing.

18           Next slide, please.

19           [Slide.]

20           One of the other things I want to impress the  
21 panel with today is that when we see a patient, and we  
22 identify hepatitis C based on antibody to hepatitis C  
23 testing, that is just the beginning. That tells us that the  
24 patient is infected with hepatitis C virus. But we have to  
25 do quite a number of other things to assess the patient. We

1 look at liver enzymes, we look at hepatitis C RNA, we look  
2 at genotype; but we also look at clinical features, and we  
3 look at histology. And our diagnoses and how we categorize  
4 and classify patients are often based on the amount of  
5 inflammation in the liver. And we have a variety of ways,  
6 based on a numerical histologic activity index, of assessing  
7 or measuring the severity of liver disease.

8 So the important point here is that hepatitis C  
9 antibody testing is used to identify infection. It doesn't  
10 allow us to distinguish between acute and chronic hepatitis.  
11 It doesn't allow us to make an important conclusions about  
12 the severity or the benignity of the liver disease.

13 Next slide, please.

14 [Slide.]

15 Although again, from a hepatologist's perspective,  
16 if a patient is referred to me with abnormal liver test or  
17 some sort of chronic liver disease, there is a whole variety  
18 of possibilities to account for this patient's hepatitis.  
19 And hepatitis C is an important one, but only one of many,  
20 one of several different viral infections, a number of  
21 autoimmune disorders, drug-induced disorders, and a number  
22 of genetic and metabolic disorders.

23 [Slide.]

24 The next slide shows you what tests we do to  
25 distinguish among this differential diagnosis, and if you

1 look at hepatitis C, the test that we do first is antibody  
2 to hepatitis C, supplemented later usually by a test for  
3 hepatitis C RNA.

4 So antibody to hepatitis C is the first test, and  
5 it is the test that we use clinically to make this  
6 diagnosis.

7 I have a few overheads to show you. One of the  
8 difficulties I had with understanding why I am here today,  
9 or why we are all here today, is that to me, the notion that  
10 we need to re-prove in the year 2000 that antibody to  
11 hepatitis C is an important test in the diagnosis of  
12 hepatitis C is a little bit counterintuitive.

13 What I have done here is I have just reproduced a  
14 table from Harrison's Principles of Internal Medicine, at  
15 least in the Northeast and probably in this part of the  
16 country considered the premier internal medicine textbook.  
17 And if you look at the various hepatitis viruses, under  
18 hepatitis C, under "Remarks," "Acute diagnosis, anti-HCV;  
19 chronic diagnosis, anti-HCV."

20 And this isn't from this year's edition; this is  
21 from two or three editions ago. This is well-known. This  
22 is almost axiomatic in clinical medicine.

23 [Slide.]

24 The next slide is just another table from the same  
25 chapter--by the way, I wrote this chapter. [Laughter.] And

1 I have been writing this chapter for 20 years. And I'm not  
2 doing it to promote myself. I am doing it to show you that  
3 when I try to summarize the state of the art in this disease  
4 every few years, I don't try to prove this. This is  
5 established. If you have a patient with acute hepatitis,  
6 how do you establish the diagnosis? If the patient has  
7 antibody to hepatitis C, that's how we make the acute  
8 diagnosis.

9 [Slide.]

10 And again, just to guild the lily, the last panel  
11 shows how we make a diagnosis of chronic hepatitis C.  
12 Again, it's another table from another chapter in the book.  
13 For chronic hepatitis, the diagnostic test that we use is  
14 antibody to hepatitis C.

15 So with that, I'll end my remarks, and we can go  
16 on. Now you'll hear about the assay and its performance.

17 Thank you very much.

18 MS. HOJVAT: Good morning. Now we get to the meat  
19 of the matter.

20 I'd now like to review the clinical studies which  
21 Abbott conducted to support the intended use of this assay,  
22 AxSYM HCV. If I could have the first slide, please.

23 [Slide.]

24 And some of this, you have heard before, but I'll  
25 just go over it again. HCV antibody testing was introduced

1 in the United States in 1990, and as we have heard, most of  
2 the cases of HCV present as asymptomatic rather than  
3 symptomatic infection, and there are many publications to  
4 support this, including the NHANES III study which you heard  
5 about this morning, too.

6           The categories of specimens tested in the clinical  
7 study, which was conducted, by the way, in 1996, when in  
8 fact using HCV RNA was not really the test recommended at  
9 the time. These assays, by the way, still are research  
10 assays, the HCV RNA, and have not been licensed by the FDA.

11           The categories of specimens we used in the  
12 clinical study were chosen to reflect the intended use  
13 populations for AxSYM HCV and as such consist of both  
14 serologically characterized, and where we had access to  
15 medical records for the patients, we were able to add  
16 clinical information as well to characterize HCV infections.

17           Next slide, please.

18           [Slide.]

19           The studies were performed at seven United States  
20 sites, six of which represented settings indicated for use  
21 of this assay, such as hospital laboratories, reference  
22 labs, and a research lab at a blood center.

23           The testing protocol compared the AxSYM HCV  
24 results to the FDA-licensed Abbott HCV EIA 2.0, which was  
25 already referred to as a second-generation assay. And any

1 positive results were supplemented by an additional licensed  
2 test, in this case, the Chiron RIBA 2.0, which is a strip  
3 immunoblot assay.

4 Just over 5,600 specimens were tested in total  
5 during the study, and specimens were obtained from  
6 individuals who met criteria defining a particular  
7 population or category.

8 Also, we had documented clinical characterization  
9 of archived asymptomatic acute and chronic HCV specimens,  
10 and this information was obtained from reviewing medical  
11 records with varying amounts of information, such as  
12 symptoms, physical signs, biochemical, histopathologic and  
13 treatment. And I will review these criteria with you later  
14 in the presentation.

15 [Slide.]

16 We grouped the results of the clinical study into  
17 the following six areas demonstrating the performance of the  
18 assay. Precision studies were designed to demonstrate how  
19 well the assay gave the same result on repeated  
20 determinations, and studies designed to give the prevalence  
21 or expected values of anti-HCV were conducted in relevant  
22 populations.

23 Sensitivity studies were designed to determine the  
24 ability of AxSYM HCV and to determine if the AxSYM HCV test  
25 results could be affected by any potentially interfering

1 substances or any possible cross-reactivity, perhaps co-  
2 infections with HBB or HIV, with other microorganisms. We  
3 also ran studies just looking at the detection of antibody,  
4 and in these studies were able to use commercialized  
5 seroconversion panels and also some archived HCV genotyped  
6 specimens.

7 [Slide.]

8 If we look at the precision studies, we ran two  
9 different precision studies. The first one shown here was  
10 performed using the NCCLS Protocol EP5-T2 as a guideline.  
11 This protocol was at the time of the study a draft document  
12 and was later approved as the protocol which you probably  
13 know as EP5-A.

14 There were seven panel members which we prepared  
15 reflecting a range of anti-HCV, and these were tested twice  
16 daily over 20 days with one reagent lot of AxSYM HCV at  
17 three different sites.

18 The total percent CV for all panel members was  
19 less than 15 percent. And included in that total percent CV  
20 was the variability brought on by between-day, between-run,  
21 and within-run variability.

22 [Slide.]

23 The second precision study was an additional  
24 study, in fact, to look at the performance and assess  
25 between-lot precision. Here, we again had six panel members

1 which we did prepare with a range of anti-HCV activity,  
2 which were tested twice daily for five days within this case  
3 three different reagent lots of AxSYM HCV at three  
4 independent sites.

5           There are three lots and three instruments in this  
6 study, and if these are factored into the analysis, in fact,  
7 we actually had a 25-day study. The between-lot variability  
8 here for all of the panel members was less than 20 percent.

9           [Slide.]

10           The next studies which we will show indicate the  
11 use of AxSYM HCV in assessing the prevalence of antibody to  
12 HCV in populations, in this case, three distinct U.S.  
13 populations.

14           In the first population of random hospital  
15 patients--and these were obtained from two different sites  
16 in New Orleans and Memphis--we found that there were 29  
17 specimens out of 999 which were positive both by the AxSYM  
18 HCV and the supplemental assay and therefore considered  
19 positive for anti-HCV. This gives an overall prevalence of  
20 2.9 percent. And by the way, all of these populations were  
21 done with fresh specimens which were drawn and tested  
22 directly on the AxSYM HCV.

23           In first-time volunteer blood donors, we obtained  
24 these from five different sites in the United States--  
25 Florida, California and Illinois--a total of 2,505 of these

1 specimens in which we had 60 that were positive both by  
2 AxSYM HCV and the supplemental assay and considered to be  
3 positive for anti-HCV, the prevalence here being 2.4  
4 percent.

5 We did test over 1,000 random volunteers, and  
6 these were repeat whole blood donors, of which we did not  
7 find a single anti-HCV positive specimen in the population.  
8 We obtained these donors from two independent blood banks.

9 Although the prevalence that you see here for the  
10 first two populations is slightly higher than the NHANES  
11 study you saw, which was about 1.8 percent, we still feel  
12 that these are within statistical boundaries, and we can say  
13 that they are similar to the NHANES III study. Again, this  
14 was carried out in 1995-1996.

15 Just some further information that was based on  
16 some discussion I heard yesterday from the panel. If you  
17 look at the positive predictive value for the assay, if you  
18 calculate this, we find that in random hospital patients,  
19 this was 78.4 percent, and for the first-time donors, it was  
20 84.5 percent. So this is a better positive predictive value  
21 than you heard when there was some discussion about it being  
22 a 50 percent positive predictive value with current EIAs in  
23 blood donors. In other words, over 80 percent of the  
24 positive AxSYM HCV determinations were confirmed by the  
25 supplemental assays. So there has been an improvement in

1 that with this assay.

2 [Slide.]

3 Let's go to sensitivity. To assess the  
4 sensitivity of the AxSYM HCV assay, we used two different  
5 sensitivity calculations. The first one, which we have just  
6 called "sensitivity," can be defined as the ability of the  
7 AxSYM HCV assay to detect HCV antibody in EIA-positive and  
8 immunoblot specimens. In other words, that is the gold  
9 standard that we were comparing to, EIA-positive and  
10 immunoblot, as being indicative of evidence of HCV  
11 infection.

12 "Clinical sensitivity" here is defined as the  
13 ability of AxSYM HCV to detect HCV antibody in well-  
14 characterized specimens from individuals with documented  
15 chronic acute or asymptomatic infection.

16 [Slide.]

17 The following nine specimen categories have been  
18 included in these sensitivity calculations. A combination  
19 of criteria, which you have heard earlier were agreed to by  
20 the agency and Abbott in very recent discussions, were used  
21 to refine the categories of the specimens tested in the  
22 study, and all nine sets of data generated from testing  
23 these categories were used to calculate the overall  
24 sensitivity of the assay. We used results of the data of  
25 testing from the first three categories to calculate

1 clinical sensitivity of AxSYM HCV.

2           If we drop down to the fourth and fifth bullet,  
3 these are two categories of specimens which do have a  
4 physician's diagnosis of chronic hepatitis. However, the  
5 agency feels that there is insufficient additional data or  
6 other evidence to support putting those specimens into the  
7 category of chronic HCV infection.

8           Similarly, with the category that is called "HCV  
9 infection with hepatitis, state not determined," these are  
10 specimens which have a physician's diagnosis of acute HCV  
11 infection.

12           If we go to the HCV antibody-positive individuals,  
13 here we only had serological data, but as we have heard this  
14 morning, from the prevalence of chronic hepatitis in the  
15 population, the probability is that about 85 percent of the  
16 specimens from these individuals were from individuals with  
17 chronic hepatitis C.

18           The hospital patients category, these were  
19 specimens from patients who were referred by physicians to  
20 the laboratory for hepatitis testing. It wasn't just HCV  
21 testing, it was hepatitis in general, so it could have been  
22 for HAV, HBV, or anything else which would indicate  
23 hepatitis to the physician. And they came from various  
24 areas of the hospital, not just from the hepatologist or the  
25 gastroenterology units.

1 In the last category, we included three different  
2 populations as individuals at increased risk for HCV  
3 infection. These were hemophiliacs, injecting drug users,  
4 and dialysis patients.

5 [Slide.]

6 The next set of slides discuss really what boil  
7 down to being inclusion/exclusion criteria for these various  
8 categories. This first category, from a clinical  
9 perspective, may not be commonly used by physicians in  
10 medical practice, but we have put 100 of our specimens into  
11 this category labeled as "Asymptomatic HCV infection."

12 These were specimens that came from normal, health  
13 individuals who had been identified as anti-HCV-positive by  
14 a licensed anti-HCV assay. Other characteristics of the  
15 population were: no known risk factors for HCV infection,  
16 they are well and in good health, and serum transaminase  
17 levels were within normal limits.

18 As we have heard from Dr. Dienstag, this would  
19 probably be the individual who is identified as being anti-  
20 HCV-positive when they go to donate blood or for an  
21 insurance checkup. And these individuals are most likely to  
22 be chronic hepatitis C patients, but they have normal liver  
23 enzymes.

24 You can see that the sensitivity of AxSYM HCV  
25 assays when we tested these 100 specimens was 100 percent.

1 We also included this information in the calculation for  
2 clinical sensitivity.

3 [Slide.]

4 Let's look at the next category, the category  
5 labeled "Acute HCV Infection." We had a total of 23  
6 specimens from individuals whom we felt could be categorized  
7 as having acute HCV infection. There were two populations  
8 of specimens which we put into this category. In the first  
9 population, a total of eight specimens. These came from Dr.  
10 Thiele's practice in Dallas. The categorization, we can  
11 just run through quickly. They all had a physician's  
12 diagnosis of acute hepatitis; unspecified signs and symptoms  
13 of acute hepatitis; their liver enzymes were greater than  
14 10-fold the upper limits of normal; they were positive for  
15 anti-HCV, but no c100 antigen reactivity on the immunoblot  
16 assay.

17 I should note here that this is a very restrictive  
18 criterion and is based on the assumption that c100  
19 reactivity appears later in many publications than other  
20 markers after infection.

21 These specimens were nonreactive for hepatitis A  
22 and hepatitis B markers, and they had a negative history for  
23 drug or toxin-induced liver disease, no serological evidence  
24 of other viral or bacterial infections and were negative for  
25 other disease states which elevate serum transaminase

1 levels.

2 [Slide.]

3 The second population, a total of 15, came from 15  
4 commercially available HCV panels which demonstrate  
5 seroconversion and therefore show acute hepatitis; elevated  
6 serum transaminase levels which were at least twice the  
7 upper limit of normal were also present and demonstrated in  
8 these panels.

9 If we add the 15 and the 8 together, we get the 23  
10 specimens that we feel we can classify as acute HCV  
11 infection, and the AxSYM HCV assay detected antibody to HCV  
12 in all 23 of these specimens.

13 [Slide.]

14 Let's now turn to chronic HCV infection, where a  
15 total of 30 could be classified in this conservative  
16 categorization of specimens.

17 As we have heard, evidence of chronic HCV  
18 infection--ideally, you would have specimens where you could  
19 demonstrate that at least six months before the study  
20 specimen was collected, an HCV RNA result could be shown.  
21 In fact, as I mentioned, at the time when we did this study,  
22 this was not the general standard of practice, but we can go  
23 to additional evidence, and that is there was HCV antibody-  
24 positive, there was a result greater than six months before  
25 the study specimen was collected, and evidence of HCV

1 activity. In many of these specimens, there were biopsy  
2 results; HCV-associated histopathologic changes were  
3 demonstrated, and there was knowledge that the patient had  
4 been put on interferon therapy at any time during the time  
5 frame that this individual was being studied. In some  
6 cases, we did have an HCV RNA result, but this was one that  
7 we ran either on the same date or later, and not before the  
8 specimen was collected.

9 We used this data to calculate both the  
10 sensitivity overall calculation and the clinical  
11 sensitivity, and again, AxSYM HCV was able to detect  
12 antibody to HCV in all 30 of these samples from patients  
13 with chronic HCV infection.

14 [Slide.]

15 We now get to what is really sort of a sub-  
16 categorization of the specimens that were from individuals  
17 who had actually a physician's diagnosis of chronic  
18 hepatitis C, but there was less information available to be  
19 able to put them in the earlier category I just showed you.

20 There were a total of 26 specimens which could be  
21 classified as HCV infection with chronic hepatitis, but  
22 state not determined. In these specimens, we did have the  
23 HCV antibody result as being positive less than six months  
24 before the study specimen was collected or on the same date,  
25 indicative of HCV infection; and there was histopathologic

1 evidence of chronic hepatitis to be able to say with chronic  
2 hepatitis. There was also additional supporting evidence in  
3 just over 50 percent of the specimens which strengthened the  
4 association with HCV infection but did not establish that  
5 the study specimen was collected during chronic HCV  
6 infection. These included a demonstration that the patient  
7 had been put onto Interferon therapy at any time, and in  
8 some cases, there was an HCV RNA result on the same date  
9 that the study specimen was drawn or at a later date.

10 The sensitivity of the AxSYM HCV assay here,  
11 again is 100 percent; all 26 of these specimens did  
12 demonstrate positivity by the assay for antibodies to HCV.

13 [Slide.]

14 Here is another group of specimens where we had a  
15 little less information. Again, they had been diagnosed as  
16 chronic hepatitis C by a physician, but in this case, we  
17 have to put them in a category that is called "HCV  
18 infection, state not determined." And there were 113  
19 specimens that fell into this category.

20 Here we had the HCV antibody positive result, less  
21 than six months before the study specimen was collected or  
22 the same date, but we had no histopathologic evidence of  
23 chronic hepatitis C at any time, or chronic hepatitis in  
24 fact. This was because either the individuals were not  
25 biopsied at all, and we could not find evidence in the

1 histories of a biopsy, or for others, if a biopsy was run,  
2 there was no evidence of chronic hepatitis.

3 The sensitivity of the assay here again is 100  
4 percent. All 113 of these specimens did demonstrate anti-  
5 HCV activity with the AxSYM assay.

6 [Slide.]

7 The next group of specimens, n equals 10, we have  
8 put into a category that is called "HCV infection (with  
9 hepatitis), state not determined."

10 Here we had HCV antibody positivity, which is  
11 demonstrated, but in this case, it had c100 antigen  
12 reactivity on the immunoblot assay. They have elevated  
13 serum transaminase and signs and symptoms of acute  
14 hepatitis.

15 These are 10 patients of Dr. Thiele's. He does  
16 have additional information on the medical history of these  
17 individuals, and we have been given permission for Dr.  
18 Thiele to come up at the end of my presentation just to  
19 present to you the additional medical findings that he has  
20 on these 10 specimens.

21 The sensitivity again of the AxSYM assay in this  
22 group, all of these specimens did show anti-HCV reactivity  
23 in the AxSYM test.

24 [Slide.]

25 If we put all of this information into one big

1 table, we can call it "Sensitivity based on determination of  
2 HCV antibody positivity," and again, the definition of HCV  
3 antibody positivity or gold standard is positive by an FDA-  
4 licensed EIA and an immunoblot assay.

5           You have already seen this information on  
6 asymptomatic, acute, and chronic HCV infection for these  
7 patients, with all 100 percent sensitivity for the AxSYM  
8 assay. We have grouped together all of those other  
9 categories, some of them with a chronic hepatitis  
10 physician's diagnosis, and also, acute hepatitis, but they  
11 were felt not to have sufficient information to be able to  
12 put them up into these highly characterized buckets.

13           There are 149 of those if you add them all  
14 together. Again, 100 percent sensitivity for the AxSYM  
15 assay.

16           Here, we are looking at the HCV antibody-positive  
17 individuals, AxSYM HCV detected in all of those specimens,  
18 antibody to HCV. These specimens all came from our Memphis  
19 site. And if we look at the hospital patients with  
20 physician's orders for hepatitis testing--again remember  
21 this was for all forms of hepatitis--we found that in this  
22 population--and I believe this was out of California, from  
23 the Stanford lab--they had five specimens which were  
24 identified as being positive for anti-HCV out of the 99, and  
25 that's about a 5 percent prevalence of this particular

1 population, all of which were picked up by the hepatitis as  
2 having antibody to HCV.

3           If we look at the individuals at increased risk  
4 for HCV infection--and just to remind you, this was a group  
5 of 50 hemodialysis patients, 50 hemophiliacs, and 50  
6 injection drug users--we found there was about a 60 percent  
7 prevalence of anti-HCV in this particular population, a  
8 total of 91 specimens positive for anti-HCV and also  
9 positive for anti-HCV in the AxSYM assay.

10           So the total number of positive specimens that we  
11 identified in total in this study was 526 positive samples,  
12 all of which were identified as containing antibody to HCV  
13 by the AxSYM assay.

14           Could I have the next slide, please?

15           [Slide.]

16           As we mentioned before, we used only the  
17 clinically characterized groups of specimens to calculate  
18 clinical sensitivity, and you have seen this information  
19 before, but it's a total of 153 specimens, all of which were  
20 detected by the AxSYM HCV as containing antibody to HCV. So  
21 we estimate the clinical sensitivity of the assay to be 100  
22 percent.

23           [Slide.]

24           If we now look at specificity of the assay--and  
25 this is based on determination of HCV antibody--we used

1 these two categories, which again you have seen before--99  
2 specimens from hospital patients with physicians' orders for  
3 hepatitis testing, and the group of individuals at increased  
4 risk for HCV infection, a total of 150 specimens from there.

5           The specificity of the assay in this group of  
6 specimens was 98.94 percent. There was one patient who  
7 could be considered to have a potentially false positive  
8 AxSYM result. This was an AxSYM positive, but it was EIA-  
9 negative, and it was RIBA-negative. So there is only a  
10 98.94 percent specificity in this group that we tested.

11           In the individuals at increased risk of HCV  
12 infection, you see a lower specificity, and this was due to  
13 the fact that there were six patients which you could call a  
14 potentially false positive AxSYM result. These came  
15 entirely from the dialysis population, and I'd just like to  
16 give you some information on those six patients.

17           Five of those patients in fact showed an AxSYM-  
18 positive, EIA-positive, but a RIBA-indeterminate--four of  
19 them--or negative result. On the indeterminate, we saw  
20 bands for c33 or the c22, and in discussions with Dr. Thiele  
21 last night, he said that he has seen this, and it seems to  
22 be common in renal failure patients. So perhaps in fact  
23 these are not false positive AxSYM results or false positive  
24 EIA results, but it is just that the banding on the RIBA  
25 comes up as indeterminate, maybe due to immunosuppression.

1 That's just a theory that we were considering last night,  
2 and in fact the specificity in this group may be better than  
3 89.47 percent, and in fact, there may have been five  
4 patients who were truly antibody to HCV-positive.

5           Could I have the next one, please?

6           [Slide.]

7           This obviously is an issue, the issue of false  
8 positives, and it has been addressed in various publications  
9 such as the NIH Consensus Statement in 1997, where the  
10 recommendation was to use supplemental testing, as Dr.  
11 Dienstag has mentioned. So in fact in our package insert,  
12 we have put in this recommendation, and I'll read it to you.

13           "It is recommended that reactive specimens be  
14 investigated by an additional, more specific or supplemental  
15 test such as a strip immunoblot assay or nucleic acid  
16 amplification assay for HCV RNA." So that is in our  
17 labeling.

18           [Slide.]

19           Let's look at another way of looking at  
20 specificity--analytical specificity or cross-reactivity.  
21 Here, we had 200 specimens that we obtained from 24  
22 different categories of potentially interfering substances  
23 that were tested for cross-reactivity.

24           In this group of specimens, just for your  
25 information, are specimens from individuals who were

1 obviously co-infected with HCV and HIV and HBV and HCV,  
2 which you would suspect because of the commonality of some  
3 of the high-risk groups between those infections.

4 Out of these 200 specimens, there were in fact 15  
5 specimens that were reactive for antibody to HCV. Thirteen  
6 of these were confirmed by the supplemental assay. Some of  
7 those were in the categories of HIV infection and HBB  
8 infection.

9 There were two specimens, however, that could be  
10 classified perhaps as false positive AxSYM results, and this  
11 was one, which came from an individual with a yeast  
12 infection and one with a chronic HBV infection that we would  
13 consider to be false positives. But in fact I think our  
14 conclusion is that there is no clustering of cross-  
15 reactivity found in a single category of specimens.

16 [Slide.]

17 Looking at detection, very often, as you know, we  
18 use commercially available HCV seroconversion panels, and we  
19 had 15 available to us from three different vendors. These  
20 were characterized as having elevated serum transaminase  
21 levels in all of the panels, and we did have RNA results in  
22 11 of the panels. In the other four panels, there were no  
23 RNA results done, so we assume that they hadn't been tested -  
24 for RNA.

25 The results of the testing of these seroconversion

1 panels, we found that anti-HCV was detected earlier by the  
2 AxSYM assay than the licensed assay in 9 of the 15 panels.  
3 It was detected earlier by the licensed assay in one of the  
4 panels over AxSYM HCV, and in five of the panels, the bleed  
5 that first demonstrated anti-HCV was the same, one that was  
6 detected by both assays.

7 [Slide.]

8 I'll just show you one of these panels which I  
9 know you are familiar with. Here, we have a panel of  
10 specimens, bleeds, that were taken from a single  
11 individuals. The bleed dates are shown in this column. You  
12 can see that bleeds were taken over a 56-day period. As we  
13 heard yesterday, these are usually from plasma donors, and  
14 how they come into existence is up pops an anti-HCV result  
15 as being positive; the companies will go back and look in  
16 their files or the plasma house and pull out the preceding  
17 draws, and we can construct this seroconversion.

18 We don't actually have in this case a bleed that  
19 did not have RNA, so we don't know the actual date of  
20 infection with HCV of this individual, but it is probably  
21 close or a few days or weeks beyond here.

22 We show in this column the ALT result, and you can  
23 see in this individual, fairly low numbers for the normal  
24 values, rising to perhaps two or three times the upper limit  
25 of the normal. We do have seroconversion panels where you

1 see immediately a very high jump in the ALT levels, so it  
2 does seem that the ALT rise is quite variable between  
3 individuals in acute hepatitis.

4 We show the AxSYM HCV assay here as the sample-to-  
5 cutoff value, and below, you can see that anything above  
6 1.21 is considered reactive in the AxSYM assay, and  
7 alongside it, we show the EIA with a sample-to-cutoff where  
8 the cutoff value is considered to be anything above one.

9 We also show two different versions of the  
10 supplemental assay. You can see that with time, the  
11 increase in the sensitivity of these versions going from  
12 indeterminate to positive, and you can see that in all of  
13 the bleeds, there was a measurable amount of HCV RNA by a  
14 research assay. You can also note what we have heard  
15 before, that RNA is the first marker, and there are cases at  
16 the beginning of the infection where you are not able to  
17 detect antibody to HCV.

18 I should also point out that the AxSYM assay did  
19 detect antibody to HCV 24 days earlier than the current EIA  
20 assay.

21 [Slide.]

22 We felt that we had to address this issue of  
23 nonreactive test results, and the above two statements are  
24 included in the proposed AxSYM HCV labeling as limitations  
25 of the assay procedure. It is recognized that presently

1 available methods of antibody to HCV may not detect all  
2 infected individuals. But a nonreactive test result does  
3 not exclude the possibility of exposure to HCV or early  
4 acute infection with HCV, as you saw on the previous slide.

5 [Slide.]

6 We also needed to look at whether the AxSYM HCV  
7 assay could detect HCV antibody in specimens with various  
8 genotypes, and we were able to get 127 specimens which were  
9 well-characterized in terms of their genotyping. Their  
10 geographic origins were from North America, South America,  
11 Africa and Asia, and research genotyping by several  
12 different kinds of methods depending on the source of the  
13 specimens were used to characterize the genotype. And just  
14 to emphasize here, genotyping is looking at the RNA, so you  
15 would expect all of these obviously to be HCV RNA positive.

16 When we tested these specimens on the AxSYM HCV  
17 assay for antibody, you can see that two of them did not  
18 demonstrate antibody to HCV. These were probably specimens  
19 from early acute infection stages. And in fact those two  
20 specimens were also negative for antibody to HCV by the  
21 licensed EIA and the RIBA assay. So we felt that in a  
22 calculation of HCV antibody sensitivity, we could remove  
23 these two from the calculation.

24 [Slide.]

25 So in conclusion, we feel that this data

1 demonstrates that the AxSYM HCV assay has performance at  
2 least equivalent to the licensed HCV EIA. You have heard  
3 from Dr. Stewart that the AxSYM offers enhanced automation  
4 to the diagnostic lab while maintaining sensitivity in  
5 detecting anti-HCV. And the results from the AxSYM HCV  
6 clinical study do support the intended use statement, which  
7 you have heard from a couple of people and I won't repeat  
8 reading it here.

9 At this time, I would like to ask Dr. Thiele to  
10 come up to the podium and just show the additional  
11 information we have on those 10 acute specimens.

12 Dr. Thiele?

13 DR. CHARACHE: Dr. Hojvat, I wonder if we could  
14 limit Dr. Thiele's time of discussion to no more than  
15 perhaps 5 minutes.

16 DR. HOJVAT: It's about 5 minutes.

17 DR. CHARACHE: Good, because we have to permit the  
18 panel to address questions.

19 Thank you very much.

20 Dr. Thiele?

21 DR. THIELE: Let me start by explaining why I am  
22 here today. I am here as a paid consultant for Abbott  
23 Laboratories. My involvement in this assay and the  
24 development was as a physician who supplied serum specimens  
25 to Abbott Laboratories.

1 I think the FDA and the panel have been provided a  
2 copy of a manuscript that actually documents some of the  
3 earlier studies that we were involved in with Abbott  
4 Laboratories, looking really at all patients in our center  
5 who came in with a clinical syndrome that was consistent  
6 with what used to be called "acute non-A/non-B hepatitis."  
7 And actually, academically, I have been more interested in  
8 those who didn't have hepatitis C--those who had the non-  
9 A/non-B/non-C/non-D/non-E.

10 But during a period of time from, as best I can  
11 tell, April 1995 and May of 1996, all of the specimens that  
12 we collected from patients with a syndrome of acute  
13 hepatitis who in the end we thought clinically had acute  
14 hepatitis C were used in the study with this AxSYM system.

15 [Slide.]

16 Many of the earlier studies looking at antibody  
17 reactivity and acute viral hepatitis have collected patients  
18 at various time points in what I would call the time course  
19 of acute hepatitis C. Following infection--and this may not  
20 be the right time point for being able to say that we can  
21 now diagnose viremia--but there is a period of time before  
22 readily detectable levels of virus appear in a person's  
23 serum. In general, as Dr. Dienstag reviewed earlier, there  
24 is a mean interval of around six weeks or so, but it can  
25 vary widely before the first abnormal biochemistry occurs.

1           However, many patients who develop abnormal  
2 biochemistry never develop symptoms and would not come to  
3 clinical consideration unless they were involved in some  
4 prospective study.

5           Where I have been involved with patients who have  
6 been out here as a supervising physician in an outpatient  
7 liver clinic at a busy city/county hospital, Parklawn  
8 Hospital in Dallas, Texas, where we see patients who come in  
9 with signs and symptoms, in general, there is some delay  
10 between the first biochemical abnormality and any symptoms.  
11 The most common symptoms are clearly nonspecific GI  
12 symptoms, usually something in the spectrum of anorexia,  
13 nausea or vomiting, and in patients who develop these  
14 symptoms and also develop jaundice, these symptoms generally  
15 occur before they detect jaundice.

16           In my experience, the one symptom that almost  
17 always causes a patient to consult a physician is when he  
18 turns yellow. Before that, the symptoms are too  
19 nonspecific, and we can be sure that there are many people  
20 with acute hepatitis and icteric who never come to see a  
21 doctor.

22           But I see the patient here, collect a variety of  
23 biochemical tests, historical data, send off tests for serum  
24 diagnostics, and follow the patient. And I think the one  
25 thing that helps to distinguish people with acute viral

1 hepatitis from those with other more chronic syndromes is  
2 the fact that generally, these acute symptoms and jaundice  
3 are fairly self-limited, especially in most patients with  
4 acute hepatitis C. And with hepatitis C, we always follow  
5 these people long-term, because they have a high rate of  
6 chronicity.

7 [Slide.]

8 The 18 specimens that were collected from our  
9 center and were used to assess this AxSYM assay are shown  
10 here. These are the ID numbers--I guess they have been used  
11 in communications between Abbott and the FDA. I have gone  
12 back recently and reviewed the charts on all 18 of these  
13 patients and have listed in this table the symptoms that  
14 were listed by a physician in the chart on each of these  
15 patients. As I mentioned before, very commonly, the only  
16 people who come in are those who are actually icteric,  
17 although in the broader spectrum of acute hepatitis C, it is  
18 only a minority of people who become icteric. Only one of  
19 our patients did not have icterus or other signs of icterus  
20 such as dark urine. Virtually all of them had GI symptoms  
21 and a variety of other complaints.

22 The point here is that, really, all patients had  
23 some combination of symptoms. It was a full-symptom  
24 complex. And I guess the other thing I should say is that  
25 subsequently, the patients were broken up into two groups--

1 those who were anti-c100-positive and those who were anti-  
2 c100-negative. Out here, I have just by hand marked in  
3 those who were c100-positive. I think you can agree with me  
4 that there is no way to distinguish the symptoms between  
5 those who were c100-positive or negative.

6 [Slide.]

7 As Dr. Hojvat mentioned, in collecting patients  
8 with symptomatic acute non-A/non-B hepatitis, we have set a  
9 fairly high threshold for consideration as acute hepatitis.  
10 We have required they have at least 10-fold elevation of  
11 aminotransferase. Certainly, in prospective post-  
12 transfusion studies where you have the luxury of baseline  
13 numbers, you can use much lower cutoffs and pick up many  
14 more patients. And most of our symptomatic patients are  
15 well above a 10-fold cutoff. I think the mean elevation of  
16 ALT was about 30-fold; the mean elevation of AST is about  
17 50-fold. And again, I have darkened in the figures for  
18 those who were anti-c100-positive, these 10 that were broken  
19 out from the group, and they are scattered throughout.  
20 There is not a distinguishable difference in levels, from my  
21 view, from those who were c100-positive and c100-negative.

22 [Slide.]

23 I guess this gets to the crux of the matter. We  
24 don't have an IGM-type test for acute hepatitis C to  
25 distinguish acute from chronic, and early on when the c100

1 test was being developed, and people were working a little  
2 earlier in the time line, using the first abnormal ALT as a  
3 starting point, the concept was that people would be sero-  
4 negative when they first came in and become sero-positive  
5 later. But since the second-generation assays have been  
6 available, as Dr. Dienstag mentioned, we just don't see very  
7 many patients early enough in their course to document that  
8 they are truly sero-negative.

9           One of the things that we have become accustomed  
10 to, because in our studies in which Abbott Laboratories  
11 have been assaying our samples as well as using our hospital  
12 testing, we have been able to look at multiple sets of raw  
13 data on these patients, and in a publication with some of  
14 the non-A through E patients that also includes 74 acute  
15 hepatitis C patients, we looked at whether we could find  
16 rising levels of reactivity in those with acute C, and we  
17 were able to see rising levels of reactivity in acute and  
18 convalescent sera in that study group in about 87 percent of  
19 patients, at levels of changes in reactivity that we saw in  
20 less than 10 percent of chronic C patients who were followed  
21 over similar time intervals.

22           In this subgroup, we didn't have the other  
23 research assays. All we had was the commercially-available  
24 EIA-2 testing. I went through my logbooks, and during this  
25 time interval between early 1995 through about mid-1996 that

1 we were collecting acute C specimens, here we also collected  
2 a number of chronic hepatitis C specimens that were also  
3 sent to Abbott Laboratories for their use but also in which  
4 I wrote down the actual raw OD value, and I have 18 of  
5 those, and they were all 18 that were collected during that  
6 time interval; it just happened to be the same number.

7           The point is that this assay is really an all-or-  
8 nothing assay in most of our chronic C patients. Most of  
9 them max out--they have greater than 2.2 OD. So it's not a  
10 very dynamic assay.

11           In the patients that we had classified clinically  
12 as having a syndrome and the remainder of their clinical  
13 presentation being consistent with acute hepatitis C, we  
14 found a much broader range of initial OD values. Some had  
15 already been maxed out, but most were not. Then, I went  
16 through--we have had a tendency, especially in those who  
17 come in with initial OD values of less than 2 or 1.5, to try  
18 to collect a second test and look at the OD value later, and  
19 as shown here, they generally rise.

20           Now, we don't have adequate convalescent sera on  
21 many of these patients. Some of these intervals--for  
22 instance, this interval here is only about a week, and some  
23 of these others are only seen over a period of about a week--  
24 -I don't have late convalescent titers on these--but again,  
25 if you look at the c100-positives versus the c100-negatives,

1 they really overlap a great deal. And you can see some  
2 c100-positives that you can begin to imagine you are seeing  
3 rising titers of antibodies consistent with our clinical  
4 diagnosis of acute C.

5 And just the final piece of additional clinical  
6 data--

7 DR. CHARACHE: Excuse me. It has been 11 minutes.  
8 I wonder if we could wrap up.

9 DR. THIELE: Okay. This is the last one.

10 [Slide.]

11 I just wanted to point out that we followed these  
12 patients, and when possible, we have had three or four who  
13 have been lost to follow-up, mostly injection drug users who  
14 don't come back, but in general, this is a self-limited  
15 syndrome. With the exception of one unfortunate patient who  
16 went on to die of liver failure, all of them resolved their  
17 signs and symptoms, and the expected number had chronicity.

18 DR. HOJVAT: Thank you, Dr. Thiele. I would also  
19 like to thank the panel and the agency for allowing us to  
20 show this additional information.

21 I should add that the agency had not seen this  
22 information; it was something we put together last night,  
23 basically. And we would like the panel to consider whether  
24 these eight specimens could be transferred from the category  
25 that you saw before back into the acute hepatitis category.

1 Thank you.

2 DR. CHARACHE: Thank you.

3 We would like to now permit the panel to ask for  
4 any clarification or information they'd like on the material  
5 they have heard or other material from the data that we have  
6 received.

7 I would like to perhaps begin with a clarification  
8 question of my own, and that pertains to Overhead 17 of  
9 Sally Hojvat's presentation.

10 DR. HOJVAT: Okay--is 17 the one that has--

11 DR. CHARACHE: The prevalence of anti-HCV.

12 DR. HOJVAT: All right.

13 DR. CHARACHE: I would personally like to commend  
14 the data that we have received classifying the types of  
15 disease into its various categories, which I found very  
16 helpful. And I also found very helpful the ability to show  
17 that when you had defined cases of hepatitis C as shown by  
18 supporting evidence, either clinical, as in this case, or  
19 your previous evidence of the RIBA testing and so on, that  
20 this AxSYM was able to pick it up.

21 One of the problems I have been concerned about  
22 with hepatitis C antibody testing is not whether the  
23 antibody testing is valuable, but rather, the problem of the  
24 false positives. Therefore, I was looking in the data for  
25 that type of information.

1 We heard of two studies today that we didn't have  
2 copies of--your patients whose physicians requested  
3 hepatitis testing, and for patients at high risk of  
4 hepatitis--we did not happen to have that data. This data,  
5 I am pretty sure is the same as in Table 4 of your package  
6 insert, in which there were random hospital patients of  
7 which 60 in prevalence were positive, and there were first-  
8 time blood donors that were 60 and 27 in the other. But  
9 those were the results of the confirmatory tests, where the  
10 AxSYM had 37 false positives, and the AxSYM HCV showed 71  
11 positives in the second group, of which there were 11 false  
12 positives.

13 So overall--and there was one in the last group--  
14 there were only 80 percent true positives, 20 percent false  
15 positives, and that was the only study we had where we could  
16 look at that.

17 DR. HOJVAT: Correct.

18 DR. CHARACHE: Am I correct in that?

19 Dr. HOJVAT: Yes, you are. And I think we feel  
20 that this represents low-risk populations. The other ones  
21 that you mentioned are the more high-risk populations.

22 DR. CHARACHE: But even there, based on the  
23 information you just provided us with, in the dialysis  
24 group, there were six that were not confirmable at this  
25 time.

1 DR. HOJVAT: Correct.

2 DR. CHARACHE: So I think this raises the question  
3 not of whether antibody is important, but how we work with  
4 the test that has high false positives as it will be used.  
5 We can't predict what patients are going to be screened for  
6 hepatitis C. It is physicians now to see whether they are  
7 likely to transmit bloodborne infections and so on. So it  
8 is not only high-risk people who will be tested with this  
9 assay.

10 My question, then, is how do we call to the  
11 attention of the user in the laboratory the fact that it  
12 remains a problem with specificity with this type of test--  
13 or do you agree that there is a problem with specificity?

14 DR. HOJVAT: There is the same kind of, if you  
15 call it problem, with specificity as the existing assays,  
16 but I did give you--and I know it wasn't in your  
17 presentation there--we did calculate the positive predictive  
18 value to indicate that in this case, approximately 80  
19 percent of the positive AxSYM HCV results were confirmed by  
20 the supplemental test, which is an improvement over previous  
21 assays where, in these populations, possibly only 50 percent  
22 would have been confirmed.

23 So there is an increase in the specificity of this  
24 particular assay, but as with all low-prevalence  
25 populations--we see it in all of the blood-banking-type

1 populations--you will get this kind of false reactivity, and  
2 the percentage appears greater because of the low prevalence  
3 in the populations.

4 DR. CHARACHE: This is the only specificity data  
5 that we had to look at--

6 DR. HOJVAT: Correct.

7 DR. CHARACHE: --so perhaps there is additional  
8 information available on specificity.

9 DR. HOJVAT: No. We felt that these numbers were  
10 statistically correct to indicate the level of false  
11 positives that you would see in a low-risk population. I  
12 think we are not denying that. As in most package inserts,  
13 we are putting into the limitations of the procedure the  
14 indication that we recommend a positive result on the AxSYM  
15 HCV--if you could put that pu, Gene. I refer you again to  
16 this--that it is recommended that all reactive specimens be  
17 investigated by an additional, more specific or supplemental  
18 test such as a strip immunoblot.

19 DR. CHARACHE: I could not find that in the  
20 package insert of 12-27, so it may have been added--I just  
21 may have missed it.

22 DR. HOJVAT: No; it was in there.

23 DR. SPECTER: If I could comment on that, I looked  
24 rigorously for it with the help of Dr. Gutman and did  
25 finally find it. My point is simply that it is there, but

1 it is kind of buried, and something to make it more  
2 prominent would easily solve that problem.

3 DR. HOJVAT: Would that be the recommendation,  
4 then, of the panel, to make it more prominent?

5 DR. CHARACHE: We'll come back to that. But I was  
6 obviously concerned because of the impression that if you  
7 had this test positive--that's in the intent and so on--that  
8 it was true.

9 May we have other questions and comments?

10 Dr. Reller?

11 DR. RELLER: The patients that we heard about with  
12 renal failure, some but not all of whom were confirmed with  
13 RIBA--I think there were four that were left over--were  
14 those tested by HCV RNA, or could they be tested? This is  
15 for interest--whether that testing was done, because there  
16 was the suggestion that those with indeterminate RIBA, in  
17 fact, owing to immunosuppression, may have been missing one  
18 of the bands; but if they were immunosuppressed, I would  
19 have thought, given all that we have seen, that those  
20 patients especially might have been HCV RNA-positive if they  
21 had been tested. And I wondered if that were done or if it  
22 could be done.

23 DR. HOJVAT: No, we did not have any information.  
24 Those were specimens that were obtained through a vendor,  
25 and we had no RNA data on those.

1 Dr. RELLER: Because if the hypothesis be true, it  
2 would be kind of interesting that there may be a blind spot  
3 in immunologic reactivity in a set of patients, but those  
4 patients may be--in fact, looking back, it's not a false  
5 positive test but in fact a blind spot that you'd miss on  
6 the RIBA confirmation that the HCV RNA would pick up and  
7 confirm them as being actually true positives with a more  
8 sensitive initial assay.

9 DR. HOJVAT: I understand we do still have those  
10 specimens, so we could run the RNA on that to try to confirm  
11 the hypothesis.

12 DR. RELLER: I'd be very interested in knowing if  
13 it were positive--to be enlightened.

14 DR. HOJVAT: I thought it was an interesting  
15 hypothesis. I know it's not the kind of thing you present  
16 at these panels, but it did seem to be a good explanation  
17 for why, in those particular patients, we did have these  
18 unusual results.

19 DR. CHARACHE: Dr. Thrupp?

20 Dr. THRUPP: I was going to ask the same question  
21 concerning the Table 4 and 17 data. The table in the  
22 package insert does not give the RNA result; it compares it  
23 to the RIBA.

24 DR. HOJVAT: And we did not have RNA results on  
25 those. It was not part of our algorithm at the time we did

1 this study.

2 DR. THRUPP: But it would be very instructive in  
3 terms of the clinical implication of the test to know if any  
4 of those were RNA-positive that were--presumably, there will  
5 not be any false negatives, but that would be interesting to  
6 know.

7 DR. CHARACHE: Dr. Edelstein?

8 DR. EDELSTEIN: Dr. Hojvat, just out of curiosity,  
9 is there any correlation between the sample of the cutoff  
10 ratio and the likelihood that a sample will be falsely  
11 positive--in other words, unconfirmable by immunoblot? Are  
12 those samples with a higher--I can't say OD, but higher  
13 fluorescence--less likely to be those that are falsely  
14 positive?

15 DR. HOJVAT: I don't think so. I think it's  
16 across-the-board, which we often see with these kinds of  
17 tests.

18 DR. EDELSTEIN: Thank you.

19 DR. CHARACHE: Dr. Tuazon?

20 DR. TUAZON: I have two questions. One is just to  
21 follow up on the false positive. Did you also do HCV PCR on  
22 the two false positives, the one with the yeast infection  
23 and the one with the chronic HBV infection?

24 DR. HOJVAT: No, we did not. Again, as I  
25 mentioned, there still are not FDA-licensed assays for HCV

1 RNA. And I know it is a standard practicing using those  
2 assays by physicians, but in fact, they are not standardized  
3 at this point, and we felt that the data could perhaps  
4 muddle the picture, and we did not use it at the time we ran  
5 this clinical study.

6 DR. TUAZON: I think it would still be important  
7 to assess if these are really true false positives.

8 DR. HOJVAT: Right.

9 DR. TUAZON: And the other question I have is did  
10 you encounter the false positivity secondary to the  
11 carryover from total P-3?

12 DR. HOJVAT: Well, I think that is mentioned in  
13 the package insert as one of the limitations and--

14 DR. TUAZON: Right, but you didn't encounter it in  
15 your clinical specimens?

16 DR. HOJVAT: No, no, we did not, no.

17 DR. TUAZON: Okay.

18 DR. HOJVAT: That's part of looking at every assay  
19 that we develop. Because there were so many AxSYM assays  
20 on that instrument, we had to look and see if, run in  
21 combination with other AxSYM assays, is there any crossover,  
22 and in that particular study, there was some indication that  
23 we would potentially get a false positive reaction. Other  
24 studies subsequently have not backed that up, but we felt we  
25 needed to put it into the package insert.

1 DR. CHARACHE: Dr. Nolte?

2 DR. NOLTE: I have a basic question about the two  
3 assays, the reference assay and the new assay. The antigen  
4 mix in the EIA-II and the AxSYM is identical?

5 DR. HOJVAT: Yes.

6 DR. NOLTE: So this would be considered a second-  
7 generation EIA.

8 DR. HOJVAT: Correct.

9 DR. NOLTE: And the confirmatory test was a  
10 second-generation RIBA, and there is a match there between  
11 the antigens and the two assays.

12 DR. HOJVAT: It is slightly different because the  
13 RIBA assay matches more of the Ortho assay. They are  
14 slightly different, I understand, so there is a difference--  
15 and perhaps that's good, because you're using a separate set  
16 of antigens to confirm.

17 DR. NOLTE: And forgive me if this data was in the  
18 submission. Because I was a guest, I don't have the  
19 opportunity to review that. But is there a difference in  
20 the false positive rate between the EIA-II and the AxSYM  
21 assay, and if it is, what are those differences?

22 DR. HOJVAT: Do we have those numbers available?  
23 I believe they were fairly comparable, although as I  
24 indicated, we did get better positive predictive value than  
25 is seen in general. But in this particular study, I need to

1 get that information for you.

2 DR. NOLTE: That's what I wasn't clear about, in  
3 terms of your saying "better positive predictive value"--in  
4 comparison to what--the EIA-II or earlier generations of  
5 assays?

6 [Pause.]

7 DR. HOJVAT: Can I get back to you a little bit  
8 later when we have the information? We do have it.

9 DR. NOLTE: Sure. And one different question. In  
10 terms of Overhead 34, the genotype panel, the two misses, if  
11 you will, by AxSYM, you offered up an explanation that  
12 perhaps these were patients that were early in their disease  
13 process and perhaps hadn't made antibody yet. An alternate  
14 explanation might be that that does have some issues in  
15 terms of detecting different genotypes, or antibody  
16 responses in patients that are infected with different  
17 genotypes. Is there any more information--

18 DR. HOJVAT: I have not seen--perhaps someone else  
19 knows of publications--but at the moment, it is felt that  
20 the current EIA assays do pick up antibody in all of the  
21 genotypes, and we felt in this case, because it was EIA-  
22 negative and RIBA-negative, that was my explanation. AxSYM  
23 was negative also because there was no antibody present in  
24 that particular specimen.

25 DR. NOLTE: But clearly an alternate explanation

1 might be--I mean, is there any more information about the  
2 clinical state of the patient from which the genotype--

3 DR. HOJVAT: No, there was not. It took us quite  
4 a while to source these specimens, in fact, and they came  
5 from several research labs throughout the United States and  
6 NIH, and they obviously had no medical histories; they had  
7 just received the specimens and then had done their research  
8 genotyping on them. So unfortunately, we don't have any  
9 medical information on that.

10 DR. CHARACHE: Dr. Thrupp?

11 DR. THRUPP: That still remains, clinically, in a  
12 broad sense, a very important point, however, because  
13 granted, the majority of the genotypes in the U.S. are one,  
14 but around the world, there are lots of 2's and 5's, et  
15 cetera, and the denominator for these data was 127, so there  
16 is almost 2 percent that could be a false negative.

17 DR. HOJVAT: I would like to answer that, and  
18 maybe it's not in fact, but as you saw, this assay has been  
19 available in the rest of the world for five years now, and  
20 we have had no reports, and there have been no publications  
21 of the possibility of missing antibody in a particular  
22 genotype. So it is rhetorical, but that's the only  
23 information I can tell you at this point. It is being used  
24 throughout the world where presumably, there are different  
25 subtypes of HCV being more predominant than those found in

1 the United States.

2 DR. CHARACHE: Dr. Seeff?

3 DR. SEEFF: I must say in general that I find this  
4 data very impressive. I have a couple of questions which  
5 are really for my edification rather than in helping make  
6 the decision.

7 One goes back to this prevalence data that you  
8 have given us in first-time volunteer blood donors. This  
9 2.4 percent is confirmed?

10 DR. HOJVAT: Yes.

11 DR. SEEFF: That's confirmed. Are these paid  
12 volunteer donors?

13 DR. HOJVAT: No. These are first-time volunteer  
14 blood donors from regular blood banks.

15 DR. SEEFF: My understanding is that 2.4 percent  
16 generally is much higher than one would get in the average  
17 Red Cross or blood bank, and I wonder what that population  
18 was. If you compare it to the NHANES data, I'm not quite  
19 sure they are the same group. These are volunteer blood  
20 donors, and presumably have already been prescreened by  
21 answering all the questions. And how you came up with 2.4  
22 percent is somewhat of a surprise to me.

23 DR. HOJVAT: Well, you know we can't throw data  
24 out.

25 DR. SEEFF: No--I understand that.

1 DR. HOJVAT: So I can give you the names of the  
2 institutions. You have them there--

3 DR. SEEFF: I know there is an explanation, but  
4 it's somewhat of a surprise to me.

5 DR. HOJVAT: One thing we were looking at, and  
6 maybe Miriam can help us with this, is they were West Coast  
7 and Southern populations--any difference there?

8 DR. CHARACHE: Dr. Alter, I didn't call on you  
9 because we weren't allowed to, so I'm hoping that you'll  
10 address this later.

11 DR. ALTER: If I don't, remind me.

12 DR. CHARACHE: I will.

13 DR. THRUPP: The footnote on that population, if  
14 my old eyes can read the little footnote key there, says  
15 "individuals from nonintended use populations." What does  
16 that mean?

17 DR. HOJVAT: Nonintended use is what we will be  
18 putting in our package insert, and that's the statement that  
19 this is not to be used for screening blood donors.

20 DR. THRUPP: Okay.

21 DR. CHARACHE: Dr. Seeff?

22 DR. SEEFF: There is one more item of interest to  
23 me, and perhaps again there is no answer to this. This was  
24 the seroconversion panel. I was interested to see that  
25 these people have fairly high levels of virus, at least

1 initially--they seemed to drop down when the antibody became  
2 positive--and yet were negative by RIBA-II and positive by  
3 RIBA-III.

4 DR. HOJVAT: Yes. We looked into that, and I  
5 guess I can't make comment on the sensitivity of a licensed  
6 test, but perhaps there is something that--

7 DR. SEEFF: It's just somewhat of a surprise. I  
8 would have expected the ELISA-II, the RIBA-II, to be part of  
9 it, but I guess it isn't, and it's interesting that--I  
10 didn't realize that RIBA-III was that much more sensitive.  
11 And why should it be negative when everything else was  
12 positive, with a quite high titer in the virus. It's just a  
13 surprise to me; I guess it's not--

14 DR. HOJVAT: No.

15 DR. CHARACHE: Just one other question similar to  
16 the one about the high prevalence in those particular blood  
17 donors. There were 150 patients at high risk for HIV  
18 infection tested, and 99 physician orders. How many  
19 institutions were those studies done in?

20 DR. HOJVAT: That was just done at Stanford.

21 DR. CHARACHE: So both of these were done in a  
22 single location?

23 DR. HOJVAT: No. The physicians' orders were at  
24 the Stanford Medical Center, and the other population--I'm  
25 sorry--the interfering substances?7

1 DR. CHARACHE: No. That was the high-risk  
2 patients.

3 DR. HOJVAT: Yes, the high-risk. As I said,  
4 those, we obtained from three different vendors, so  
5 presumably, they were from many different sources.

6 DR. CHARACHE: Plus they did it in a single  
7 location.

8 DR. HOJVAT: They were tested in a single  
9 location; correct.

10 DR. CHARACHE: I think--and this may be my bias--  
11 but I think it is helpful when such studies are done in more  
12 than one so they represent how the ordinary world would use  
13 such an assay, because I think many people use three  
14 institutions or so.

15 Dr. Specter?

16 DR. SPECTER: I'd just like to follow up on  
17 something that was said earlier and something that you  
18 invoked, and that is this idea that there may be something  
19 special about the hemodialysis patient population because of  
20 renal failure was suggested in a statement made part of the  
21 presentation. You recently invoked the fact that this test  
22 is used internationally, and there have been millions of  
23 tests done. Is there any evidence, or has anything come up  
24 in this foreign use to show that in fact you are seeing  
25 something special in a hemodialysis patient population?

1 DR. HOJVAT: Not that I have heard of, and perhaps  
2 I shouldn't have brought this into the picture after all.  
3 It was just really a discussion with Dr. Thiele and Dr.  
4 Dienstag yesterday evening. So perhaps if you want them  
5 later on to address some of those thoughts, we could do  
6 that.

7 DR. CHARACHE: We've gone about 10 minutes over,  
8 so I'd like to thank the sponsor very much for the  
9 presentation.

10 We will take a 10-minute break and reconvene at 20  
11 after 10.

12 [Break.]

13 DR. CHARACHE: We'd like to continue now.

14 The next item on the agenda is the FDA  
15 presentation and panel discussant Miriam Alter. Dr. Alter  
16 also had a contribution to make on one of our earlier  
17 discussions on renal dialysis patients, and we have asked  
18 her to expand on that at this time if she can.

19 I beg your pardon. First, Dr. Seeff had a point  
20 to make.

21 DR. SEEFF: I just want to mention that during the  
22 break, staff came to me to point out that something happened  
23 during Dr. Dienstag's presentation that may represent a  
24 problem, and I just wanted for the record to indicate that  
25 it shouldn't be seen as that say, and that is that he

1 referred to the fact that I gave him the slide on the  
2 elephant, and maybe he perceived that I helped him with his  
3 presentation.

4 This is an old slide that I gave him three years  
5 ago--

6 MS. ALTER: I have one, too.

7 [Laughter.]

8 DR. SEEFF: --and I didn't even know he was going  
9 to be here, frankly, so for the record, I had no involvement  
10 whatsoever with Dr. Dienstag and making this particular  
11 presentation, and I hope he continues to use the elephant  
12 for a long time to come.

13 DR. CHARACHE: Dr. Seeff, do you have some other  
14 copies?

15 [Laughter.]

16 DR. CHARACHE: Dr. Alter?

17 DR. ALTER: Thank you.

18 What I would like to do in terms of my comments on  
19 the dialysis patients and a few other issues that came up  
20 during the discussion is include them in my presentation,  
21 and if I forget, then remind me after I'm done.

22 You will see as I go through my slides that in  
23 fact there is quite a bit of redundancy with several other  
24 speakers, so I will try to move past those without feeling  
25 the need to repeat myself, although that is sometimes

1 difficult.

2           What I would like to do today is provide a  
3 perspective on the use of the anti-HCV enzyme immunoassay as  
4 a diagnostic assay in the real world, not specifically  
5 addressing this particular assay but the available assays  
6 that are currently in use.

7           [Slide.]

8           I know that some of the speakers have covered the  
9 clinical features of HCV infection, but I thought it would  
10 be useful to just point out a few features that were not  
11 mentioned, one of which is the average incubation period,  
12 which is about 6 to 7 weeks, with a range as short as 14  
13 days, which we have observed in some individuals after  
14 needle-stick incidents, to as long as about 26 weeks.

15           Acute illness can be extremely mild and often goes  
16 unrecognized, with less than 20 percent of patients coming  
17 to medical attention who have newly-acquired infection.  
18 Persistent infection, however, develops in 75 to 85 percent,  
19 and chronic hepatitis in 70 percent, most of whom are  
20 asymptomatic, which presents some areas of unique issues in  
21 terms of the diagnostic assay in asymptomatic individuals,  
22 and as we know, no protective antibody response has been  
23 identified.

24           In the United States, actually, the highest  
25 incidence of HCV infection in this century probably occurred

1 in the seventies and eighties, with the peak in the  
2 eighties, averaging about 240,000 infections annually. The  
3 incidence has declined dramatically by more than 80 percent  
4 to 36,000 newly-acquired infections primarily as a result of  
5 the decrease in cases among injecting drug users.

6 Deaths from acute liver failure are rare, but as  
7 shown by Dr. Dienstag, 1.8 percent of the general population  
8 is shown to be anti-HCV positive as determined by both EIA  
9 and supplemental testing corresponding to 3.9 million  
10 Americans who have been infected with HCV. This is based on  
11 the Third National Health and Nutrition Examination Survey  
12 which was conducted during 1998 to 1994 and is a  
13 representative sample of civilian, noninstitutionalized  
14 population, which means this is likely an underestimate  
15 since it excludes institutionalized individuals,  
16 particularly incarcerated individuals, of which a large  
17 proportion are drug users, and therefore, a large proportion  
18 of those will be positive, as well as homeless populations,  
19 a large proportion of whom may be positive.

20 Of this 3.9 million, about three-quarters, or 2.7  
21 million, were determined to be viremic on the basis of a  
22 single sample, and HCV corresponding to almost 3 million  
23 Americans with chronic HCV infection.

24 HCV-related chronic liver disease accounts for  
25 about 40 to 60 percent of all the chronic liver disease in

1 the U.S., the tenth-leading cause of death, and deaths from  
2 chronic disease per year related to HCV are about 8,000 to  
3 10,000.

4 [Slide.]

5 I should mention that since the majority of  
6 infections are in adults between the ages of 30 and 50, it  
7 is possible that even if only a small proportion of those  
8 progress to the more severe consequences that as this cohort  
9 ages, we expect to see an increase in morbidity and  
10 mortality from HCV-related chronic disease in the next 10 to  
11 20 years.

12 HCV is most efficiently transmitted by direct or  
13 repeated percutaneous exposures to blood, such as through  
14 injecting drug use, receipt of clotting factors before viral  
15 inactivation, and transfusions and transplants from infected  
16 donors.

17 Unsafe therapeutic procedures involving  
18 percutaneous exposures have also been shown to be associated  
19 with infection, as encountered by hemodialysis patients, and  
20 health care workers experiencing needle sticks are at risk  
21 of acquiring infection at an average of about 2 percent.

22 Transmission also occurs by perinatal exposure at  
23 a rate of about 6 percent and through high-risk sexual  
24 activity, that is, exposure to an infected sexual partner,  
25 although the efficiency of transmission in this setting is

1 quite low.

2 [Slide.]

3 Why do we test? Well, as with other assays, we  
4 test to make a clinical diagnosis of acute or chronic  
5 disease, but in fact, people who actually come to clinical  
6 attention because they feel ill are the minority of the 3  
7 million-plus individuals infected, and in fact we test  
8 mostly asymptomatic individuals to identify ongoing  
9 infection or chronic disease for the purposes of providing  
10 medical management and possible therapy, as well as  
11 counseling to prevent further harm to the liver and to  
12 prevent transmission to others, and as a matter of fact, in  
13 1998, CDC published an MMWR based on a consultants' meeting  
14 containing recommendations for the prevention and control of  
15 HCV infection and HCV-related chronic disease, which  
16 contains recommendations for identifying, counseling and  
17 testing individuals at risk for HCV infection.

18 [Slide.]

19 There is only one serologic marker for HCV  
20 infection, and that is antibody. It is detected in new  
21 chronic and resolved infections by enzyme immunoassay, with  
22 a supplemental assay needed to determine specificity.

23 [Slide.]

24 There are performance issues with respect to any  
25 screening assay, and with anti-HCV, there is delayed

1 seroconversion during the acute phase. This is true of all  
2 anti-HCV assays. In the early incubation period, there is  
3 about an average of an eight- to nine-week window period  
4 during which anti-HCV is not detectable. For example, one  
5 of the benefits of the third-version assay that was approved  
6 for screening of donors is that it detects infection  
7 somewhat earlier than do the second-version assays, meaning  
8 that even though they may not be RIBA-confirmed, it prevents  
9 the donation from being transfused and therefore prevents  
10 transmission of infection, because as the individual is  
11 seroconverting, EIA repeat reactivity comes first, even  
12 though it will be RIBA-negative, then the individual becomes  
13 RIBA-indeterminate, and finally, RIBA-positive.

14           There also can be a prolonged delay in  
15 seroconversion in a very small minority of patients;  
16 individuals who are HCV RNA-positive but do not seroconvert  
17 until six to nine months or longer after exposure. And then  
18 there is what is called the "immuno-silent" infection, also  
19 a very small minority. Sometimes immunosuppressed patients  
20 have this pattern in which they never seroconvert to anti-  
21 HCV but are persistently HCV RNA-positive. We have observed  
22 this in our cohort studies in a small percentage of patients  
23 who are not immunosuppressed, so it indicates a sensitivity  
24 that is below 100 percent.

25           And in fact dialysis patients are well-described

1 in the literature as reacting less well to the approved  
2 enzyme immunoassays than do other patients, and in the  
3 studies that have been done among anti-HCV-negative chronic  
4 hemodialysis, a median of about 3 percent of these patients  
5 will be HCV RNA-positive.

6 The other issue with respect to performance of the  
7 EIA is the false positivity assay, which varies somewhat  
8 between populations and between versions of assays, but in  
9 general ranges between 30 or 20 to 50 percent in low-  
10 prevalent populations, those with a prevalence of less than  
11 10 percent.

12 [Slide.]

13 In terms of the diagnosis of clinical disease, I'm  
14 going to spend very little time since you have already seen  
15 this with Dr. Dienstag. I just want to point out that even  
16 though this says "typical," I don't know if there is  
17 anything typical about people with hepatitis C, except that  
18 there are a lot of them, and that most individuals are  
19 asymptomatic, and we rarely see individuals with acute--or,  
20 the clinician rarely sees--individuals with acute HCV  
21 infection. At CDC, we go out and beat the bushes for them,  
22 so we see them, but they don't come to medical attention  
23 very often.

24 [Slide.]

25 As also pointed out, the large majority of these

1 patients progress to chronic infection, and what I want to  
2 point out from this slide is two features, one of which is  
3 extremely characteristic of this population, and that is  
4 their fluctuating pattern of ALT activity, in that not only  
5 does it tend to go up and down, but it will often return to  
6 normal in between periods of abnormal activity, and  
7 therefore, a single determination on any patient in terms of  
8 either their liver disease or in fact their viremia is  
9 insufficient to make a diagnosis if in fact it is normal.  
10 And we observe in a small percentage of patients  
11 intermittent viremia, which actually can persist for  
12 prolonged periods of time before viremia is again  
13 detectable.

14 [Slide.]

15 In terms of the performance in asymptomatic  
16 individuals, similar to what I reviewed yesterday, the  
17 probability that a person with a positive test is a true  
18 positive varies depending on the prevalence of infection in  
19 the population being screened, and false positives occur  
20 even with the best tests.

21 [Slide.]

22 So let's look at two populations. Given that the  
23 sensitivity of anti-HCV assays is 95 percent or greater, and  
24 the specificity is about 99 percent, and it really probably  
25 wouldn't matter much if I increase that sensitivity to 99

1 percent--let's take a population of 1,000 people in whom the  
2 prevalence is about 10 percent. This might be a dialysis  
3 population, it might be a population of individuals  
4 transfused prior to donor screening, and out of that 1,000  
5 individuals, 100 would be truly positive, would be truly  
6 infected with HCV or truly positive for anti-HCV, and 95 of  
7 these would be detected by the test. But the test would  
8 also detect nine individuals as being positive on the enzyme  
9 immunoassay who actually were not infected and had never  
10 been infected, so that the positive predictive value, the  
11 ability of the positive test to predict a true positive is  
12 91 percent, which is very good.

13           If we take a prevalence of 1 percent, which  
14 applies to a great many individuals who are being tested  
15 these days, we find that only 10 out of every 1,000  
16 individuals would have been truly infected with HCV. The  
17 test might detect all 10 of them, but it would also call 10  
18 people positive who were not positive, and the positive  
19 predictive value would actually be 50 percent.

20           [Slide.]

21           So that it is important to not only look at the  
22 prevalence of HCV infection in the various groups that are  
23 being tested but also the frequency with which these groups  
24 occur in the population, not only in terms of the  
25 performance of the test but also when making recommendations

1 for testing.

2           So that the CDC and its consultants recommended  
3 that individuals at the highest risk be routinely tested for  
4 HCV infection, and these include persons with hemophilia who  
5 were treated with clotting factor concentrates prior to  
6 widely implemented effective inactivation procedures,  
7 individuals who have ever injected drugs even once or twice  
8 a long time ago, chronic hemodialysis patients, as well as  
9 individuals with liver disease and persons at risk of  
10 transfusion-transmitted HCV.

11           You'll note that as the prevalence goes down in  
12 individuals, even though they might be at some risk of  
13 infection, such as STD populations and health care workers,  
14 the prevalence of the group in the population--people with  
15 the characteristic--increases, which means that if you have  
16 a prevalence of only one or two percent like you do for  
17 health care workers, but you want to screen all health care  
18 workers, you are screening almost 10 percent of the  
19 population when only one percent of that group is expected  
20 to be positive.

21           So this has to be taken into account when making  
22 recommendations, and it will also affect the performance of  
23 the assay.

24           [Slide.]

25           So that on a scale of one to 10, if you want to

1 look at the false positivity rate in that way, look at a  
2 variety of populations which have been tested to some  
3 extent, and we find that the false positivity rate  
4 increases, obviously, as the prevalence of infection  
5 decreases. So if we look to the right, where we have  
6 patients with non-A/non-B hepatitis, most of whom are  
7 hepatitis C, or individuals with ALT abnormalities with no  
8 other etiology, then most of them are infected with HCV, and  
9 the test is virtually always accurate--I'd say it's 100  
10 percent accurate, but is anything 100 percent?

11 The performance of the test in injecting drug  
12 users is similar. They have very high prevalence rates of  
13 infection, and EIA is rarely a false positive.

14 In the dialysis population as well as actually in  
15 transfused patients with an average prevalence in the United  
16 States of about 10 percent, we see a false positivity rate  
17 of about 15 percent with all of the approved or assays in  
18 use, in addition to the fact that it is an immunosuppressed  
19 population and they respond less well to these anti-HCV  
20 assays than do immunocompetent individuals. This has been  
21 well-described in the literature throughout the world.

22 So that individuals who test positive on this test may have  
23 an indeterminate RIBA, or they may test negative at a higher  
24 rate than other populations even though they are HCV RNA  
25 positive.

1           Then, finally, we have unselected populations of  
2 health care workers, active or retired military, excluding  
3 VA populations, clients in STD clinics, unselected pregnant  
4 women who have a prevalence of 5 percent or less and in whom  
5 the false positivity rate can be as high as 50 percent--in  
6 some studies, it is 30 percent, in others it is 20 percent,  
7 it could be 40 percent, but still, out of every 100 you  
8 test, you would be telling 20 or 50 of those people a result  
9 that is false if in fact it hadn't been tested with a more  
10 specific test.

11           The answer to the problem of false positivity is  
12 often the use of HCV RNA by RT-PCR, particularly in the  
13 clinical setting, and that is fine when you have a variety  
14 of tests at your disposal to evaluate the patient.

15           However, HCV RNA can be negative even in people  
16 who are truly infected. Individuals may resolve their  
17 infection at a rate of 15 to 25 percent. There is  
18 intermittent viremia, and then there are low levels of virus  
19 that are below the sensitivity of most of the assays that  
20 are used in commercial laboratories. And there is also a  
21 sample-handling issue that I think most physicians--not  
22 hepatologists, obviously, but most other physicians--might  
23 be unaware of--not to mention it is not FDA-approved, and so  
24 there are issues in terms of standardization, et cetera.  
25 But in clinical practice, PCR for HCV RNA is commonly used,

1 and we need to recognize that fact, but we also need to  
2 recognize its limitations in its use as a diagnostic in the  
3 broader sense.

4 [Slide.]

5 Because of that, we published a testing algorithm  
6 for use in the real world--not by the hepatologists, like  
7 Dr. Seeff and Dr. Dienstag, who have a great deal of  
8 experience in evaluating patients and a lot of information  
9 to bring to their decisionmaking about the patients, but in  
10 fact there is an increasing number of persons being tested.  
11 A lot of nongovernmental organizations and private industry  
12 are encouraging testing of a lot of individuals, some of  
13 whom don't really fall into truly high-risk groups, and  
14 because of the sheer numbers of HCV-infected people in the  
15 United States, hepatologists can't see everybody. A lot of  
16 these patients are going to be evaluated by primary care  
17 physicians and other specialties who are not familiar with  
18 the use and application of these assays. And in fact, I  
19 understand waiting lists these days are six months or longer  
20 if you are a newly-identified patient.

21 So that it is important that there be some  
22 standardized way to evaluate individuals for HCV infection  
23 that isn't dependent entirely upon a large battery of tests  
24 by someone who is very experienced in this field. So that  
25 this algorithm was intended to take into account not only

1 that not all physicians are experts in this area but also  
2 the fact that a lot of testing is taking place outside the  
3 clinical setting, and when CDC gets its budget for hepatitis  
4 C, hopefully in my lifetime, we will be funding public  
5 sector counseling and testing programs, which will take  
6 place in health departments where State and county health  
7 department laboratories I imagine will be doing a lot of  
8 this testing, and there will be no clinical information to  
9 evaluate these individuals because most of them will be  
10 otherwise healthy. An ALT will be available, et cetera. So  
11 there has got to be some way to report back to that patient  
12 an accurate test result.

13           So we are recommending that after an EIA for anti-  
14 HCV be done--if it is negative, obviously, you don't do  
15 anything--and if it is repeatedly reactive or positive, you  
16 can choose to do either a RIBA or supplemental assay for  
17 anti-HCV such as RIBA, or RT-PCR for HCV RNA if that's what  
18 you want to do. And if it is positive, then you go on and  
19 do medical evaluation, et cetera, or refer the patient, or  
20 in consultation with and work the patient up for chronic  
21 liver disease. And if it is RIBA-negative, then we presume  
22 it is a false positive.

23           But if the HCV RNA is negative, you can't stop.  
24 You still then have to determine whether that antibody was  
25 real or not, and the only way to do that, actually, in

1 general is by using a supplemental antibody testing, because  
2 you still don't know--maybe that patient had previous  
3 infection--something the patient might want to know--or  
4 maybe the patient has intermittent viremia, and that  
5 antibody is real, and you want to bring the patient back and  
6 retest him, or you want to go further and do ALTs or  
7 whatever. So we have to take that into consideration when  
8 implementing testing for anti-HCV in the clinical setting.

9 [Slide.]

10 So based on recommendations that we have been  
11 trying to implement as well as educate about, testing for  
12 HCV infection is performed in many settings and many of  
13 these do not provide clinical services, and therefore don't  
14 have access to a large amount of information that helps them  
15 assess an enzyme immunoassay.

16 Therefore, repeatedly reactive EIA results should  
17 be, quote, "confirmed," with a more specific test before  
18 results are reported to the patient. And if RT-PCR is used,  
19 and the HCV RNA is negative, then supplemental antibody  
20 testing should be done.

21 A good example of this is anti-HIV in the sense  
22 that I don't know how it happened, but in practice, no  
23 matter where anti-HIV testing is done, the result isn't  
24 reported out if it is repeatedly reactive without a Western  
25 blot or other confirmatory test being done. It doesn't

1 matter whether it is a clinical setting or not, in general.

2           And I would like to encourage the panel as well as  
3 FDA to promote that same type of practice with respect to  
4 anti-HCV testing. I think it is extremely important because  
5 we can educate and educate and educate and put  
6 recommendations out there. We must have sent out 500,000  
7 copies of audiotapes, videotapes, the MMWR, little pocket-  
8 size algorithms and a variety of other materials to try to  
9 educate physicians about the appropriate use of these tests,  
10 and I can tell you I don't even think we've put a thumb in  
11 the dike.

12           So to clarify a possible misconception from  
13 yesterday about my opinion regarding making recommendations  
14 for use, it isn't that I didn't think we should make  
15 recommendations for use; it is that I think we need to do  
16 something more than that. I think that in order to make  
17 something happen, recommendations aren't enough; that there  
18 has to be a standard for carrying out these test results  
19 such that the patient does not suffer from reporting of  
20 false positive results.

21           I also want to bring up one other issue. One of  
22 the reasons that I think supplemental testing is not  
23 routinely used in addition to the fact that there are many  
24 people who don't understand the issues is the cost. The  
25 supplemental assays are very expensive. And I can't really

1 comment further on that other than that they are very  
2 expensive, and like in the public health setting, they can't  
3 afford to purchase these tests, or that is an issue.

4 We are currently investigating other ways of  
5 supplementing these results with a more specific evaluation,  
6 one of which, of course, is to evaluate the use of a signal-  
7 to-cutoff ratio. The American Red Cross has data showing  
8 that only about 5 percent of volunteer donors with a sample-  
9 to-cutoff ratio of 3.8 or greater are false positives--that  
10 is, they don't test positive by RIBA. So that in the public  
11 health setting, for example, that might be something  
12 reasonable to consider, but those are the types of things  
13 that we need to look at. We should not just be reporting  
14 out results to patients without a reasonable assurance that  
15 they represent a true result.

16 Thank you.

17 DR. CHARACHE: Thank you, Dr. Alter.

18 Are there any questions at this time?

19 Dr. Tuazon?

20 DR. TUAZON: Can we go back to the slide before,  
21 the second-to-the-last slide--the algorithm.

22 DR. ALTER: Yes. It will just take him a second  
23 to pull it up.

24 DR. TUAZON: Is there a scenario where you would  
25 have a negative EIA, a negative RIBA, and you'd have to do

1 the PCR?

2 DR. ALTER: No, no. If it's negative by EIA, you  
3 just stop. That's at the top, to the right. If it is  
4 positive by EIA, meaning it is repeat reactive, because  
5 that's the way the tests are all labeled to be done--if it  
6 is initially reactive, you have to repeat it in duplicate,  
7 so that's the way the test is done--then, you need to  
8 evaluate that with a more specific test. So we are  
9 recognizing that in the clinical setting, where you have a  
10 lot of information, that if someone comes to Dr. Seeff with  
11 an unconfirmed, let's say, anti-HCV test result, or let's  
12 say with an elevated ALT based on insurance physical, he is  
13 going to get anti-HCV, but he is going to order HCV RNA.  
14 He's not going to get RIBA, because the person has an  
15 elevated ALT, and he is going to evaluate them. They are in  
16 his office. He is a specialist. Okay. So he is going to  
17 evaluate them, and he is going to understand when it gets  
18 the results what they are and what to do about them and what  
19 else he needs to do.

20 On the other hand, if some individual is at his  
21 family practitioner for hypertension, and the family  
22 practitioner takes our recommendations to heart and decides  
23 to screen this person, but the person maybe falls into a  
24 sort of iffy risk group kind of thing, sort of borderline,  
25 and they get an anti-HCV, and they just use the EIA, it may

1 or may not represent a true positive without any other  
2 information.

3 Or, many health departments now, even without  
4 funds from the Feds, are setting up counseling and testing  
5 programs, and you get a lot of the "worried well" who come  
6 in there. The laboratory doesn't know, and even people who  
7 are evaluating these individuals don't know truly, who is a,  
8 quote, "high-risk" and "low-risk" person. So I don't think  
9 you can have algorithms that distinguish high-risk from low-  
10 risk. I think the laboratory shouldn't have to make that  
11 decision. I think the laboratory has to promote a standard  
12 for providing the results.

13 DR. TUAZON: But there is the scenario where you  
14 would have a negative EIA and negative RIBA, such as in the  
15 setting of seroconversion, that your HCV PCR will be the one  
16 that is positive.

17 DR. ALTER: Yes, but unless you have an individual  
18 with--in the real world, these donors from whom these  
19 seroconversion panels come are not even going to be seen at  
20 that point--

21 DR. TUAZON: Would be extremely rare.

22 DR. ALTER: --and so if you have someone, let's  
23 say, with hepatitis who comes to see you, and their EIA is  
24 negative, but they have hepatitis, and maybe you didn't get  
25 an RNA, and you still can't find an etiology, you are going

ah

1 to want to repeat the test or get an RNA, because they might  
2 be in the early incubation period.

3 But this was actually not in the context of acute  
4 disease, really.

5 DR. CHARACHE: Thank you, Dr. Alter.

6 Dr. Ticehurst?

7 DR. TICEHURST: Good morning. I'd like to start  
8 by attempting to address a question that Dr. Dienstag  
9 brought up. He asked if it was appropriate at this point in  
10 time to prove the clinical utility of anti-HCV assays, and I  
11 think the issue before the panel today is not to do that--it  
12 is to evaluate the safety and effectiveness of this  
13 particular assay, which is usually the case with most of the  
14 new assays we bring before you.

15 In the brief comments I'm going to make, I want to  
16 point out that there is at least one characteristic of this  
17 assay that is significantly different from those that are  
18 already on the market, and this directly follows from some  
19 of the comments that Dr. Alter just mentioned which, if I  
20 was listening carefully, I think she prefaced by saying her  
21 comments pertained to those assays that were already on the  
22 market.

23 I also have to mention the conflict of interest  
24 that I have with Dr. Dienstag's talk. I was actually at the  
25 original Woodstock Music and Art Fair in August of 1969, and

1 it wasn't "groovy"--it was "far out." And as to some of the  
2 other effects there, I had to leave it early, because our  
3 car was stuck in the mud, we had to get a farmer to pull it  
4 out, and I had to get back to a hospital lab job.

5 DR. SEEFF: You didn't inhale.

6 [Laughter.]

7 DR. TICEHURST: So what I'd like to do here is  
8 refer to a couple of considerations that pertain to this  
9 submission.

10 [Slide.]

11 These two concepts are discussed in detail in a--  
12 this is Government-ese here--in a CDRH for comment draft  
13 guidance document which is available at these two web sites,  
14 and I'll read them out: [www.fda.gov/cdrh/ode/1353.html](http://www.fda.gov/cdrh/ode/1353.html) for  
15 the hyper text version, and .pdf for the portable document  
16 format version.

17 The comment period is now over--I think it ended  
18 on January 6th--but we will be collating comments and  
19 presumably re-editing this document with a goal of  
20 eventually providing advice and recommendations to  
21 manufacturers and people in the field, including reviewers  
22 at FDA, on how to look at different HCV assays. But I am  
23 particularly referring here to concepts in this document  
24 about qualitative assays for anti-HCV like the one being  
25 discussed today.

1 [Slide.]

2 The first one pertains to a so-called "non-  
3 diagnostic" indication for use. The reason that term is  
4 used--actually, in the document, it refers to "non-  
5 clinical"; currently, I like "non-diagnostic" the best--the  
6 idea here is that many of the assays we review in the  
7 Microbiology Branch have an indication that directly leads  
8 to a diagnosis. It often becomes the key factor in making a  
9 diagnosis.

10 The point here is that we felt in drafting this  
11 document that there is useful information that can come out  
12 of a qualitative anti-HCV assay that doesn't necessarily  
13 have to specify the state of disease, so, as the folks from  
14 Abbott stated, in conjunction with the other information,  
15 can lead to the diagnosis.

16 The way we expressed that in the draft guidance  
17 document was that an assay for anti-HCV would provide  
18 evidence of HCV infection which was not specified with regard  
19 to the state of infection or HCV-associated disease.

20 In doing so--and in coming up with that, we  
21 discussed this with a number of people around the country  
22 who have expertise in this area--we based it on a couple of  
23 reasons. The vast majority of infected Americans are  
24 chronically infected with or without hepatitis--and you have  
25 heard two previous speakers this morning say the same thing--