

1 MEETING OF  
2 ARMED FORCES EPIDEMIOLOGICAL BOARD  
3 THE ISLAND CLUB  
4 NORTH ISLAND NAVAL AIR STATION  
5 3629 Tulagi Road, Building 4  
6 San Diego, California 92155

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8 TRANSCRIPT OF PROCEEDINGS  
9 December 1, 2004

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1 SAN DIEGO, CALIFORNIA, DECEMBER 1, 2004

2 10:30 a.m.

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4 ARMED FORCES EPIDEMIOLOGICAL BOARD MEETING

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6 DR. OSTROFF: Anyone who is going to be  
7 leaving before 2:00 p.m., step out after the next  
8 presentation so arrangements can be made to get you back  
9 to the airport.

10 I think we'd all agree it was a very  
11 informative and interesting tour of the Mercy this  
12 morning, and we really appreciate their efforts in  
13 hosting us and the efforts of Colonel Gibson and crew  
14 being able to set that up.

15 Before we get started, as we always do, we  
16 have to acknowledge the designated federal official who  
17 is, as you can tell, not Ms. Embrey, it's Colonel Cox.  
18 So I'll let him make his brief comment and say we'll  
19 make a modification to the schedule. Initially, we were  
20 going to come back and have lunch and then hear from  
21 Dr. Kaplan on the other serum repository. But to  
22 accommodate schedules, we'll have him make his  
23 presentation before lunch and then break for lunch.

24 COL. COX: I knew I couldn't fool this group  
25 here. On behalf of Ms. Embrey, as the acting designated

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1 federal official for the Armed Forces Epidemiological  
2 Board, the federal advisory committee to the secretary  
3 of defense, which serves as a continuing scientific  
4 advisory body to the assistant secretary of defense for  
5 health affairs and the surgeons' general of the military  
6 departments, I hereby call the winter 2004 meeting to  
7 order. Let the games begin.

8 DR. OSTROFF: You have a rare and new talent.  
9 This presentation arises from concerns that were  
10 expressed by a number of Board members when it came to  
11 our attention that there were some issues regarding the  
12 fate and future of the Warren Air Force Base serum  
13 collection and requested that this particular agenda  
14 item be put on the agenda for this meeting. And  
15 Dr. Kaplan, who has a long and illustrious career, has  
16 been so kind to come out to San Diego to give us a  
17 presentation on this particular issue. And we welcome  
18 him to the Board and look forward to his presentation.

19 DR. KAPLAN: Thank you. Did we find a  
20 pointer? Thank you very much for the opportunity to  
21 come. Those of us from Minnesota will go most anywhere  
22 this time of the year, although it wasn't a lot warmer  
23 last night. I'm grateful to come. It's been a long  
24 time since I've been at an official function of the  
25 AFEB.

1           In fact, it's been since the old strep and  
2 staff commission, which I'll show you in a moment, was  
3 disbanded. This is a photograph of Dr. Rammelkamp.  
4 I think for most people in the room his contributions to  
5 the AFEB over the years are well remembered. One only  
6 has to read the book on the history of it. And he was  
7 responsible for, not only this collection, which I'll  
8 tell you about in more detail, but also responsible for  
9 my becoming the guardian, if you will, of this.

10           Just for those who are history buffs -- and  
11 it's not a very good picture, but this is one of the  
12 last meetings of this strep and staff commission in  
13 1972. And when I deal with this collection, I have to  
14 tell you that I think about people like Lewis Wannamaker,  
15 Dr. Rebecca Ramsfield, Rammelkamp, and Dick Krause, and  
16 many other people who were there at the time looking  
17 over my shoulders and yelling at me like they did  
18 30-some odd years ago if I did anything wrong with this  
19 collection. So I have a conscience. I got this  
20 collection just as an aside from Dr. Rammelkamp  
21 when he was about to retire. And he called me up one  
22 day and said he had what he said was 50,000 odd sera  
23 that were at Western Reserve at the old Cleveland Metro  
24 Hospital from the Fort Warren studies. But he wondered  
25 if I was interested because he wanted to give them to

1 somebody who would look after them and use them  
2 scientifically at that point. So I went out and spent  
3 the day with him, and it was a rather remarkable day. I  
4 found this collection in a walk-in freezer under a  
5 dripping condenser. So it was like a woolly mammoth. It  
6 was all encased in ice, completely, and had been like  
7 that for years. We agreed it would be a good thing for  
8 them to be transferred from Cleveland to Minneapolis,  
9 but the question was how to get it there.

10 We went through a lot of trying to decide how  
11 to do that. What happened was a remarkable story in  
12 itself, which is probably worth telling. And that is,  
13 my neighbor down the street owned a trucking company. I  
14 went down and presented him with my problem about how to  
15 get them out there. He said he didn't have any frozen  
16 trucks but -- trucks with freezers, but he had a friend  
17 who might be able to help me. So I went to the Shano  
18 Trucking Company in St. Paul. And this company was  
19 taking Geno's frozen pizza from Minnesota out to the  
20 East Coast and bringing trucks back empty from the East  
21 Coast. We struck a deal -- they would stop in Cleveland  
22 and pick up these 83 trays -- homemade trays about this  
23 square of sera and wouldn't charge me a nickel, but I  
24 had to let them write this up in the Teamsters' Union  
25 Journal so they could show they were all in favor of

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1 medical research. And we sent one of the technicians  
2 from the lab out to Cleveland. And in 12 hours the  
3 Shano's truck backed up to the back door of the  
4 building, and the samples were transferred free of  
5 charge, and we got all kinds of publicity from the  
6 teamsters, for whatever it's worth. We then got a  
7 little bit of money from the NIH. And we stored these  
8 away.

9           These -- this -- in addition to what you have  
10 on the piece of paper in front of you, which we'll go  
11 through after this, tells you a little bit about the  
12 collection. These samples were taken from Air Force  
13 recruits. And from a practical point of view, it  
14 probably was good that it was from the Air Force because  
15 the morbidity and mortality associated with the Korean  
16 War would probably be less among Air Force than it would  
17 be among Army or perhaps Navy personnel. So the  
18 mortality associated immediately was less.

19           As you know or may know, rheumatic fever was a  
20 huge problem in the military at that time. There were  
21 -- during World War II there were estimated to be  
22 approximately 27,000 cases of acute rheumatic fever in  
23 the Navy alone. One doesn't have figures for the other  
24 branches of the services. So these recruits were at  
25 Fort Warren in Wyoming. And a number of studies were

1 carried out there, and many of these people were bled  
2 more than once as a part of looking at antibody behavior  
3 following streptococcal infection. So you can see here  
4 the total number of serum samples available and here the  
5 number of study participants. In other words, there  
6 were a little over 1,000 from whom we had one sample.  
7 There were about 3500 who we have two samples from and  
8 so on down the line, and a few who we have a huge number  
9 of samples from at this point. So this gives you an  
10 idea.

11           When the samples were transferred, also the  
12 records from these samples were transferred along with  
13 them. We also received the lyophilized strains  
14 of streptococci, which unfortunately most of had died in  
15 the lyophilized tubing. But now we're with molecular  
16 techniques trying -- seeing what we can do to  
17 characterize them.

18           They all came in 3-by-5 cards. And I hope I'm  
19 not breaking HIPPA laws or some kind of laws. You can  
20 see that this is what was on each of the cards. There  
21 was a name, a service number. And written on each of  
22 the cards were the various studies that went on during  
23 that period of time at the Warren Air Force Base that  
24 each -- that this particular individual -- the  
25 individual participated in. And each one of those came

1 with handwritten records of these studies.

2           We were finally -- with the help of --  
3 particularly the help from WRAIR at the time -- able to  
4 get some new equipment as we began to catalog these and  
5 got ready to do one of the first studies that we had  
6 done with this. And we were able then to purchase  
7 industrial strength freezers. They had been in Sears  
8 and Roebuck freezers up to that time. These sera had  
9 never been frozen to minus 70. And as far as we know,  
10 these, for many decades, have never been thawed. And  
11 they were not thawed when the truck moved them to  
12 Minneapolis. So we have a number of freezers.

13           And in each of the freezers are the sera that  
14 are stored. Also, with the help of several small grants  
15 and at the time Dick Miller and his group at WRAIR, we  
16 were able to get enough money to computerize this  
17 collection.

18           These are -- what some of the original ones  
19 looked like. Now, what we've done with these. We went  
20 through and were able to identify approximately -- with  
21 the help of the medical follow-up agency -- 10,000  
22 people by service number and then convert the service  
23 number into social security number. And we took one  
24 specimen, and we aliquotted one of the specimens from  
25 each of these people. We broke it up into 1 millimeter

1 aliquots -- and as I'll show you -- refroze that so we  
2 wouldn't have to go through a freeze/thaw cycle again.  
3 The original ones are in these old rubber lipped vials.  
4 And you can see that on each of the tubes is the  
5 identifying information of when it was collected -- this  
6 is, for example, March 1949 at this point -- and the  
7 study with which this was associated.

8           What we did -- and that gives you a closer  
9 idea of what the samples looked like that are there.  
10 When we thought that they were not tight, we reinforced  
11 the cover. We had students come in and basically  
12 measure the amount in each tube by simply setting up an  
13 empty tube with various amounts of fluid in it, and then  
14 we had a little system where they just put them two by  
15 two and made a rough estimate of how much was in there,  
16 put it into the computer. And we had them do this  
17 twice. And then by using a program, anything that  
18 didn't match, we went back and looked at again to  
19 resolve any inconsistencies between the record keeping.  
20 So we're pretty comfortable about how this was taken  
21 care of.

22           Those that are aliquotted are in yet another  
23 freezer. And they are all cataloged in the computer as  
24 with the other samples that have not been aliquotted.  
25 We know exactly which box, which row, and how much is

1 there.

2           These are readily available. You can see what  
3 the 1 millimeter aliquots looked like in the boxes that  
4 they're in.

5           Now, one of the problems is that we've never  
6 had funding to -- for maintenance of this collection,  
7 and this is something that has worried us tremendously.  
8 We've been able, by gosh, to scrape together what needs  
9 to be. But if this is a valuable collection, which we  
10 think it is, it's a disaster waiting to happen with  
11 regard to the freezers, power outages, and so on. This  
12 is an example of what happened within the last year when  
13 we saw a recent ice buildup due to a malfunction of one  
14 of these, quote/unquote, new freezers. And this is  
15 literally the tip of the iceberg here because the whole  
16 bottom was filled with ice too. And we were able to get  
17 it fixed, but they need to be -- we need to have some  
18 kind of guarantee. If one of our freezers blows up,  
19 we're in, perhaps, big trouble.

20           This collection we think is unique. It's now  
21 more than 50 years old. In 1996 when we did one of the  
22 studies -- I'll tell you about in a second -- the  
23 mortality in these people was about 22 percent, as I  
24 recall. So at this age we would expect -- and it hasn't  
25 been looked at yet, it's perhaps going to be for reasons

1 I'll explain -- we expect this probably to be in the low  
2 30s in terms of mortality. But to be honest, we don't  
3 really know. The medical follow-up agency, which, as  
4 you know, was headed up by Dick Miller, the same one who  
5 helped us initially, has provided wonderful records and  
6 has all these records also cataloged and computerized.  
7 These represent classic papers in the field of  
8 streptococcal infections and their sequelae. And we  
9 think, from current and future, this offers a chance to  
10 do prospective studies retrospectively. And when you  
11 stop to think about the expense of this, long time now,  
12 over 50 years, we think they're very valuable. Some  
13 examples of the -- some of the papers that came  
14 utilizing these were -- here's one. You can just go  
15 through these. Here's another one that was done. The  
16 studies of penicillin, which, of course, has been used  
17 as the basis for prophylaxis in the military for years.  
18 These were the well-known barracks studies.

19           Now, when we brought this -- started getting  
20 this information recently back together, one of the  
21 first questions that came up and we asked the collection  
22 was: Could we get any information about Hepatitis C?  
23 This was a collaborative effort between WRAIR, ourselves,  
24 the NIH, and the VA. And representatives of those  
25 groups are listed in the paper that was published in the

1 annals of Internal Medicine three or four years ago.  
2 Bonnie Smoke came out and pulled, at the time, 2500 just  
3 out of the freezer without knowing who they were or  
4 what. And we found the prevalence of Hepatitis C  
5 antibodies from the late 1940s and early 1950s to be  
6 essentially quite similar to what it was at this point.  
7 So that prompted us to go ahead and do the 45-year  
8 follow-up study of Hepatitis C in then healthy, young  
9 adults. The data from that study suggested that perhaps  
10 Hepatitis C might not be a death sentence, in quotes.  
11 And, in fact, Leonard Seeff, who's now at the  
12 NIH, went out and tracked many of these survivors down  
13 to be able to do liver function studies on them in a  
14 manuscript that he claims is being worked on constantly.  
15 But it's been worked on so long that I have little hope  
16 it will ever see the light of day.

17           At the present time, to anticipate questions,  
18 there are several other groups with pending proposals  
19 that would be utilizing this. One is a study with  
20 Joe Murray who is interested in celiac disease at the  
21 Mayo Clinic, a study looking at hemochromatosis from our  
22 own institution. And the New York State Health  
23 Department, and the CDC are quite interested in looking  
24 at levels of various toxic products in people who come  
25 from various states in the country. The problem with

1 the later study is that it takes an awful lot of blood,  
2 and we're being very careful about the circumstances  
3 under which we agree to this.

4           Are these samples any good? How have they  
5 decayed in the last 50 years? I can only give you the  
6 little bit of evidence which is, I guess,  
7 circumstantial. They had, at the time that these  
8 studies were being done at the Warren Air Force Base,  
9 pooled controlled serum to use for standards for ASO  
10 titers, and that titer was 250. And since I've had  
11 these -- on occasion when we do those controls, the  
12 titer hasn't changed one dilution in that period of  
13 time. That doesn't -- I realize that's indirect and  
14 probably not enough, but it gives us some idea there's  
15 not been total decay.

16           Could we put on the next one? It's what's on  
17 that piece of paper -- the next presentation -- this is  
18 what you have in front of you. Although it's marked  
19 "confidential," that means that -- simply that I'm  
20 not -- although it's marked "confidential," it means I'd  
21 rather it not be released to the press under the  
22 circumstances.

23           COL. GIBSON: Dr. Kaplan, this a transcribed  
24 meeting. So if you don't want to talk about this  
25 document -- this will go on -- the transcriptions will

1 go on the web. The Board members wouldn't release a  
2 copy of this. But the fact that this exists will be on  
3 the web if you continue to talk about it.

4 DR. KAPLAN: Well, it's nothing that's really  
5 confidential in that sense, I mean. I just don't want  
6 anybody to sell it. You can get from this -- I won't go  
7 through this, but you can see that the average amount  
8 was about 4 millimeters in each tube. You can get an  
9 idea -- I'm not going to read through it because I don't  
10 want to waste your time. We found the matches for  
11 approximately 9400 individuals.

12 Keep scrolling. I think there's one more  
13 page. Well, you can have -- if you look at it, you can  
14 ask questions as to what's there. I'm here today  
15 basically to point this out to you and to say that we  
16 would like very much to have your support in saying this  
17 is a worthwhile collection. I don't come to you for  
18 funding. But in your advisory capacity, I would hope  
19 that you would agree that this is a collection that  
20 probably shouldn't be trashed and should be kept for the  
21 future. I'd be happy to answer your questions.

22 DR. OSTROFF: Thanks very much. I do have a  
23 couple of quick questions for you before I open it up to  
24 the Board. One is: Can you give us an idea of what it  
25 costs to maintain this collection currently? And the

1 second is: With the various proposals, what is your  
2 process for making decisions about which -- what gets  
3 done with these specimens?

4 DR. KAPLAN: I've tried to cost this out in  
5 terms of the time that it takes for us -- the bits and  
6 pieces of maintenance that goes in. We think it's  
7 somewhere probably between -- around 10 to \$15,000 a  
8 year in terms of time. Ten is probably a bottom figure.  
9 They don't just sit in the freezer. It takes time and  
10 effort. And what frightens me is the fact that if a  
11 freezer goes down we're in big trouble. And the second  
12 question was --

13 DR. OSTROFF: How do you make decisions  
14 about --

15 DR. KAPLAN: By myself, to be honest with you.  
16 There have been proposals for having committees and so  
17 forth and so on. At one time another agency was  
18 interested in this, and we couldn't agree on how much  
19 supervisory role I should have in this. And I felt that  
20 because of the agreement that I originally had with  
21 Dr. Rammelkamp that I had to keep a part of it. One of  
22 the things that is indirectly asked is: What's going to  
23 happen to this collection if I get run over by a  
24 streetcar or retire or what have you? And that is a  
25 concern. If there's no provision made for this, my

1 guess is it will end up in the river someplace, and  
2 that's what I don't want to happen.

3 DR. OSTROFF: Let me just say on behalf of the  
4 Board, we strongly endorse your coming here to discuss  
5 this and thank you profusely for your stewardship of  
6 this collection over the years. And I think it's  
7 particularly timely to have a discussion about this  
8 repository, being that we have this question before us  
9 about the 36 million specimens that are currently being  
10 collected as part of the larger serum repository.  
11 Because I do think these types of issues are issues that  
12 need to be thought of in terms of the -- not only the  
13 continued collection of specimens to add into the  
14 DoD serum repository, but what the future of the  
15 existence of the future specimens happens to be. So  
16 it's a very timely and important discussion.

17 Let me open it up --

18 DR. KAPLAN: Before you do I'd like to make  
19 one comment. When I was having coffee this morning, a  
20 group of you were talking about collecting specimens,  
21 and I couldn't help but overhear some of the discussion  
22 and chuckle to myself that you were addressing questions  
23 from the other side that we had met those problems in  
24 terms of dealing with specimens like this. And it's a  
25 very difficult issue, and I'm grateful for your voicing

1 support.

2 DR. OSTROFF: One other question I have is for  
3 those individuals in whom there are multiple specimens  
4 -- I see some have 25 or more specimens -- what's the --  
5 not knowing all the nuances and details of how the  
6 Warren studies were conducted, what's the temporality of  
7 those specimens? Were they collected weekly or always  
8 in recruits --

9 DR. KAPLAN: They were almost always in  
10 recruits. And most of these were acute and convalescent  
11 specimens from the point of view of streptococcal  
12 infection, so they would be within four to six weeks,  
13 which means that if one is doing other kinds of studies  
14 looking for things that are not antibody related and so  
15 on, they could all be really, I think, pooled at that  
16 point. We obviously are not going to do that. Most of  
17 them are acute in convalescent serum. They're not more  
18 than ten weeks, I'd almost be willing to guess.

19 DR. GARDNER: Thank you so much for coming and  
20 for this wonderful collection. I have two questions.  
21 One, you alluded to HIPPA, but it seems to me HIPPA --  
22 looks like they're going to lock horns in an unhappy  
23 way, and I wonder what you've done with that. And then  
24 I did miss a little bit. At the beginning you told us  
25 about some of the problems in the early storage in the

1 transport. And the studies to evaluate deterioration --  
2 I didn't really catch what you felt had been done to  
3 validate the sanctity of these specimens.

4 DR. KAPLAN: Well, we have, from time to time,  
5 and not on a regular basis because -- when we were  
6 running ASO titers, for example, as a part of other  
7 projects and so forth, we'll dip into the controls just  
8 out of curiosity to see if they stay stable. So it's  
9 irregularly irregular, not any systematic way to look  
10 at. They have never -- for probably as long as I've  
11 been in Cleveland, they have never been thawed. What  
12 happened when they were around the original point of  
13 collection, I can't speak to.

14 DR. GARDNER: And what about the HIPPA?

15 DR. KAPLAN: In the studies we've done and the  
16 studies that are pending, they've been through more IRBs  
17 than I ever knew existed before. They've been blessed  
18 by the Institute of Medicine by the V.A., by the  
19 NIH, and by the University of Minnesota. Each group, as  
20 you can imagine, having no standards, has it's own  
21 little bit of -- own little unique differences. We've  
22 managed to overcome these.

23 DR. GARDNER: You did mention studies in which  
24 people track down -- those clearly had to be --

25 DR. KAPLAN: And without going into the

1 details, which we could always get from Leonard Seeff at  
2 the NIH, that was all on the up and up. And, in fact,  
3 there was -- among the patients, there was one who  
4 refused to participate. It's interesting. There was an  
5 article about this collection in the New York Times  
6 Science about three or four years ago. And one of the  
7 reasons I was careful about this was it just brought all  
8 kinds of people out of the woodwork. I got letters from  
9 people who'd been Air Force recruits at Fort Warren in  
10 the 1940s, and Warren didn't know what their ASO titer  
11 was at that time.

12 DR. GARDNER: Increasingly, you're dealing  
13 with people now probably with a mean average in their  
14 early 70s.

15 DR. KAPLAN: Let's say they're 20 so --

16 DR. GARDNER: So 70-plus you will not be able  
17 to get informed consent in a little bit.

18 DR. KAPLAN: As terrible as it sounds, that  
19 makes it a lot easier.

20 DR. BROWN: If you're going to do some  
21 interesting studies that you might use these samples  
22 for, would you not face having to go through IRB  
23 approval and the -- specifically getting informed  
24 consent from the participants or not?

25 DR. KAPLAN: Yes and no. This has

1 been -- this has largely been taken care of by the  
2 people who live in and around the Washington area. And  
3 I know the conclusions rather than the details of  
4 studies. But in some instances that is the case. It  
5 depends on what they'll be used for. Even though we  
6 have Sam Jones's name on every tube, we have no idea who  
7 Sam Jones is. The follow-up information, for example,  
8 is at the medical follow-up agency in Washington. We  
9 don't have that.

10 DR. BROWN: The second question I had was  
11 that -- you mentioned the data that these individuals  
12 had in the 1950s had similar rates of Hep C as current  
13 groups. That seems -- isn't that -- that's a surprising  
14 finding, isn't it?

15 DR. KAPLAN: Not being an expert, the experts  
16 said, mm-hmm, and that's about as much -- you can  
17 interpret that either way.

18 DR. OSTROFF: Because the rates went up  
19 significantly in the 1980s. That's when everybody  
20 became aware of the problem. So it would be surprising  
21 to have rates that were that high in 1950.

22 COL. RUBERTONE: Dr. Kaplan, I was wondering  
23 -- I'll put this in context. I was recently approached  
24 to see whether the DoD could take on the Warren Air  
25 Force Base specimens. My initial response was that

1 these were collected for research purposes initially,  
2 have been maintained as a research serum collection, and  
3 that would be very different from the way the DoD serum  
4 repository currently exists. Although we support  
5 research, there is a difference. They're not maintained  
6 as research specimens, and it allows us to perform some  
7 research. Could you shed a little light on the initial  
8 collection and whether it was truly a kind of research  
9 study where there was informed consent at that time to  
10 obtain them or --

11 DR. KAPLAN: The words "IRB" and "informed  
12 consent" had not been invented at that time, Mark. And  
13 the other thing is that you know better than I do that  
14 these were almost exclusively volunteers in the military  
15 at that time. And you understand the connotations of  
16 that also. So they were definitely research. I mean,  
17 the purpose was to show -- that's why I put those papers  
18 up there, to address questions which were not addressed  
19 otherwise, and they were signal studies. So they were  
20 research studies. These didn't come from the hospital  
21 lab.

22 DR. OSTROFF: Can I ask two more questions?  
23 Other than the article in the New York Times a couple of  
24 years ago, how has the existence of the repository been  
25 made known to the research community? And then the

1 second question is: In this follow-up study of  
2 Hepatitis C, which was just done recently, where -- if  
3 you say you went back to a significant number of these  
4 individuals to look at their liver functions, assumedly  
5 additional specimens were collected, were they -- was  
6 there any thought given to adding those more recent  
7 specimens to the repository? Because that sort of --  
8 the 50-year follow-up specimens are actually in and of  
9 themselves highly valuable.

10 DR. KAPLAN: The answer to the second question  
11 is no. And I'd be delighted to have your strong arm to  
12 convince Leonard Seiff that that's a good idea at this  
13 point.

14 DR. OSTROFF: I think it enhances their value  
15 tremendously.

16 DR. KAPLAN: It would. Those were all  
17 collected with all of the necessary -- and the first  
18 part was --

19 DR. OSTROFF: How have you otherwise --

20 DR. KAPLAN: Yeah. I really have not.

21 DR. OSTROFF: It seems to me there are a lot  
22 of good ideas out there about what might be done --

23 DR. KAPLAN: I'm sure. In fact, there were  
24 some inquiries -- not very many people new about this  
25 because it was sort of stored in the basement for that

1 period of time. There was some talk when the existence  
2 of HIV came in to go back and look at that, and nothing  
3 ever came of it. The National Cancer Institute was very  
4 much interested in this collection for a while, and we  
5 had some ongoing discussions with them. They  
6 were -- they wanted the collection without sharing with  
7 the general public. In short, we couldn't work this  
8 out, and they drifted away.

9 DR. HALPERIN: The other thing that makes this  
10 a valuable collection is you're saying medical follow-up  
11 agency has done mortality follow up on the entire -- so  
12 we know if people are deceased what they died from at  
13 least --

14 DR. KAPLAN: Yes, yes. And they've really  
15 done a magnificent job at this. There is now funding  
16 been asked for to update it. The last time it was  
17 really done was 1996. But funding, as a part of these  
18 other requests, have -- it's extraordinarily expensive  
19 and time consuming, as you can imagine, to get that.  
20 But everybody recognizes that's the value or one of the  
21 value aspects of it.

22 DR. OSTROFF: Well, again, speaking for the  
23 Board, let me thank you, first of all, for your  
24 willingness to come out here and brief us on this  
25 subject; secondly, for your tremendous stewardship of

1 this collection. The Board is extremely tied to its  
2 history, and this is clearly a legacy collection from  
3 the early days of the AFEB. And I think it behooves all  
4 of us to do what we can to assist you in making sure  
5 that this collection is protected, is utilized to its  
6 fullest, and that we do service to the history of those  
7 who took the care and effort to collect these in the  
8 first place. And so anything that we can do to help to  
9 make sure that these are maintained in a way that they  
10 will be maximally utilized for, not only the benefit of  
11 the individuals who did all of this, but for medical  
12 science, please let us know.

13 DR. KAPLAN: I will. And I'm very grateful to  
14 you for allowing me the opportunity. I don't want  
15 anybody to be misled by this confidentiality business.  
16 The confidentiality is to keep the people away who cause  
17 me -- write me bad letters and things like this. But  
18 what you can do -- and if any of you have ideas and so  
19 forth, I'd be very grateful.

20 DR. OSTROFF: Thank you again. Why don't we  
21 break and take a half an hour for lunch, if that's  
22 acceptable to the Board, come back at 1:00. We have  
23 several presentations on the issues of chlamydia and  
24 adenovirus, subjects that many of the Board members have  
25 been very interested in that we have additional

1 discussions on. So hopefully we'll be able to have as  
2 great a participation as possible during the afternoon.

3 (Lunch recess.)

4 DR. OSTROFF: We have a series of  
5 presentations on STDs in military settings. And I  
6 think, as we discussed at the previous meeting in San  
7 Antonio, this is an issue which has been on the mind of  
8 the Board for a number of years. We used to have fairly  
9 regular discussions of this issue in the need to reach  
10 some level of consensus and standardization among the  
11 services in terms of -- particularly the issue of  
12 chlamydia screening. And at our last meeting we were a  
13 little dismayed, I guess is the right word, to hear that  
14 there are still so many discordant approaches to dealing  
15 with this problem that we thought it was important to,  
16 once again, put this on the radar screen and hear some  
17 presentations to try to determine how the Board could be  
18 most useful in trying to move this issue forward.

19 So with that, we are very appreciative of  
20 Dr. Gaydos for -- I should say in plural -- for being  
21 here and being able to provide us with some information  
22 and hopefully be able to suggest to us some rational  
23 approaches to move into the future. So with that, let  
24 me start with an old friend of the Board, Dr. Gaydos.

25 DR. GAYDOS: Thank you, Dr. Ostroff. And

1 thank you for inviting us to speak to the subject of  
2 chlamydia trachomatis general infections in military  
3 service members. I'm going to give a general overview,  
4 and I will be followed by Dr. Mary-Ann Shafer from UC  
5 San Francisco who will go into depth on chlamydia  
6 infections and their sequelae in women. And she will be  
7 followed by Charlotte Gaydos of John Hopkins who will  
8 address chlamydia infections in men. We're also honored  
9 this afternoon to have with us two world famous military  
10 STD experts, Dr. Sherry Boyer from UC San Francisco, and  
11 we will be joined shortly by Dr. Stephanie Brodine from  
12 San Diego State University.

13 DR. OSTROFF: And let me just interpret by  
14 saying that the presentation is in Tab 7.

15 DR. GAYDOS: And we hope that this afternoon  
16 will cover some very important points to your  
17 satisfaction. And I would like to go over a couple of  
18 these. Chlamydia infections are highly prevalent in men  
19 and women. These are usually silent infections  
20 untreated in women. We have increased spread in  
21 sequelae, such as pelvic inflammatory disease, chronic  
22 pelvic pain, ectopic pregnancy, infertility. And there  
23 is a relationship between chlamydia infections and other  
24 STD infections like HIV. In men we have increased  
25 spread and possible sequelae, such as urethritis,

1 epidemtitis, prostritis, and infertility. Chlamydia  
2 infections are easy to diagnose. They're easy to treat.

3           Two general methods of control -- one is by  
4 mass screening or points of intervention which is found  
5 among new prisoners coming into detention facilities and  
6 young people coming into job-training centers and also  
7 into recruits coming into the military. The other  
8 method is individual screening of high risk people as  
9 they come into clinics for various reasons. Screening  
10 in women has been shown to be cost-effective in high  
11 risk females.

12           Screening in men may be cost-effective, but  
13 very little studies have been done of men, and more data  
14 are needed to evaluate this. Recruit training is an  
15 ideal place for an intervention, and many of the  
16 services have taken advantage of this. It's an ideal  
17 place because it's a point where many young high risk  
18 people are gathered at one point in time and screening,  
19 treating, and informational services can be provided  
20 very efficiently. The evaluation of periodic clinical  
21 screening requires reliable surveillance data to include  
22 lab data. And this is a situation where we're talking  
23 about silent infections; where we're talking about  
24 pelvic inflammatory disease that Dr. Shafer will  
25 discuss, which is not easy to diagnose; and we're

1 talking about a lot of opportunity for missed cases and  
2 misclassification.

3           The military impact of chlamydia and sequelae  
4 of chlamydia are poorly defined. We do not know a lot  
5 about the occurrence of these infections in the  
6 military. We do not know a lot about the sequelae, and  
7 we do not know a lot about the impact of the sequelae on  
8 the military health system or military operations. The  
9 AFEB has been looking at this situation for over five  
10 years -- actually, over six years. Dr. Ostroff, I  
11 think, has a desire to bring this to some sort of  
12 closure. And in asking us to give these presentations,  
13 two items came to the forefront.

14           One item was: Why is the military not seeing  
15 more cases of pelvic inflammatory disease and other  
16 serious sequelae? And Dr. Shafer will address that.  
17 And the second issue is: What should be done with  
18 chlamydia infections with men? And Charlotte will  
19 address that.

20           We got very interested in chlamydia in the  
21 early 1990s. Dr. Kelly McGee (phonetic) was working the  
22 epidemiology clinic at Fort Bragg. Charlotte was at  
23 John Hopkins, and I was at the old Army Environmental  
24 Hygiene Agency. The importance of chlamydia was  
25 becoming well known. And so we decided to look at what

1 was happening with regard to pelvic inflammatory disease  
2 and ectopic pregnancy in the Army.

3           Now, at this time we felt that the military  
4 was still a very strongly inpatient oriented healthcare  
5 system and had not yet made a strong turn toward a  
6 managed outpatient system. So in these three years,  
7 these are the cases of PID that we identified as  
8 inpatient diagnoses, and these are the rates that we  
9 saw. Now, for comparison purpose, in the 15 to 44 age  
10 group, nationally it was .3 percent. And we got 1.1 to  
11 1.6. For ectopic pregnancies we found that 1.2 to 1.3  
12 percent of women in the Army in each of these years had  
13 been hospitalized with the diagnosis of ectopic  
14 pregnancies. We had nothing to compare this to, but  
15 this is high.

16           This resulted in a Defense Women's Health  
17 Program grant, and we studied women coming into the Army  
18 as recruits at Fort Jackson South Carolina. We  
19 completed the first phase of this in '97, a screening of  
20 over 13,000 women. These data were presented to the  
21 A-FEB and published in the New England Journal of  
22 Medicine. We found an overall prevalence of 9.2  
23 percent. And depending on which risk group you looked  
24 at, this went up to about 15 percent. This study went  
25 on for an additional two years, from '96 to '99,

1 screening over 23,000 women. The overall prevalence was  
2 9.5 percent. And in this study over the four-year time  
3 period, we found that the prevalence increased from 8.5  
4 percent to 9.9 percent.

5           Using the same test, Dr. Shafer and her  
6 colleagues studied the Marines -- Marine women.  
7 Screening over 2,000 women, they found 14 percent. The  
8 Navy has been routinely screening women coming into the  
9 Navy. And for '97 and '99 over 22,000 women had been  
10 screened, and they got 4.3 percent positive prevalence  
11 for chlamydia trachomatis.

12           Now, the Navy used a probe test. These  
13 studies were done with a nucleic acid amplification  
14 test. This test has much less sensitivity than was used  
15 here. So if a nucleic acid amplification test had been  
16 used here, this percentage would have been much closer  
17 to these percentages. Now, I think it is important to  
18 look at these and realize that the healthy people 2010  
19 goal for prevalence to women is 3 percent. At Fort  
20 Jackson we found that the prevalence in incoming  
21 recruits was quite different depending on where these  
22 people were coming from. Based on their home of  
23 record, for example, we found less than 6 percent  
24 prevalence in those coming from the west and over 12  
25 percent prevalence in those coming from the south.

1                   These represent the breakdown of our  
2 population by race. And you can see we found 16 percent  
3 in blacks. This is our age breakdown. Most of these  
4 were young people, and they had a much higher prevalence  
5 than those who are above 25 years of age. Now, Dr. Howe  
6 at Johns Hopkins and her colleagues looked at the data  
7 from Fort Jackson. And based on a theoretical  
8 population of 10,000 incoming female recruits, she found  
9 that we would have 920 infections with 276 cases of PID.  
10 Screening on the basis of age -- screening for high risk  
11 people based on age, the cases of PID would be reduced  
12 by well over 200, and there would be cost savings for  
13 PID. Dr. Howe went on and did a second cost-effective  
14 in this analysis looking at what community would reap  
15 the benefit of this cost savings. And what she found  
16 was that the majority of the cost savings would go into  
17 the civilian healthcare system, although the Army would  
18 receive a significant cost savings.

19                   The reason for this is shown on this timeline.  
20 Women entering the Army at Fort Jackson during basic  
21 training have an attrition rate of about 13 percent.  
22 Now, of those women who go on and complete training at  
23 this point in time, 47 percent of them went into the  
24 National Guard or into the Army reserve. This is  
25 important for a couple of reasons. These women will be

1 leaving after they complete their training. So if they  
2 are not captured in basic training in an attempt to  
3 screen, treat, and do some sort of an educational  
4 intervention, there may not be another opportunity to do  
5 that.

6           The second point to remember is that if one  
7 looks at screening that is being done in the active  
8 force in women who are enrolled in the military health  
9 system, these people will not be included in that  
10 screening. Now, as I mentioned earlier, when we looked  
11 at this problem and we looked at PID and ectopic  
12 pregnancies in the early '90s, the military health  
13 system was still focused on inpatient care. During the  
14 1990s that focus changed to a managed care system with  
15 outpatient care.

16           Now, in spite of this occurring, Dr. Clark and  
17 colleagues decided to take a look at the people who  
18 participated in screening at Fort Jackson and those who  
19 did not for the years '96 and '97 and looked at their  
20 outcomes with regards to hospitalizations for PID and  
21 related sequelae and then also look at hospitalization  
22 for any reason. Now, what Dr. Clark found was that  
23 there was no significant difference in the sequelae from  
24 chlamydia infections. However, there were significantly  
25 less hospitalizations for any reason among those who

1 were screened. So we could be dealing with a situation  
2 of misclassification. And Dr. Shafer will address this  
3 study in more detail. To this point I've been talking  
4 about screening women in basic training.

5           Two studies have also been done in looking at  
6 men coming into the Army. And these studies showed  
7 prevalence levels that are about half of what they are  
8 in women. To the best of my knowledge, there has only  
9 been one cost-effective analysis done of screening Army  
10 male recruits. This was done by -- Dr. Shooping  
11 (phonetic) was -- presented this last September in  
12 Europe. He found that screening Army male recruits was  
13 not cost-effective. However, I want to point out, as I  
14 did earlier, that not much work has been done with  
15 regard to chlamydia infections in men and that better  
16 information with regard to the number of contacts per  
17 infected male and also better information about the  
18 military ability to identify and treat female contacts  
19 could have an impact on the effects of this  
20 cost-effectiveness study.

21           Now I'm turning to basic training to people in  
22 the force. Now, these are prevalence studies that were  
23 done of Navy and Air Force women. And you can see that  
24 these levels are high. And remember that we're talking  
25 about the 2010 objective of 3 percent. We also have

1 studies here of Marine men which are not a whole lot  
2 different from what was observed in the women. So these  
3 are prevalent studies of people out there in the force.

4 Now, looking at clinics -- looking at Army  
5 women coming into a clinic at Fort Bragg that took care  
6 of women with, generally, urinary complaints in that  
7 clinic, we had almost 12 percent prevalence of  
8 chlamydia. Now, for comparison purposes in family  
9 clinics that used the seminal sites by the CDC across  
10 the United States, the prevalence of chlamydia positive  
11 women coming into those clinics is about 5.6 percent.

12 Now, in 1999 the Armed Forces Epidemiological  
13 Board issued a number of recommendations. They  
14 recommended that all new female recruits should undergo  
15 screening, but they said this could be done in the first  
16 year of service. As I pointed out earlier, this would  
17 most likely miss many, if not all, reserve National  
18 Guard women. They also recommended that all female  
19 service members be routinely screened up to the age of  
20 25, that appropriate educational programs be developed  
21 and used, and that testing of males be encouraged, with  
22 programs to obtain more and better information on males.

23 Now, what is the current status? Let's look  
24 first at what's happening in the recruit training  
25 centers. Currently, routine chlamydia screening in

1 recruits is occurring in Navy, Marine Corps, and Coast  
2 Guard facilities. Routine screening of women for  
3 chlamydia is not occurring in the Army or the Air Force.

4           Now, how about screening out in the people who  
5 are already past training and out in the force? I'm  
6 sure most or all of you are familiar with the Health  
7 Plan Employer Data and Information Center HEDIS set.  
8 This is a performance indicator of screening for  
9 chlamydia -- is one of the performance indicators used  
10 by HEDIS. In this case an attempt is made to identify  
11 women at risk and then determine how many of these women  
12 or what percentage of these women have been screened for  
13 chlamydia. Now, what I show here for these years -- the  
14 HEDIS evaluation for commercial healthcare systems and  
15 Medicare systems. And as you can see, for commercial  
16 systems it went from 20 to 26 percent. More recent data  
17 would put this around 30 percent. For Medicaid it went  
18 from 28 to 38. More recent data would put this above 40  
19 percent.

20           Now, data on U.S. military was compiled for  
21 2001, and this placed them in the 35 percent of military  
22 women who should have been screened -- were screened,  
23 which would put them in the 90th percentile performance  
24 compared to their peers on the outside. Now, remember  
25 this does not include recruits. These are women who

1 were continuously enrolled in the healthcare system.  
2 Those -- these women have been in for a year. So this  
3 would not include the recruits and not include reserve  
4 and not guard.

5           Now, as pointed out by Dr. Brodine and Shafer  
6 and others, none of these numbers are anything to be  
7 proud of. We want to get as close to 100 percent  
8 screening of high risk women as possible. The second  
9 point is that with regard to military this low figure is  
10 especially important because these are women who could  
11 be deployed and get into areas where the availability of  
12 healthcare is limited, and for things like pelvic pain  
13 medical evacuation, could be required.

14           Now, Dr. Ostroff asked me to make  
15 recommendations. I have taken recommendations that were  
16 made by the DoD Sexually Transmitted Diseases Prevention  
17 Committee working with the DoD Global Emerging  
18 Infections and Surveillance Response System to  
19 DoD health affairs. And these recommendations were to  
20 screen all female recruits during basic training or  
21 provide good reason why they were not being screened, to  
22 follow current CDC guidelines for diagnostic tests using  
23 the preferred amplification test, and to follow  
24 CDC guidelines for clinical screen diagnosis treatment  
25 and prevention, to enforce reporting, and to

1 periodically evaluate reporting accuracy and  
2 completeness for chlamydia infections and their  
3 sequelae, to offer partner notification referral  
4 services, and to provide education and information  
5 programs, to implement pilot programs in men that the  
6 AFEB recommended in 1999, and also to determine the  
7 impact of PID and sequelae and chlamydia infections to  
8 determine the extent in the military and the impact of  
9 these on the military health system and on operations.

10 And I respectfully request that questions and  
11 discussions, other than those necessary for  
12 clarification, be held until all three of us have  
13 spoken, since we will be building on the same material.

14 With that, I turn the podium over to  
15 Dr. Shafer.

16 DR. OSTROFF: Thanks very much. Let me just  
17 open it up for any points of clarification before we  
18 move on.

19 DR. ATKINS: 35 percent, is that screening  
20 within a certain time window? 12 months or --

21 DR. GAYDOS: You're talking about HEDIS?

22 DR. ATKINS: Yes.

23 DR. GAYDOS: That was within the time period  
24 -- I believe it was a period of a year, if I remember  
25 correctly.

1 DR. OSTROFF: One other question for you: In  
2 terms of all of the studies that you presented were  
3 there significant differences in the findings depending  
4 on whether these were urine versus swab specimens in  
5 terms of the recruit studies?

6 DR. GAYDOS: I think it can be safely said  
7 that the -- what we observed in recruit studies are  
8 consistent. We'd have to look at those in terms of the  
9 individual risk factors. I think all the three studies  
10 that we presented -- those were all three urine tests  
11 using LCR test.

12 DR. SHAFER: If I can just say something for a  
13 second. We did a study where we did urines, vaginals,  
14 and cervical on 2,000 Marine women. And when you put  
15 all three together, you definitely boost by a third.  
16 And we think that cervical is probably the best, but  
17 certainly vaginals are as good, and urine is even less.  
18 I think there will be a lot of reasons why we go to  
19 swabs because it's easier to use. We can talk about  
20 that later, if anyone is interested.

21 So I appreciate having the opportunity to  
22 speak with you. I feel like an honorary military  
23 person, as my colleagues and I have been working  
24 together for over ten years with military studies.

25 The title of this actually came from a --

1 which you should have in your folder -- an editorial  
2 that Dr. Brodine and I wrote -- I think it was last year  
3 or 2003 -- regarding combating chlamydia in the military  
4 and why aren't we winning the war.

5 Chlamydia rates -- and I'm not going to go  
6 over this because some of these are repeated -- but the  
7 idea is they have continued to go up. These are the  
8 male rates; these are the females rates. Part of this  
9 in here probably has to do with better testing. What we  
10 certainly know is that we don't have massive decreases  
11 in chlamydia, especially when we look at military  
12 populations over time.

13 This shows, again, the age group that really  
14 has most -- is between 15 and 29 but -- it's really  
15 basically -- especially 16 or 17 to about 23 to 24. But  
16 this is the age group in males and in females we're  
17 trying to hit.

18 The reason I'm showing you this slide -- this  
19 is chlamydia trends in positivity over time in 15 to 24  
20 year old women civilian populations. And what I want to  
21 show you is that the only place that had an active  
22 screening program in the country during that time is  
23 really the northwest. This is when the rate went down.  
24 If you look at the rest, not a lot is happening. This  
25 is an active broad-based screening program. I thought I

1 would talk with those who are not familiar with PID --  
2 we're trying to do -- by doing screening programs in  
3 chlamydia, this is really trying to avert a number of  
4 major reproductive sequelae. And the most obvious right  
5 now is really pelvic inflammatory disease or PID.

6           What we do know is polymicrobial, that about  
7 two-thirds are related to gonorrhea, chlamydia, and then  
8 also other bacteria. Sometimes they're together;  
9 sometimes they're single. It's all over the place  
10 depending on is this our first infection, et cetera, et  
11 cetera. We haven't made great leaps in this in the last  
12 10 or 15 years. About a third are due to anaerobes and  
13 aerobic facultatis (phonetic) as well. Symptoms, almost  
14 two-thirds -- and in some cases more -- have absolutely  
15 no symptoms. I'll go through some of the study, how we  
16 found that out.

17           But there is a study where they went in and  
18 actually laparoscoped women. We did endometrial  
19 biopsies, and they proved that women that have positive  
20 chlamydia actually have PID, and they have very little  
21 or no symptoms. It's very important to know that. So  
22 two-thirds don't come in really complaining of much.  
23 About a third have mild to moderate. And only 4 percent  
24 of the severe women who's bent over has fever, is toxic,  
25 and you have to put her in the hospital. The acute

1 complications then from this, around the early part of  
2 pelvic inflammatory disease, is going to be tubal  
3 ovarian abscess, which is an abscess around the ovary,  
4 the tube, and the pelvic organs in general. You know,  
5 and that's only the studies of people that were in the  
6 hospital.

7           Another thing we're trying to avoid is  
8 Fitz-Hugh-Curtis Syndrome, which is an inflammatory  
9 infectious response, again, from the pelvis up to the  
10 liver. You can check on this because you see these  
11 string-like scar tissue, and it's very painful, and the  
12 women can be quite toxic.

13           The long-term complications we mentioned are  
14 tubal, factor, and fertility. That is the main cause of  
15 infertility in women in the United States. If you have  
16 PID, you're going to be about ten times more likely than  
17 those who don't of having infertility. The episodes, as  
18 you increase from first, second, or third episode, go  
19 from about 8 percent to about 40 to 50 percent of being  
20 infertile. We're not going to address that, but there  
21 are major psychosocial and financial costs to being  
22 infertile both for men and women.

23           The second major worry we had was ectopic  
24 pregnancies, tubals. You know, it's going to be harder  
25 to understand -- we know that ectopic pregnancies -- a

1 number of them actually resolve on their own. They have  
2 some pain, and they kind of resolve on their own. So  
3 the one we tend to see are the ones that cause major  
4 problems. So we do know there is about a 7 to 10 fold  
5 increase in ectopic pregnancies once you've had PID, and  
6 that increases by your episodes. So about one in four  
7 to one in five have an ectopic after their third episode  
8 of PID.

9           What we know least about is chronic pelvic  
10 pain because it's hard to define, people don't come in  
11 for it, or they're misdiagnosed. But when they're  
12 carefully looked at, we know about 20 percent of women  
13 who have had PID documented have pelvic pain. And,  
14 again, it increases by number of episodes of PID. We  
15 also know that there's more readmits for pelvic pain in  
16 women that have had PID. It's very expensive to deal  
17 with chronic pelvic pain and very difficult for women  
18 and their partners to deal with it as well.

19           The diagnostic criteria is very challenging  
20 because -- I'm going to show you most of the criteria we  
21 use are really subjective on the part of the clinician  
22 and the patient. We ask for minimal criteria,  
23 uterine/adnexal -- it has to do with the ovaries and so  
24 forth -- tenderness. It could be one sided or both.  
25 Cervical motion tenderness. Again, when you examine the

1 individual and you move the cervix around, it hurts.  
2 There are additional criteria that may give you  
3 increased specificity but has decreased sensitivity. So  
4 we can look at inflammatory things such as C-reactive  
5 protein, body temperatures, white cells on a saline prep  
6 of a vaginal swab, mucopus coming out of the cervix on  
7 an exam, chlamydia, gonorrhea tests that are positive or  
8 abnormal. Except for this, they're really nonspecific  
9 tests, and they could have any inflammatory process  
10 going on. We have more definitive tests. They are more  
11 expensive. We don't know by doing them if they change  
12 the outcome at all of fertility and so forth. That has  
13 to do with endometrial biopsy, ultrasound, and  
14 laparoscopy.

15           So I wanted to move -- I gave you really what's  
16 the obvious clinical picture that's textbook from the  
17 CDC of how we define pelvic inflammatory disease. Any  
18 medical student can figure out how to diagnose that, but  
19 the more subtle part. Those other, perhaps, two-thirds  
20 or more of cases are really either subclinical. If we  
21 look a bit, we might find it or really no symptoms  
22 whatsoever. So we're going to move towards the case for  
23 subclinical pelvic inflammatory disease.

24           Some of the questions people have is: How  
25 come we're not seeing more of it? Well, there's an

1 excellent study done by some of our former colleagues.  
2 It had to do with lower genital tract infections and  
3 endometritis, insight into subclinical PID. That was  
4 published in 2002. I'll go through that quickly with  
5 you.

6           The subjects were about 500 women. They took  
7 women who were either -- had mucopus cervicitis on exam;  
8 they had either a GC, and/or chlamydia that were  
9 positive on a test; they had bacterial vaginosis  
10 diagnosed by Amsel's criteria, which is clinical  
11 criteria; and/or they had a male contact who had  
12 gonorrhea, chlamydia, or NGU. These are the women in  
13 ambulatory settings that they went out to recruit. And  
14 they made sure they hadn't been treated yet. And then  
15 what they did is they excluded any women that fit the  
16 1998 PID criteria by the CDC. So here, they are pretty  
17 healthy women that had some risk factor. They did a  
18 complete exam. They did cultures. Again, they did  
19 tests for chlamydia and gonorrhea. And they did  
20 histology of an endometrial biopsy of the uterus. There  
21 are definitions -- the strongest definition for  
22 PID where you get uterine lining infection is going to  
23 be greater than or equal to five polymorphonuclears in a  
24 superficial endometrial biopsy. This is a pretty strong  
25 indication for PID. They also took a clinical history

1 of the women at the time of the biopsy.

2           What they found is subclinical PID in 27  
3 percent of the women who had chlamydia, 26 percent of  
4 the women who had gonorrhea. And they concluded that  
5 more than one in four women with positive chlamydia  
6 and/or gonorrhea had subclinical PID. These are women  
7 that normally would not be treated for this. The reason  
8 this is important is there's a question -- when we get  
9 to treatment -- that when we treat PID we tend to treat  
10 them longer than if we were just treating an  
11 uncomplicated case of chlamydia or gonorrhea. That's  
12 important to know. We may not even be treating a fourth  
13 of the people.

14           The study I want to talk about is -- these are  
15 two studies. You now have looked at a -- very  
16 clinically apparent cases of PID that we know is kind of  
17 the classic, but they're very subjective on how you do  
18 it. Then I took you into the subclinical. We see there  
19 that we're missing at least 25 percent of cases -- or I  
20 shouldn't say that. But one in four women that have  
21 chlamydia or gonorrhea have a PID that's not clinically  
22 apparent. But then we have to take a look at what if we  
23 take a step back further. And we took a look at  
24 population studies around PID and what do they show.  
25 I'll go through the two that we can compare and

1 contrast.

2                   One, I think, is a classic study by Scholes,  
3 (phonetic) and that had to do with the Puget Sound HMOs  
4 up in the Seattle area. The other is the study that was  
5 already mentioned -- really the Army HMO compared to the  
6 population northwest HMO, Puget Sound. So the targets  
7 were young women between the ages of 15 and 24 in most  
8 of those studies. The outcome that they could actually  
9 measure in the study -- they had options to look at  
10 hospital and outpatient -- electronic and paper records  
11 for the codes for PID. The Army study did not have that  
12 available. It was retrospective. They did not have  
13 that available to them. They could only use the  
14 hospital code. The design of the Scholes was a  
15 randomized, controlled trial. It was -- those women who  
16 were screened, they were randomized to being screened.

17                   The Clark study was somewhat of a convenient  
18 sample, which was a bias. Because of what they had --  
19 it was a good study for what they had. They looked at  
20 women that were screened and not screened. But it  
21 wasn't planned. They knew who was screened and not  
22 because it was a subset they were studying. The methods  
23 they could use for Scholes or the questionnaire chart  
24 review -- they had electronic data. And for Clark they  
25 had the hospital code on the electronic data only, did

1 not have any chart review verification. This study from  
2 Scholes actually went back and verified some of the  
3 positive cases by chart review. The results then were  
4 one year after being screened and treated or not being  
5 screened. They took a look at PID rates, and remember  
6 how they were looking at it.

7           One group was looking at inpatient/outpatient.  
8 The other group was inpatient only. What they found is  
9 a decrease in the PID rate among those screened in the  
10 randomized control trial, which is a stronger study. As  
11 was mentioned, Clark found an increase in  
12 hospitalization for any reason. Again, there was no  
13 chart review, so we don't know what that meant. It's  
14 kind of interesting that even in that study they had a  
15 less of a chance to be controlled. There was a  
16 significant finding. The limits then that the  
17 tests were used -- originally the Scholes study were a  
18 little bit less sensitive. But the fact that you found  
19 something very significant even makes them more  
20 important because you found something, and your tests  
21 aren't even as good.

22           So, again, in summary, the old  
23 cost-effectiveness-type studies -- because now you have  
24 to then march out and say, What about  
25 cost-effectiveness? Doing preventive care is never cost

1 savings. You have to put money out no matter what. We  
2 could look at that. Many of the old studies were flawed  
3 data, that PID is largely subjective and not an  
4 objective diagnosis at all, and that populations and  
5 definitions of PID vary. Most are based on inpatient  
6 codes for PID which are inaccurate and don't include  
7 outpatient codes. As I mentioned, a lot of what is  
8 done -- you take the original old studies out of  
9 Sweden -- they were only doing cultures at that point,  
10 which are probably one-third of the people who were even  
11 picked up by culture. You looked in there with scopes,  
12 and you had trained GYN do laparoscopy, they were doing  
13 exams and -- in a very controlled study like that. They  
14 only got it right about 60 percent of the time. So they  
15 were missing it 40 percent of the time in very  
16 well-trained control studies. You can imagine what  
17 happens when an individual who is taking a look at a  
18 woman in an Army base somewhere who is -- may only have  
19 one or two years of training, and you can imagine how  
20 many mistakes are made in that situation. Most, as I  
21 mentioned, were based on the inpatient.

22           Most PID is subclinical, and it's probably  
23 missed and can lead to severe sequelae. So you take a  
24 look at cost-effectiveness. One of the things we'll  
25 look at -- I don't know if I included it or

1 not -- probably most of the costs aren't actually  
2 incurred between one and three years after PID. These  
3 don't necessarily happen as civilians later on in ten to  
4 20 years down the line. We don't know because no one  
5 has ever carefully looked at the data. If you screen or  
6 treat, you could get rid of a lot of expense of  
7 outcomes. They may be, quote, rare, but the cost is so  
8 high that you could probably get rid of them by  
9 screening right off the bat. So that's what's happening  
10 here. This was a study that was just published. It's  
11 excellent. I recommend that people that are interested  
12 read it. It's the best study there is on  
13 cost-effectiveness. And we hope to do the same thing  
14 with military data as soon as we get some colleagues to  
15 help us do it, and we can do the same study with some  
16 help.

17           So the objective is that we assessed  
18 cost-effectiveness based on CDC screening guidelines on  
19 who should be screened, young women, basically 15 to 24.  
20 The methods were a state transitioned simulated lifetime  
21 cost, which is state of the art for cost-effectiveness.  
22 The population where sexually active 15 to 29 year olds  
23 -- they extended this, and I'll show you how they did  
24 this -- out of 100,000 women who are sexually active  
25 population base, and then they separated it out into

1 groups -- 15 to 19, 20 to 24, 15 to 29 -- and they  
2 looked at four different strategies. So what ifs.  
3 Here's what ifs. What if we didn't do any screening,  
4 whether they were recruits or active duty? What would  
5 happen if we did annual screening of all women? That's  
6 the current recommendation from the CDC actually. What  
7 if we did annual, and then we followed up with repeat  
8 screening in the high risk group once -- every three to  
9 six months or so? That's what the current CDC is  
10 recommending actually. And then the fourth is: What if  
11 we did annual screening, and then we repeated it every  
12 six months? In addition, we would also retest if there  
13 was any history of positive chlamydia. So that was kind  
14 of an all-inclusive group.

15           So the most -- what they first found is that  
16 chlamydia screening would prevent between 11 and 42  
17 percent of the sequelae depending -- you know  
18 type -- the equation on No. 2, 3, or 4 of the  
19 population; that annual screening of 15 to 29 year olds  
20 plus rescreening every six months was the most  
21 cost-effective; and using more modern data on sequelae  
22 and costs and so forth. And the measurement they use is  
23 always called a Kaly. And then -- it's very  
24 cost-effective using that because they put in a lot of  
25 more modern measures into this. What's interesting is

1 they used a 6 percent. They said, Well, the average in  
2 the United States is about 6 percent chlamydia rate, the  
3 military we're finding 8 to 12 to 14 percent chlamydia.  
4 So you can imagine how much more cost-effective it would  
5 be for the military to screen women.

6 This is one of the things we try to prevent,  
7 the Fitz-Hugh-Curtis. This is on laparoscopy, seeing  
8 these violin-like strings between liver capsule and  
9 other pelvic organs.

10 So I'd like to do a word about STI prevention  
11 among military women and where we are, the state of the  
12 art currently. It's really an evaluation of the  
13 cognitive behavioral group randomized controlled  
14 intervention study to prevent sexually transmitted  
15 infections and unintended pregnancies in young women.  
16 It's online currently and will come out in paper form in  
17 2005.

18 So the -- the focus intervention is on the  
19 choices you make that will affect your future. That is  
20 the intervention group that was done in the Marine women  
21 recruits. These are colleagues, both military side and  
22 civilian side. The objective's really to evaluate,  
23 first of all, could we do this in the military setting  
24 with recruits that are so busy? Could we do a cognitive  
25 behavioral intervention? Because it shows that if you

1 do so many hours, if you do in multi-level, and do so  
2 many things at once, it is the biggest impact you could  
3 have on behavior. And we do screening and treatment as  
4 well for infections. And reduce the risk of HIV, STDs,  
5 nonplanned pregnancies in young women throughout the  
6 U.S. who were entering recruit training in the Marines  
7 at Parris Island. So we had 2,157 Marine women during a  
8 12-month period that entered recruit training and  
9 finished the program.

10           The methods were randomized control trial of  
11 eight hours of interactive didactic, skills building,  
12 and STI screening during recruit training; that the  
13 groups would enter intervention group. And when they  
14 were randomized into intervention group, focus, or  
15 controlled fitness, which was also an eight-hour  
16 preventive health around fitness and nutrition, the  
17 results, which was approximately 12 months after we  
18 began -- when these women were on active duty for almost  
19 12 months, there was an increase in STIs, and unintended  
20 pregnancies was greater in the control group than it was  
21 in our study group. The other thing that is actually  
22 embargoed was that the acquisition rate during the  
23 first 12 months was greater than 10 percent. So this  
24 was a cohort of women that were originally screened with  
25 urine, vaginal swabs, and cervical swabs, had a rate of

1 approximately 14 percent of chlamydia at recruit  
2 training, were then treated -- we got it all before they  
3 left and went on to other things -- and approximately 12  
4 months later, we tracked them, and we restudied them,  
5 and if we found -- these are using -- found a rate of  
6 greater than 10 percent infection rate again. And it's  
7 not the same women. There is some crossover.

8           So the conclusion was that a cognitive  
9 behavioral intervention was effective to decrease STIs.  
10 And as a side, which will be published, we found an  
11 incredible acquisition rate during that first year. So,  
12 again, it addresses these issues of recruit training and  
13 what do you do during that first year to active duty.

14           So what does all this mean to the military?  
15 We know that military women -- the chlamydia rate's very  
16 high. It's well above the average family planning  
17 clinic. It's much more like an inner city-type or very  
18 rural population, which, of course, is where these women  
19 come from. In recruits it's about 9 to 11 percent in  
20 all the studies that we've done. Active duty, we know  
21 it's about 7 percent in the Navy. And as I mentioned,  
22 we have greater than 10 percent in our acquisition.  
23 Most chlamydia infections have no symptoms, and most  
24 PID has no symptoms, and the costs are incurred within  
25 the first one to three years, which would be during

1 first tour of duty.

2           We know that chlamydia screening is pretty  
3 easy to do. You can do urine based on the conventional  
4 -- doing self-swabs, to be honest. That's what we did  
5 in our original Marine study because they're more  
6 stable. You can put them in an envelope and mail them,  
7 and you don't have an extra dirty step to do. It is  
8 already approved by the FDA, by some of the tests, that  
9 chlamydia screening is cost-effective. But I have to  
10 question, being in the field and working with the  
11 CDC and military, will the lack of screening prove to be  
12 a threat to readiness with sequelae and PID? We don't  
13 know that. We have to look at that. And will women  
14 veterans hold the military or the government or all of  
15 us responsible in the future for providing less than  
16 standard of care for chlamydia screening? The standard  
17 of care currently is you screen all sexually active  
18 women between the ages of 15 to 24. And now, actually,  
19 it may be extended. There's been a call on a recent  
20 paper -- it could go up to 29 because we're seeing more  
21 chlamydia now in older women than we did before.

22           Chlamydia is the most common bacterial  
23 infection in women. Recruits age parallel to peak age  
24 for chlamydia. We know that, especially that first tour  
25 of duty as well. We know that high STI rates are given

1 at risk for PID and severe sequelae, that chlamydia  
2 likely increases risk for HIV acquisition. There are  
3 definitely trends and significant findings now that  
4 women that have infections, such as chlamydia, such as  
5 gonorrhea, bacterial -- but, actually, because of the  
6 inflammatory response breaking down the natural  
7 protection, there are independent findings that  
8 independently things like chlamydia actually increase  
9 HIV transmission rate, given everything else equal.  
10 Chlamydia also seems to be associated with increase of  
11 HPV infection. And of that, we know there's a subset  
12 that leads to cervical cancer. Untreated chlamydia  
13 persists -- it's transmitted not only to other men and  
14 then to other women but it's also to their neonatal  
15 infections, pneumonias, and so forth. Untreated  
16 PID develops in about 10 percent up to a third of women  
17 who have chlamydia and that greater than 60 percent or  
18 more is subclinical or has no symptoms at all.

19           So what's the bottom line? Well, we know  
20 there are well designed cost-effectiveness studies that  
21 show it's cost-effective. It's cost-effective to screen  
22 women for chlamydia. All national guidelines, including  
23 the AFEB, have recommended screening for women.  
24 Military women recruits enter with a high STI burden and  
25 continue acquisition after a year. PID must be

1 overdiagnosed and overtreated because it's difficult to  
2 diagnose. You just have to overcall it and treat it to  
3 avoid getting PID. You need to do the right thing by  
4 women's health; and you need to consider screening men,  
5 since most military women have sex with military men;  
6 and we need to take a look at the cost-effectiveness of  
7 that.

8           So the recommendations from our original  
9 editorial of "Combating Chlamydia, Why Aren't We Winning  
10 the War" are to develop, implement, and track a  
11 comprehensive Tri-Service chlamydia control program,  
12 including primary and secondary prevention intervention  
13 to decrease chlamydia acquisition, transmission, and  
14 morbidity; to immediately implement universal screening  
15 for all female recruits using urine-based chlamydia  
16 testing; and to consider universal screening for active  
17 duty women as well at least annually; address the gap  
18 between the CDC and DoD in practice and policy regarding  
19 chlamydia screening; evaluate the need for screening  
20 males and recruits as well as active duty males; and  
21 develop a comprehensive Tri-Service surveillance system  
22 with data sharing among the military organizations and  
23 national local Public Health Departments to really  
24 target the needed services and measure the outcomes of  
25 programs designed to control chlamydia; and support and

1 develop and evaluate epidemiological and behavioral  
2 cognitive intervention designed to prevent acquisition.  
3 So really, primary intervention of STIs, especially  
4 chlamydia and HIV.

5           So after years of fitting in, maybe it's time  
6 to stand out. So do the right thing. Thank you very  
7 much.

8           DR. OSTROFF: Thanks very much. As with the  
9 previous presentation, can I ask if there are any points  
10 of clarification before we move on to the third  
11 presenter? If not, the other Dr. Gaydos.

12           DR. GAYDOS: Dr. Ostroff, Colonel Gibson,  
13 Members of the Board of the AFEB, and ladies and  
14 gentlemen, thank you. It's a pleasure to be here today.  
15 Thank you for having me. Today I'm going to discuss  
16 chlamydia in men, what we know, and what we don't know.  
17 Dr. Shafer has alluded to some of this. My talk today  
18 will have background, objectives, talk about chlamydia  
19 studies in the male that have been done in the military,  
20 chlamydia studies in males have been done in civilian  
21 institutions, and talk about the cost-effectiveness of  
22 the few studies that have been done for screening in  
23 males. And we'll allude to some of the things that we  
24 don't know for chlamydia in males.

25           So now, chlamydia infections are common. But

1 there are no official recommendations for who to screen  
2 as far as men go. Right now we only screen if men come  
3 into a clinic with symptoms of urethritis. Dr. McGee  
4 has published a study from Fort Bragg that has shown  
5 that of men that present with urethritis 35 percent of  
6 them are positive for chlamydia. But as I said, there  
7 are no official recommendations.

8           So many reasons exist for this. Most  
9 appparent is limited resources. We need information to  
10 guide programs, both in the civilian and in military  
11 installations. We need to know the local prevalence.

12           There is some information that's been  
13 published that has associated male chlamydia infections  
14 with infertility. We know there is a risk of  
15 epididymitis. About 3 to 5 percent of men who have  
16 chlamydia infections will go on to develop epididymitis.  
17 Two studies published showing that antibody to chlamydia  
18 in men is associated with infertility. This last one in  
19 human reproduction was just published, and it showed  
20 that if you had an IGG antibody in a male partner of an  
21 infertile couple, this was correlated with reduced  
22 likelihood of achieving pregnancies.

23           So why do we consider treating men? We would  
24 like to treat asymptomatic infection. Here, I think, we  
25 need to make the distinction between screening and

1 testing. Testing usually has the connotation that if a  
2 man comes into a clinic with symptoms he's going to get  
3 screened or he's going to get tested. So testing is for  
4 people that come in that have symptoms. Screening is  
5 doing sort of outreach and going outside of the clinic  
6 and doing a test on someone just to do the test to find  
7 out if they're infected because they may not have  
8 symptoms. As has been pointed out previously, about 90  
9 percent of women that have chlamydia have no symptoms.  
10 And about 50 to 70 percent of men that have chlamydia,  
11 don't have symptoms. So we like to treat asymptomatic  
12 infection. We'd like to reduce transmission to female  
13 partners, and we'd like to reduce the burden of  
14 chlamydia in men. However, the primary reason to screen  
15 men is to reduce the burden of the sequelae that occur  
16 in women.

17 I'm going to try to share the prevalence of  
18 chlamydia in males in the military and civilians and  
19 then identify some of our gaps. Hopefully, you will be  
20 able to know this at the end of the presentation.

21 Brodine has already been mentioned, has  
22 published two military studies that have been done in  
23 males in the Marines and the Navy, and the prevalence  
24 here range from 3.4 to 5.2 percent.

25 As part of our female chlamydia study at Fort

1 Jackson, we studied men for a couple of weeks, and we  
2 screened about 2,000 Army recruits reporting for basic  
3 training, and about 5.3 percent of them were chlamydia  
4 positive. Associated in a multi-varied analysis with  
5 risk of chlamydia infection was black race, a new  
6 partner, and a history of trichomonas infection.

7           Then there was one study that was published  
8 recently in ROTC cadets at Washington State, and at that  
9 point they found a 2.5 percent prevalence in college  
10 ROTC cadets. We recently published a study that we did  
11 with some funding from the CHPPM called the Health  
12 Promotion Initiative. This was published this past  
13 July. And we studied about 4,000 men at Fort Jackson,  
14 incoming recruits, within three days of them presenting  
15 to the Army for training. We found a prevalence of 4.7  
16 percent. These are all urine studies. You cannot do  
17 anything but amplified testing in urine. So you have to  
18 use the best test that's available when you're doing  
19 urine. If you're doing a cervical sample, you can do  
20 some of the DNA probe tests, which are only about 60  
21 percent sensitive. These are what are used mostly  
22 throughout the United States. But the state of the art  
23 test that is recommended by CDC is the amplified test  
24 and can be done on swabs and on urine. So associated  
25 with risk of infection in this study in a multi-varied

1 analysis was age less than 20 or a little higher odds  
2 ratio in age about 20 to 24, again, black race, Hispanic  
3 ethnicity, and a multiple sex partner.

4 I want to point out that during this whole  
5 study we had a questionnaire and only about .5 percent  
6 of the men alluded to any kind of symptomatology at all.  
7 And of these -- there's only about 17 men, and only one  
8 was chlamydia positive. So again, this emphasizes the  
9 fact that chlamydia is asymptomatic in men as much as it  
10 is in women. And these were pretty risky boys. When we  
11 did questionnaires on the women, about 92 percent  
12 reported being sexually active. In this cohort 92.2  
13 percent reported that they had had sex, 27 percent had  
14 had two or more partners in the last 90 days, 47 percent  
15 answered they hadn't used a condom at last sex, and  
16 about 25 percent reported that they used a condom every  
17 time in the last seven acts of intercourse. So again, a  
18 very risky population that we're dealing with coming  
19 into the military here.

20 So this is a bar graph showing some of the  
21 risk factors. Again, the rate was higher in a higher  
22 odds ratio associated with being age 20 to 24 and also a  
23 much higher prevalence in the black population but a  
24 significant prevalence in whites and Hispanics.

25 We also geomapped these like we did the women

1 when they came in from their home state of record. And,  
2 again, these recruits brought their chlamydia with them  
3 from their home state because they were tested within  
4 three days of joining the military. You can see in the  
5 Midwest similarly to -- in the Northwest similarly to  
6 what the women studies showed, the prevalence is the  
7 lowest, 2.5 percent. The prevalence in the south is the  
8 highest at about 6.0 percent. A significant proportion  
9 here, 4.8 in the Midwest; and 3.7 in the Northeast.

10 Now we're going to turn -- that's really about  
11 all we know about military studies. We're going to turn  
12 to some civilian studies for comparison sake. A very  
13 large study was published from the Region 10 area of the  
14 United States, the Pacific Northwest out of  
15 Jeannie Morotso's (phonetic) group in Seattle. They  
16 screened 43,000 people and the infertility initiative  
17 screening and STD clinics and found they had a  
18 prevalence of about 10 percent. This prevalence is  
19 probably higher, even though they were listed as  
20 asymptomatic men, just because they were attending an  
21 STD clinic. But, again, they stated they were  
22 asymptomatic, and only about a fourth of them had any  
23 signs of urethritis. So again, pointed to the  
24 asymptomatic nature of chlamydia.

25 I'm going to tell you a little bit about a

1 CDC funded study that I've been a part of, a  
2 multi-center study that we have just finished. This is  
3 done in four cities across the United States. We  
4 screened about 23,000 primarily asymptomatic men. Some  
5 sites had some symptomatic men ages 15 to 44.

6           These studies were done in Baltimore, where I  
7 was involved, Denver, San Francisco, and Seattle.  
8 Consisted of two parts -- a demonstration study looking  
9 for prevalence, and the men who were infected attempted  
10 to be enrolled as volunteers in a longitudinal study to  
11 look at the possibility of reinfection and how often we  
12 might see men being reinfected once they were identified  
13 with chlamydia infection and were treated. These were  
14 only done in Baltimore, Denver, and San Francisco. So  
15 we tested about 3,000 men in Baltimore, 3,500 in Denver,  
16 16,000 in San Francisco, and only about 700 in Seattle.  
17 So you can see our prevalence overall was about 7  
18 percent; 12 percent in Baltimore; 10 percent in Denver;  
19 5 percent in San Francisco; and 1 percent in Seattle,  
20 pretty much reflecting what we saw when we did our  
21 asymptomatic male urine study at Fort Jackson, that  
22 geography is very definitely important for determining  
23 what the prevalence is. And if you look at the  
24 CDC ranks when they rank cities with populations with  
25 greater than 200,000 people, you can see Baltimore ranks

1 No. 3; No. 1 being the highest, and Seattle ranks 59th  
2 in order of cities. You can see the prevalence pretty  
3 much mirror images what the CDC national reporting  
4 standards are for chlamydia. Again, taking these 23,000  
5 men, breaking them down by age, you can see that the  
6 highest prevalence, about 8 percent, was in those age 20  
7 to 24. This is sort of different from women because  
8 women -- the highest prevalence is the younger age  
9 group. But whether this a reflection -- people often  
10 hypothesize that men may be having sex with younger  
11 women and older men, younger women. So we have a little  
12 bit of a delay here in the positivity rate. So these  
13 were the different venues. And as much as geography is  
14 important in determining prevalence in chlamydia, the  
15 venue is also. You can see here street outreach, and  
16 particularly in Denver -- has a high prevalence of 10  
17 percent. College clinics only about 8 percent. These  
18 were high schools, 15 percent -- or I'm sorry -- 5  
19 percent in San Francisco whereas in Baltimore in high  
20 schools we have a prevalence rate of about 9 percent.  
21 Adolescent primary care in Baltimore, a very high  
22 prevalence. But as I said, this group here probably  
23 includes a lot of symptomatic men. Adult detention in  
24 Denver is 14 percent, in Baltimore 9 percent, and  
25 juvenile detention 9 percent in Denver, and 3 percent in

1 San Francisco.

2           So that's about it for the demonstration  
3 project. But when we looked at the repeat infection and  
4 realizing now much lower numbers because we only were  
5 able to enroll those men who were positive and then who  
6 volunteered to be in the one-year longitudinal follow-up  
7 study. Overall, our reinfection rate is very similar to  
8 what we see in women, and all the published studies, 12  
9 percent. Ranged from a high of 28 percent in the  
10 adolescent clinic in Baltimore to a low of 5 percent in  
11 the school clinic. The adolescent clinics in Denver had  
12 a repeat infection rate of about 28 percent, San  
13 Francisco 12. But, overall, about 12 percent  
14 reinfection rate. This is highly comparable to what we  
15 see in women.

16           I guess the cost-effectiveness slides were  
17 deleted. As a result of this study, there were -- there  
18 has been a cost-effectiveness study that was done in  
19 males, and this has been very thoroughly done, looking  
20 at a high cost for PID and a low cost for PID, has been  
21 looking at whether or not there's partner notification  
22 or no partner notification in the studies. Basically,  
23 this study shows that unless the prevalence is higher in  
24 men than in women, which we are not seeing, that's when  
25 screening men becomes cost-effective to prevent disease

1 in women. So as a result of these line graphs that I  
2 had in the presentation -- but I guess they were removed  
3 -- all things being equal, the prevalence in men has to  
4 be 6 percent versus 1 percent for a program to be  
5 cost-effective, so to screen men before you screen  
6 women. So the bottom line is that it's more  
7 cost-effective to screen women than it is to screen men  
8 unless you have a population where the prevalence is  
9 higher in men. If you had a prevalence of women of 4  
10 percent at a low cost of PID, you would have to have a  
11 prevalence of 15 percent to make it cost-effective as  
12 opposed to a high cost, hospitalized cost, for PID you  
13 would have to have a prevalence of 6.5 in the men.

14           So screening men can benefit women by reducing  
15 the number of infectious men. As we know, chlamydia is  
16 transmitted between men and women with an efficiency of  
17 about 70 percent per sex act. If we screen men, we can  
18 lead to the treatment of asymptomatic women by partner  
19 notification. So if we have an infected man, we can  
20 find a woman who is his partner and she can be treated.  
21 Screening can be cost-effective -- many of the studies  
22 have shown conflicting results, and there will be more  
23 to come for sure. Right now it seems it's only  
24 cost-effective from a societal point of view if the  
25 prevalence among the unscreened women -- can be screened

1 -- is lower than the prevalence among the men that can  
2 be screened. Everything else being equal.

3           So what we know is CT infection is common  
4 among males. It varies by geography, by city, and by  
5 state. Young age and specific areas are associated with  
6 a higher prevalence of male chlamydia infection. Repeat  
7 infections are very similar to females, about 12  
8 percent. Screening males -- because it's easy to  
9 collect a urine sample and you don't have to get a  
10 urethral sample now, it's highly accepted by both  
11 providers and the patients, and we know that male  
12 screening for CT can be cost-effective in certain  
13 instances.

14           What we need to know before you make a  
15 decision whether or not to screen males is what the  
16 prevalence is by the geography or the area that the men  
17 are coming from. You also need to know whether or not  
18 the females are being screened. Screening men will be  
19 more effective and more cost-effective if women aren't  
20 being screened, will be less so if a program is offering  
21 screening to females. You need to know what tests are  
22 available and how much the test is going to cost. Right  
23 now for huge contracts, screening using an amplified  
24 test can brought down to about 10 or \$12. Whereas if  
25 you have a single clinic using amplified testing and

1 sending their test to a commercial lab -- is going to  
2 cost around \$100 a test. But large public health  
3 contracts can drive the cost down. You need to know  
4 whether or not you are going to have to set up a new  
5 screening program or if you can expand some screening  
6 that is already going on. And you need to know the risk  
7 characteristics of your population.

8           There are many variables that are going to  
9 influence the best use of the dollar to prevent  
10 infertility. The bottom line is screen the women first.  
11 We have to use amplified testing if you're going to use  
12 urine. You need to know whether or not you are going to  
13 have to put money into a new program. Or if you can  
14 just expand an existing program, it's going to be  
15 cheaper. You have to have support for screening males  
16 before it will be successful, and you also need to make  
17 sure you have adequate coverage for females and that  
18 you're screening the females first. You want to do it  
19 where the prevalence is high. The military certainly  
20 meets this requirement. It's easier to do it in venues  
21 where many symptomatic men are already being evaluated.

22           So in summary, the prevalence of chlamydia in  
23 asymptomatic males is approximately 5 percent in our  
24 military studies. There are many variations in  
25 prevalence depending on each individual study that you

1 look at in civilian sites. Women should be screened  
2 before men, and screening men will be able to prevent  
3 reinfection in women as well as the sequelae in women.  
4 So many costs and logistical factors will effect the  
5 decision to screen men. But I think, as Dr. Shafer has  
6 pointed out, the right thing to do is to screen the  
7 women. And we need a lot more information before we can  
8 decide whether it's cost-effective to screen men. If  
9 you want to do the right thing and prevent women from  
10 getting reinfected regardless of the cost, then it's  
11 prudent and ethical to also screen men. Thank you.

12 DR. OSTROFF: Are there any questions?

13 DR. ATKINS: One question. You had a slide  
14 about cost-equivalence of men and women. Was that cost  
15 -- or equivalent cost or equivalent cost-effectiveness?

16 DR. GAYDOS: Cost-effectiveness.

17 DR. ATKINS: And one issue that seems to  
18 really affect the male versus female screening is how  
19 effective the partner notification is. Do we -- so my  
20 question is: Who is responsible for partner  
21 notification in the military, and do we know anything  
22 about the different way men and women deal with  
23 informing their partners and the likelihood that their  
24 partners get treated?

25 DR. GAYDOS: In the military in recruit

1 studies, since men are leaving home and coming into the  
2 military or women are leaving home and coming into the  
3 military, no partner notification was done. They were  
4 asked to tell their partners. But if someone is coming  
5 to Fort Jackson from Hawaii, it's very difficult to do  
6 partner notification. However, in the military for the  
7 active duty force, I believe, at least in the Army, that  
8 it's a preventive medicine responsibility and that when  
9 men or women are found to have a sexually transmitted  
10 disease they are sent to -- for counseling to a  
11 preventive medicine clinic. I can't speak for the other  
12 services, but that's what used to happen at Fort  
13 Jackson. So one of the wonderful things that has been  
14 tried with great success in California is patient  
15 delivered therapy. And when a patient comes in, is  
16 treated for chlamydia infection, it's actually okay with  
17 the state law now in California to give the therapy to  
18 the partner to dispense and take home to their partner.  
19 This could be done in the military because you don't  
20 have any state laws to get around. We tried it in  
21 Baltimore but couldn't get around the state laws. Yes,  
22 you're quite right in that the high reinfection rates  
23 that we see are most often reflected because of the fact  
24 that the women either get a new partner or the men get a  
25 new partner or they go back to their old partner who

1 never got treated in the first place. So that's a very  
2 important component.

3 DR. JOEL GAYDOS: I think you're asking the  
4 question about what is happening now as far as practice  
5 in the military. I think there are two important  
6 points. One is that in one case anecdotally and in  
7 another case was supposedly based on data. The extent  
8 of what is going on with regard to STDs and the  
9 diagnosis treatment and management of these is -- in the  
10 military is probably a situation that's not going to be  
11 probably defined unless the military community and the  
12 surrounding civilian community look at the whole  
13 situation because we do have situations where some of  
14 the communities have said that they feel that they are  
15 taking care of a lot of military members. With regard  
16 to military community, I have not seen any information  
17 at all to indicate how effective the military community  
18 has been in identifying contacts and following up on  
19 contacts.

20 DR. GARDNER: Just some follow-up on this.  
21 I'm stuck on these numbers. If a single heterosexual  
22 contact is 70 percent efficient in transmitting  
23 chlamydia, I'm surprised that the reinfection rate is as  
24 low as it is. It was 12 percent, I guess. I assume  
25 that sexual activity hasn't changed dramatically, but

1 that's another question. So I'm trying to think why  
2 shouldn't that 12 percent be much higher particularly if  
3 they're going back to the untreated sex partner. And I  
4 guess it may be -- if you're doing better than we can  
5 document in terms of getting the undocumented treatment  
6 to the sex partners, I guess that might explain it. But  
7 the 70 percent efficiency was higher than I was  
8 thinking. I come away with an even stronger sense that  
9 one can't really approach this problem as a uni-sexual  
10 problem. You have to go after both sides of this if  
11 you're going to make a dent. Perhaps the military is a  
12 better place to do that than other settings.

13 DR. GAYDOS: Partner notification is very  
14 important. And the studies that come up with the 12  
15 percent, these are very regimented studies where women  
16 get documented to get treated or men get documented, and  
17 then they're asked to come back. They don't all come  
18 back. So of the ones that come back, probably the  
19 reinfection rate is much higher. But the studies are  
20 where you actually have hard data where you can get them  
21 to come back -- and it's not easy to get them to come  
22 back or to find their partners. These are what the data  
23 showed. But we can guess that probably the reinfection  
24 rates are much higher.

25 DR. SHAFER: I'd like to make a couple

1 comments. One is that there are no studies of men that  
2 have taken a look at a population base that didn't enter  
3 a clinic and document what their infection is and do it  
4 in another three, six, nine months. We've done it in  
5 women now in the military. That's the only place we've  
6 had a cohort of women that did not come in for care who  
7 were coming into the military. We documented they had a  
8 high rate to start with, we treated them, and we  
9 documented they had a high rate in a year. The same  
10 study can be done -- we hope to do it actually, but has  
11 not been done yet in the military.

12           The second thing that needs to be talked about  
13 with men, which we can't do with women, you know, is the  
14 original studies for men are a piece of cake to deal  
15 with. All you have to do is have them pee. You can  
16 even go back to the old dipstick with just looking for  
17 white cells. It's 50 percent good. So we missed a few  
18 percent but we get 50 percent. These tests cost  
19 17 cents a strip. You dip it in urine. A guy can even  
20 pee on it. If it's positive, which is probably going to  
21 happen in this population, you assume in 10 percent of  
22 the people, then for those individuals you go on to a  
23 more elaborate test. That would be very inexpensive. I  
24 guarantee that if you redo your numbers it will be  
25 cost-effective because it's so cheap to do it this way.

1 So I recommend where you have -- we can't do it always  
2 in civilian populations. But when you get a whole bunch  
3 of men, they get up in the morning, you want that first  
4 urine, they all have their little stick, and they pee on  
5 it. And if it's positive, then they get the urine sent  
6 off, and it gets tested. That's the kind of analysis  
7 and simple stuff -- we don't have to be super  
8 sophisticated -- that we go back and do.

9 We had done those studies a long time ago in  
10 young boys in detention. They'd let me do that. Once I  
11 showed them the dipstick, then at that point I actually  
12 had to use a swab, and they'd even let me do that. So I  
13 think that I would like to see what you did actually  
14 redone.

15 DR. GAYDOS: We actually did do an LE test on  
16 the subsection -- subset of these men. You're right.  
17 It was about 50 percent sensitive. But it's cheap if  
18 you want to screen 93,000 men, which is about what the  
19 military brings every year. You're going to screen them  
20 for pennies. And if they have pus, then they go on to  
21 have a more expensive test to find out whether or not  
22 they have chlamydia.

23 DR. OSTROFF: Can I ask the question, stepping  
24 one step back from partner treatment, are we quite  
25 certain that currently the -- when females are screened

1 in the military that they're appropriately treated?

2 DR. GAYDOS: In our study we documented that  
3 100 percent of women were treated at Fort Jackson. We  
4 had two that were discharged from the military for  
5 PID, which was an exclusionary diagnosis during basic  
6 training, and they were sent certified letters.

7 DR. OSTROFF: Do we know for a fact that  
8 across the services there is adequate treatment?

9 DR. SHAFER: I can comment on our study. Of  
10 the 2,000 Marine women recruits, they were screened, and  
11 then we did not -- we weren't in charge of treating  
12 them. The test was forwarded to the appropriate person.  
13 What we found is that, again, you had a very high rate  
14 of appropriate treatment. There were a few people that  
15 fall through the cracks between recruitment, they go on  
16 leave, they have different things. So there were a few  
17 that did not get it, but that was probably -- that was  
18 about 5 percent or so. Those individuals we had to kick  
19 forward and try to go ahead and go after them and help  
20 move that forward. A vast majority were treated. It  
21 also depends on the turnaround time. How long does it  
22 take to get your test back, and are the women still  
23 there?

24 DR. JOEL GAYDOS: I can't address your  
25 question specifically. But in your references there is

1 a study there by Vaughn, which was done at a very large  
2 military treatment facility, and they looked at positive  
3 test for chlamydia. And then they went back to see how  
4 many of those were reported and what percentage of those  
5 women had tests for other STDs. I think the percentage  
6 that had them report it was something like 14 percent.  
7 And I believe that it was either 30 percent who had been  
8 tested for other STDs or 30 percent that had not been  
9 tested. But there was a very large percentage of those  
10 women who were not followed up with tests for other  
11 STDs.

12 DR. GAYDOS: It's a policy in the Army that if  
13 women tested positive in our study for chlamydia that  
14 they were brought into the clinic for their appointment  
15 where they were given their treatment, and they were  
16 also screened for all of the other STDs at the same  
17 time. So they got a complete STD work-up with the  
18 prompting of the one single positive test.

19 DR. BROWN: I had a question for Dr. Shafer.  
20 I was unclear about something. You may have addressed  
21 it, and I just missed it. But you talked about the very  
22 serious long-term consequences of PID -- symptomatic  
23 PID if left untreated, and you talked about  
24 asymptomatic. It wasn't clear to me what the long-term  
25 consequences of asymptomatic PID was. So do you see the

1 same outcomes?

2 DR. SCHAFER: Well, probably is the same.  
3 But the main thing is infertility. No one has followed  
4 the cohort long enough to say we're just finding  
5 subclinical now. But we have to go back to the old data  
6 of, say, 10, 20 years ago where they took a look at  
7 tubal infertility, they found chlamydia antibodies, and  
8 in certain French studies they found chlamydia in women  
9 that had tubal infertility. And it was a significantly  
10 higher rate of evidence of prior chlamydia infection in  
11 women with tubal infertility who had never had symptoms.  
12 It's interesting that what we do know -- and this is  
13 brand new data -- showing that in subclinical PID that  
14 the inflammation may be a little less. We're not sure  
15 yet. So does that mean there will be a little less  
16 tubal infertility? We don't know. We know the  
17 infertility's here, we know there was evidence of  
18 chlamydia, and we know these women are in trouble.

19 DR. BROWN: It could still lead to significant  
20 morbidity.

21 The second -- when we were at Lackland Air  
22 Base looking at health procedures that were used for new  
23 recruits in the Air Force just a few months ago, my  
24 impression was they're using prophylactic -- they're  
25 using antibiotics to prevent -- I forget what the

1 disease was -- for streptococcus. Would that effect  
2 chlamydia rates or --

3 DR. GAYDOS: No. We tried in the women study  
4 to do a mass therapy option where one would be given  
5 mass therapy using azithromycin, which would treat their  
6 strep and their chlamydia and their gonorrhea and their  
7 chlamydia -- and we were successful in getting this  
8 through the Hopkins IRB, but the Army IRB said no, even  
9 though the Army has a long history of prophylaxis or  
10 streptococci.

11 COL. COX: Returning to Dr. Shafer's  
12 presentation, I was interested in one of the bullets  
13 about will the lack of screening prove to be a threat to  
14 readiness. And so on behalf of Ms. Embrey, I would like  
15 to briefly address that. By that, did you mean women  
16 who have gone to deployed settings may suffer their  
17 attack and have to be moved out of the theatre and that  
18 would be the cost to readiness?

19 DR. SCHAFER: We don't know because we haven't  
20 looked at all the numbers. But one, obviously, ectopic  
21 pregnancies. And there have been, again, anecdotal  
22 -- of people having to get shipped out of war theater  
23 back to the states. The other that isn't really  
24 measured is amount of either work loss or visits or  
25 hospitalizations around chronic pelvic pain. We don't

1 know. You look at ectopic pregnancies, chronic pelvic  
2 pain, and infertility. Infertility may or may not be  
3 tested during that, say, three to four years after PID.  
4 But I'm referring to any of those consequences.

5 COL. COX: I certainly think, from the  
6 standpoint of forced health protection, many of the  
7 things you're talking about are more on the in-Garrison  
8 at home side of things. Infertility -- of course, if  
9 the woman is infertile, some senses that might be a  
10 benefit. The real issue would be: Does the individual  
11 have to be pulled out of the theatre? We can move  
12 beyond that. We do have an excellent capture rate of  
13 health event data for people leaving the theatre. Now,  
14 that doesn't address all issues of chlamydia infections,  
15 obviously, because there are things that occur  
16 in-theatre, and people don't have to leave. The ability  
17 to make the diagnosis, though, in-theatre is limited.  
18 So where we run into trouble is we can look at  
19 preliminary diagnoses that are put on the person's  
20 paperwork that gets them on the plane to leave, and it  
21 may be things like abdominal pain. It could be -- and I  
22 rule out ectopic pregnancies -- it might even be  
23 labelled as PID. But, obviously, it's not at the level  
24 of diagnostic standard that we would like. But it would  
25 be along the lines of what Colonel Rubertone presented

1 with the mental health. We can't accurately identify  
2 the cohort of women who leave the theatre for medical  
3 reasons and then compare those with the healthcare  
4 utilization and inpatient/outpatient settings within 30  
5 days of the date that they were moved from the theatre  
6 and see what the final type diagnoses were that showed  
7 up for those individuals. Obviously -- I know it's not  
8 a common thing. We don't commonly see women -- of  
9 course, we don't deploy as many women percentagewise as  
10 there are in Garrison setting anyway. We certainly can  
11 help.

12 DR. SHAFER: We can also take a look on  
13 -- take a look at what is happening, days lost to work,  
14 or whatever, as well due to undiagnosed, you know --

15 MR. PATRICK: Really a great presentation.  
16 Very informative. I want to drill into this partner  
17 delivered therapy a little bit. My whole life was in  
18 student health in California. We were one of the first  
19 student health centers in California to be doing routine  
20 screening and found a 10 to 12 percent rate and  
21 ultimately ended up tipping over into this partner  
22 delivery, which my impression is it's very effective.  
23 These people are really ready to do something. A lot of  
24 these people, whether they are or not, think they're in  
25 a relationship that is going to go on forever, and so

1 they really want to make sure this is going to be taken  
2 care of. It seems to me that that's where a lot of the  
3 money might be here and really moving forward -- very  
4 impressive behavioral cognitive intervention that you  
5 demonstrated here. This notion of how to add partner  
6 delivered component to other types of intervention that  
7 really reach out to get the -- where this infection  
8 occurred, and it's not in the individual --

9 DR. GAYDOS: Screening and treating one sex is  
10 not going to eliminate it. Unless you look at both  
11 sides of the equation, you will not have an appreciative  
12 impact. And partner delivered therapy is inexpensive.  
13 So far I don't believe they've had any severe adverse  
14 events. They've been doing this for about four years.  
15 And for the military it would make a lot of sense to  
16 have partner delivered therapy. I think there is one  
17 other state that has -- Tennessee. There is one other  
18 state.

19 DR. PATRICK: Should that clearly be on the  
20 table when we're thinking about --

21 DR. GAYDOS: I think so. I mean, it is  
22 something that the military could mandate and save a lot  
23 of money. And you wouldn't have to spend the resources  
24 to go look for the partner if you could just give it to  
25 them and say give it to your partner otherwise you'll

1 get reinfected and you'll be right back in here with  
2 positive infections in a couple of months.

3 DR. ATKINS: I want to thank you for this --  
4 all of you -- for this presentation. But I'm struggling  
5 with what our charge is here. I mean, this was the  
6 first -- chlamydia was the first issue I remember when I  
7 joined the Board, which must have been 7 or 8 years ago.  
8 Then we came back to it when there hadn't been any  
9 progress in implementing screening primarily on the Army  
10 side. And I guess what I'm hearing is we haven't made a  
11 whole lot of progress since we looked at this last time.  
12 So my question is: Is the barrier a logistical one in  
13 terms of -- which is what I call it -- sort of being in  
14 terms of getting screening in the basic process, which  
15 is different in the Army than in the Navy? Is there  
16 resources -- is there reluctance to free up the  
17 resources to do that? Because I think that would  
18 help -- one, it would help us guide what our statement  
19 could be -- because you're really preaching to the choir  
20 here in terms of this is the right thing to do  
21 clinically. It's not cost-saving, but it's a reasonable  
22 investment of resources. But I'm not exactly clear on  
23 where the right place to push is. And it also would  
24 guide to the extent you want any advice you want from us  
25 about research. What kind of research would be helpful?

1 If it's a resource issue, then the research ought to  
2 focus on cost and cost-effectiveness. If it's  
3 logistical, then the research ought to look at different  
4 models for doing this.

5 DR. OSTROFF: I'm going to intervene for just  
6 a second because this is part -- I was going to take  
7 over the session and try to bring some closure here. My  
8 recollection was also one of the earlier issues when I  
9 joined the Board -- was that there was a fair amount of  
10 debate around this issue of the wiggleroom about when  
11 to screen and whether or not that screening should be  
12 done exclusively in the recruit setting or whether there  
13 was some -- or sufficient data to say it was  
14 insufficient to do it sometime in the first year of  
15 serving in the military. It was my recollection it was  
16 largely a logistical issue that caused the Board to, at  
17 least, give some flexibility in terms of the timing of  
18 the screening. I don't think it was so much not  
19 necessarily having sufficient data, but there was a lot  
20 of push back that it was simply not going to work to  
21 insist that it be done in the recruit setting. And for  
22 the life of me, I can't remember all the nuances of the  
23 discussion at that time. But it seems to me we now have  
24 a lot more information that tells us that that's the  
25 right thing to do. And clearly, at least, some

1 component of the services have figured out a way to do  
2 this and fulfill that responsibility. And so what I  
3 would -- it's the week after Thanksgiving, but I think  
4 it's time to talk turkey. And, you know, the services  
5 have to give me a good argument at this point as to why  
6 they can't do this the right way.

7 DR. GAYDOS: They're collecting urine anyway  
8 in basic training for pregnancy testing. So it's a  
9 matter of taking the urine that was collected with the  
10 dipstick for pregnancies, sending over here, and sending  
11 it off --

12 DR. OSTROFF: I think, to me, this is an  
13 absolute 100 percent no-brainer.

14 DR. GAYDOS: And waiting one year -- the data  
15 showed that in one year women who are infected when they  
16 come in, 40 percent of them will have PID at the end of  
17 one year for untreated. So the sooner you get them, the  
18 sooner you can be proactive in preventing --

19 DR. OSTROFF: So I guess at this point what I  
20 would like to do -- and Colonel Stanek is more than  
21 welcome to make a comment -- is to actually construct a  
22 little -- it's very helpful to see in one of  
23 Joel's slides that, yes, the Navy and the Marines are  
24 doing this, but the Army and the Air Force aren't. But  
25 I need to construct one grid that says here's what we're

1 currently doing for females, not only in terms of  
2 official screening, but also in follow-up screening,  
3 whether or not there is annual screening going on by  
4 service and what the current policies are and that. And  
5 one of the strong reasons for this particular  
6 presentation or series of presentations -- and I thank  
7 you all for them -- is that we need to standardize this.  
8 The Board has been, you know, preaching over and over  
9 again of the need to standardize approaches in the  
10 military. And unless somebody in the Air Force and the  
11 Army can give me some reason why they can't do what's  
12 being done in the Navy and Marines, my default is that's  
13 the way we ought to do it. And, you know, we ought to  
14 be able to live up to the standards of what is being  
15 done or is being recommended elsewhere, particularly  
16 given the fact that the prevalence rates are so high in  
17 our military population. It's just not acceptable  
18 anymore to say we can't do it. So I'm going to turn it  
19 over to each of my colleagues in the services and say,  
20 Why aren't you doing what you're supposed to be doing?  
21 Because, quite frankly, the Board is quite tired of it.

22 UNIDENTIFIED SPEAKER: Would you extend that  
23 to men as well as women?

24 DR. OSTROFF: Yes. For men and women. What  
25 are they doing?

1 MS. BRODINE: I was just going to make a  
2 comment that in the process of putting the editorial  
3 together and talking to the services and also talking to  
4 health affairs, I think there is a growing recognition  
5 that this is the way policy should go. And, actually,  
6 health affairs assured me that they have a draft. I  
7 think part of the Board -- what the Board could do is --  
8 there are other issues that are on the front burner --  
9 is just make this go. What I'm saying is that this  
10 board meeting could be critical in making this come to  
11 that.

12 COL. STANEK: I can tell you -- I don't have a  
13 historical background in terms of what was -- has gone  
14 on previously with that. But certainly we can get that  
15 information for you, probably very quickly, in terms of  
16 what is going on. And I have to say, at each one of the  
17 basic training stations that we have -- get that  
18 information for you very quickly. I could probably have  
19 that for you next week. I don't have an exact  
20 explanation as to what has transpired over the past two  
21 years.

22 DR. OSTROFF: To my knowledge, it's been the  
23 Army that's been the most recalcitrant.

24 The Air Force?

25 UNIDENTIFIED SPEAKER: Sir, I really don't

1 know what our policy has been. I'll have to get that  
2 for you. My understanding is there is some screening  
3 going on, but I can't tell you who, when, or how. But I  
4 can get that for you.

5 DR. OSTROFF: It strikes me that the way we  
6 can be most helpful here is -- I'm willing to push this  
7 issue and write the occasional letter that I write to  
8 health affairs and to the surgeon general saying that we  
9 just find the current situation unacceptable. I do  
10 think that in addition to that there are probably -- the  
11 suggestion that Dr. Patrick made, which is that it makes  
12 sense and is obviously quite cost-effective to pursue  
13 partner treatment in the way that was described, it does  
14 sound to me that all of you -- all the experts are  
15 saying there is still somewhat of a lack of consensus  
16 about the overall benefit of routine male screening.

17 And I do think we could probably, at least,  
18 make a recommendation that this is an area that is right  
19 for additional work, to make a determination as to what  
20 the optimal policy should be for males with the idea  
21 that hopefully over the next couple of years there would  
22 be some additional clarity that could be had to that  
23 issue. It sounds to me it's feasible. The question is  
24 that it sounds costly. And is it going to dramatically  
25 have an impact? My recollection from the previous

1 meeting is that the Air Force had indicated that in  
2 their studies that it had not significantly made an  
3 impact on the overall prevalence in females, but in the  
4 Navy apparently it did. And one would reach the  
5 conclusion that Navy male partners were different than  
6 Air Force male partners, and that would be the  
7 explanation. I don't know if that's the case or not,  
8 but this ought to be -- not be an insurmountable  
9 obstacle.

10 DR. GAYDOS: We just finished doing a  
11 cost-effectiveness study in the Job Corps, which in many  
12 respects is somewhat similar to people coming in  
13 through a capture point. And there we showed that  
14 cost-effectiveness was evident in screening males at a  
15 prevalence of 4.5 -- was the break-even point above  
16 which it was cost-effective to screen men. If money is  
17 the bottom line, the cost-effectiveness for screening  
18 women is about 7 percent in this large study that was  
19 done with the U.S. Job Corp.

20 UNIDENTIFIED SPEAKER: I just want to try to  
21 clarify something. Did you say that you thought that  
22 the Board might recommend partner treatment  
23 in -- partner directed treatment? Did I understand you  
24 correctly when you said --

25 DR. OSTROFF: Unless somebody can create a

1 downside to doing it to me.

2 UNIDENTIFIED SPEAKER: I have mixed feelings  
3 about it. But this morning someone showed me an article  
4 in the Navy Times, an article about the one woman who  
5 died ostensibly from getting multiple vaccines  
6 in -- basically at the same time. You know, I hate for  
7 the military to step out front and something new like  
8 this, partner directed treatment with antibiotics, and  
9 then have the military have the first, you know, death  
10 from anaphylactic reaction. You know, something like  
11 that, it just -- I'm a little cautious. And it is  
12 because of some of the things we've had to deal with on  
13 a day-to-day basis, that the military has to be a little  
14 more cautious.

15 DR. PATRICK: Since I was the one that raised  
16 that, I wasn't suggesting that we jump right to partner  
17 directed therapy for an approach to this. I think for  
18 the very reasons as stated -- but very clearly I would  
19 encourage that our recommendation not only be screening  
20 but appropriate intervention and then the healthy  
21 people, which was brought up several times. The healthy  
22 people 2010 objectives suggest we can get to the 3  
23 percent. I think Dr. Shafer's fourth slide is very  
24 telling -- in Region 10 it was the one region and  
25 whether this was a function of the Hansfield group up

1 there doing the work on STDs back -- have always done in  
2 the Seattle area on STDs, but that was before really  
3 good diagnostics and therapeutics. This is a very, very  
4 attainable goal of both screening and exploring  
5 appropriate intervention strategies. I think it's a  
6 constellation of things that should be included in this  
7 recommendation. There can -- there's no reason, given  
8 the population that is coming into the military, that  
9 this might not be exemplar in how these problems are  
10 being handled. I mean, why not? I mean, you've got a  
11 controlled confined system that has been pushing to  
12 bring more and more women in who are the victims of this  
13 infection. So I think it's just something that -- I  
14 would agree it's unacceptable and is something that can  
15 be done.

16 DR. OSTROFF: I can't think of any other  
17 infectious diseases other than the one that is our next  
18 topic, which is adenovirus, where anybody could find it  
19 acceptable to have this rate of prevalence and not be  
20 more aggressive in pursuing it.

21 UNIDENTIFIED SPEAKER: I have two concerns.  
22 One is will the military be able to treat civilians? If  
23 we were going to have partner directed -- I've had those  
24 policies that said we cannot treat civilians except for  
25 emergency purposes. The other thing is if we have

1 someone we know who has exposure to sexually transmitted  
2 illness, don't we have to screen them for other  
3 illnesses as well?

4 DR. SHAFER: Yes. I mean, again, if you take  
5 a look at CDC guidelines that -- if you have one  
6 infection, it's good to look for some other. Now,  
7 exactly what you look for is not really spelled out  
8 clearly. I think that what most people do, depending on  
9 your population -- I think what one of the things --  
10 we're almost the cart before the horse. You can't just  
11 wait. But at the same time, we need a better  
12 surveillance system. You probably have it in place.  
13 But no one is looking at it in the sense that if someone  
14 gets chlamydia and we go ahead and we say for the next  
15 year and so many people we will then try and look for  
16 gonorrhea, syphilis, HIV, et cetera, that will happen.  
17 But I think the things people are really looking for are  
18 -- gonorrhea and chlamydia are the main ones. And do  
19 maybe an RPR depending on the population. In the  
20 civilian population we're also adding on HIV because  
21 often individuals have never been tested for that  
22 before.

23 Actually, I just reviewed again -- the CDC is  
24 kind of wishy-washy. It doesn't give you the laundry  
25 list that says you should probably do this and probably

1 a few other things.

2 COL. GIBSON: Just two points. The -- at  
3 recruit settings, at least my experience in the Air  
4 Force, if we have a GC case come forward symptomatic, we  
5 do all the steps we are talking about here -- we test  
6 for the other infections, do partner notification, et  
7 cetera. At least for the Air Force, one of the  
8 pushbacks during the last time this went around was six  
9 weeks of training, short period of time; what's our case  
10 load going to be; how are we going to get contact  
11 notification. With respect to partner directed  
12 medications, I would encourage the Board -- and what we  
13 put into the -- to say investigate the feasibility of --  
14 because there are all kinds of issues about the base  
15 being in a state and having to, at least to some degree,  
16 be obliged to the state regulations. And as we just  
17 pointed out, we have civilians who are partners, and  
18 we're providing medications to those. Our JAG office  
19 can very well sort that out and give us an answer on it  
20 if we bring it up as an option.

21 DR. OSTROFF: Thanks very much. We really  
22 appreciate your taking the time to inform us about this,  
23 and hopefully we can make a little more progress than we  
24 have with our previous recommendations because I just  
25 think that this is a topic that is so intractable and so

1 recurrent for us. If we don't try to take the bull by  
2 the horn, to a certain degree, I just don't see things  
3 changing. And I think it's really unfortunate and  
4 unnecessary. So in the same way that it was a lot of  
5 the Board's pressure to make substantive progress on the  
6 adenovirus issue, I'm optimistic that we can do  
7 something to improve the public health of our men and  
8 women in the armed forces in this arena as well.

9           Instead of taking a break, if you don't mind  
10 -- since there's only the one last presentation -- I'm  
11 going to ask that we not take a break now and that we  
12 hold it until after the presentation, if that's okay  
13 with the Board members. Again, this is a subject that  
14 is very important to us.

15           And I really appreciate Dr. Ison traveling a  
16 great distance to inform the Board on some of the issues  
17 related to adenovirus. Unfortunately, Dr. Gray, who is  
18 the major member of the Board that has been pioneering,  
19 let's say, this particular issue, had to leave a bit  
20 early. But we're very interested in what you have to  
21 say about management of adenovirus.

22           DR. ISON: Thank you very much, Dr. Ostroff,  
23 Colonel Gibson, and the entire Board for inviting me to  
24 come to talk to you. It's very exciting to talk to you  
25 in this venue. My research is usually related to

1 respiratory viruses in the immunocompromised patient  
2 where, although respiratory viruses are important,  
3 there are rare problems. Unfortunately, for the  
4 military adenovirus is way too common. The challenge  
5 that I'm going to try to address is how best to bring in  
6 the problem of adenovirus to the military. To do this,  
7 I'm going to give you a brief introduction of  
8 adenovirus, talking about the virology. I'm going to  
9 then talk about the epidemiological with a focus on the  
10 military and the frequency of disease within recruits,  
11 talk briefly about the clinical syndrome with the focus  
12 on how much of an impact adenovirus disease has on these  
13 recruits, and then spend the majority of my time  
14 speaking about management options. I'm going to say up  
15 front, unfortunately there is very few data in humans  
16 and absolutely no prospective studies of any of the  
17 agents that are currently available for adenovirus.

18           So adenovirus was first identified in 1953,  
19 and since then 51 different adenovirus strains have been  
20 identified. These are grouped into six subgroups based  
21 on genetic differences and clinical syndromes. I've  
22 highlighted here the four viruses that are a predominant  
23 problem within the military, with seven and four being  
24 the most common. This is just a schematic of the virus.  
25 The main thing I'll point out on here is the hexon is

1 the most common protein in the capsid, which is also the  
2 component that we screen for in our studies that I'll be  
3 talking about later, it is transmitted most frequently  
4 by inhalation of aerosolized droplets or by direct  
5 contact conjunctiva. This can be accomplished by  
6 touching a contaminated surface or having droplets touch  
7 the conjunctiva itself. In the case of diarrheal  
8 disease, fecal oral spread has been recognized.  
9 There's no clear seasonal pattern in the community in  
10 general. Although, there are peaks in the autumn,  
11 particularly because of the times which recruits enter  
12 the training camps.

13           So in the nonmilitary populations, adenovirus  
14 is a particular problem, greatest in children in  
15 day-care facilities, but also in long-term care  
16 facilities for older adults and swimming pools. And  
17 outbreaks have been recognized in Job Corps training  
18 camps. My interest is in the immunosuppressed  
19 population, which although is of great interest to me,  
20 we don't have time to talk about today.

21           In the military, outbreaks of adenovirus have  
22 been recognized since the 1950s. In 1958, 10 percent of  
23 all recruits had to be hospitalized as a result of  
24 adenovirus. It is associated in the military of an  
25 attack rate of 50 and 80 percent. And this is thought

1 to be related to the stress of training, the fatigue,  
2 the amount of activity they're doing, environmental  
3 factors. These people are in close quarters instead of  
4 being spread out in their own personal rooms and the  
5 mixing of susceptible young adults in this close contact  
6 setting. There have been some studies that have come  
7 out from the Office of Deployment Health Research that  
8 have looked at the incidence of respiratory viral  
9 disease in these recruits. It is quite clear that the  
10 majority of these recruits present with adenovirus.

11           The instance of which adenovirus is different  
12 between different years and different training sites as  
13 outlined here, where in the Great Lakes Recruit Center,  
14 seven was the predominant pathogen. Where in these  
15 other three, sero group four was the predominant  
16 pathogen. Fortunately, a live attenuated oral vaccine  
17 was developed. This was a pretty amazing vaccine if you  
18 look at the data. I'm going to point out this is weeks,  
19 not months or years, after the institution of this  
20 vaccine in one training camp in 1971 in Fort Lewis.  
21 What you can see is very quickly over a very short  
22 period of time you have almost universal coverage by  
23 vaccine in the recruits. This was associated with a  
24 drop of the -- incident of disease from 6.6 adenovirus  
25 respiratory disease per 100 recruits down to a rate of

1 about two after a complete vaccination. Unfortunately,  
2 the vaccine is no longer available to us. And this  
3 slide here basically shows what has happened since the  
4 vaccine has been withdrawn from use. And you can see  
5 it's very low right -- prior to the removal of the  
6 vaccine. And after the vaccine has been withdrawn,  
7 there is a rise in the number of cases per year and per  
8 season in these recruits, suggesting that a major  
9 intervention has been lost.

10           What is the impact of this loss of  
11 vaccination? Well, there's been a trend towards more  
12 cases of adenovirus respiratory infections with three  
13 cases per 1,000 recruits per week in 1998 and '99,  
14 doubling to six per 1,000 recruits per week in 2000 and  
15 2001, with two fatal cases per year. Epidemic  
16 adenovirus outbreaks in the military basic training  
17 camps have been estimated to result in 22,800 illness,  
18 which is a huge number of illnesses when you're talking  
19 about otherwise healthy individuals.

20           How do these patients present when they get  
21 infected with adenovirus? The most common syndrome is  
22 that of an undifferentiated upper respiratory tract  
23 infection, which I'll get into detail in a few minutes.  
24 Alternatively, gastroenteritis and conjunctivitis can be  
25 a manifestation of adenovirus. Although these

1 manifestations are less frequent in the military,  
2 rarely, and mostly in immunocompromised patients,  
3 hemorrhagic cystitis can occur. Although most patients  
4 have a self-limited respiratory illness, up to 10  
5 percent of patients may progress on to pneumonia. A  
6 very small percentage may have other complications such  
7 as inflammation of the liver, the kidney, or brain.

8           In the military the most typical presentation  
9 is with a high fever, typically greater than 102  
10 degrees, nasal congestion, and sore throat. A smaller  
11 percentage have cough, and about half have  
12 gastrointestinal disturbances, usually diarrhea. Risk  
13 factors that have been identified for infection are  
14 recruitment during the autumn months, coming from either  
15 Kansas or New Mexico, and a history of smoking. These  
16 patients are -- have the problem that they have reduced  
17 activity for up to three days; they have infected  
18 respiratory systems for up to ten days, of which half of  
19 that time they are at potential risk of transmitting the  
20 disease to other recruits; 50 percent seek medical care;  
21 and 20 percent are hospitalized. Of those that are  
22 admitted, a sizable percentage are admitted for greater  
23 than one day; 10 percent develop viral pneumonia; and in  
24 one year adenovirus was associated with 90 percent of  
25 admissions for pneumonia at one hospital.

1                   How can adenovirus be diagnosed? The classic  
2 way of diagnosing it was with viral culture, although  
3 it's not terribly sensitive. Alternatives such as  
4 immunoflorescents, enzyme immunoacids, and latex  
5 gludination tests have been done. Serology can be done,  
6 although this has the problem that it takes a  
7 convalescent titer, frequently drawn at six to eight  
8 weeks, to make the definitive diagnosis. What I submit  
9 to you -- and I will not present all the data for this  
10 -- is that PCR is the gold standard for which we should  
11 be using to diagnose this. Although it's more expensive  
12 than other methods, the sensitivity is higher. It also  
13 gives you the advantage of being a quantitative measure.  
14 So you can give an exact viral load that is being  
15 expressed either in the nose or in the blood that can be  
16 monitored over the course of time. That has a clear  
17 importance if you think about clinical studies because  
18 this is a potential surrogate marker to document that  
19 you're having an impact in the disease even if there is  
20 no significant increase in rate of symptomatic  
21 improvement. If you can show the virus is gone one day  
22 sooner, that's one day less of potential exposure to  
23 other individuals. It should be noted that the virus  
24 may be shed for a prolonged period of time after  
25 recovery, which may be a limitation to this method,

1 although the titers tend to be very low.

2           Now we're going to get into the main topic  
3 that I was asked to talk about -- what are the potential  
4 management options for adenovirus viral disease? What I  
5 focused on in my research and what I'll be prepping to  
6 you today are either drugs that are currently available  
7 or are advancing rapidly to become clinically available.  
8 What I want to you focus on are the main columns here,  
9 which is the IC 50 or the 50 percent inhibitory  
10 concentration of the drug effect for the virus. In this  
11 column -- and compare that with the achievable  
12 concentration. The data I'm going to show you is  
13 probably the most important to always keep in the back  
14 of your mind. We may find there is activity of a drug,  
15 but if it's above what can be achieved clinically, it's  
16 really of no use, particularly since many of these  
17 agents are associated with significant toxicity. The  
18 other thing that I'm going to raise -- and part of the  
19 reason I've been doing studies in this field is that if  
20 you look for individual drugs, the sensitivity is  
21 different depending on which sero type you're looking at  
22 and which cell culture you're using. We'll get into  
23 that in a bit.

24           The one point I will talk briefly though about  
25 is the fact that cell cultures are very important in

1 determining which level of activity because they process  
2 the drugs in different ways. And for many of these  
3 drugs you need to phosphorylate the drug to make them  
4 active or modify them before they're in their active  
5 state.

6           So I'm going to go first with the old drugs  
7 that I don't think we should be using and move to the  
8 drugs I think show the most clinical promise and present  
9 to you first the in vitro data and then the in vivo data  
10 if there's animal models and lastly the very limited  
11 data in humans. So vidarabine, one of the first  
12 antiviral agents, was developed. It had very marginal  
13 activities, 50 to 250 micrograms per ml. The 50 is at  
14 the upper limit of what is achievable. Its activity was  
15 dependent on which cell line, and it was found to be  
16 more efficacious when it was combined with the adenosine  
17 deaminase inhibitor. It was found to be clinically  
18 effective in the management of two cases of adenovirus  
19 associated hemorrhagic cystitis in the stem cell patient  
20 of population, but no other data is available for it.  
21 It's associated with significant toxicity and marginal  
22 activity. So I, therefore, don't feel it's a useful  
23 drug for this indication.

24           In this animal model, rats were given  
25 adenovirus II intranasally and then either given saline

1 by oral or increasing doses of DDC. As you can see from  
2 this graph, which just basically shows development of  
3 pneumonia, there was a significant decline in the number  
4 of patients that developed adenovirus pneumonia when the  
5 higher dose, 75 milligrams per kilogram, which is  
6 similar to the dose -- actually is about three times the  
7 dose that is given to humans, was associated with a  
8 decreased risk of developing pneumonia, suggesting that  
9 it may be active. They also looked at -- over time at  
10 this higher dose to see if there was any changes in the  
11 lungs to suggest inflammation and found that,  
12 particularly at the early time points, there's markedly  
13 reduced histopathologic evidence of inflammation in  
14 patients that are treated with this higher dose of DDC.  
15 Unfortunately, there is no data in humans with regard to  
16 adenovirus and DDC. I'll share you with in a few  
17 minutes -- it does not appear in studies we've done to  
18 be terribly active.

19 Mycophenolate we were very interested in  
20 looking at because there is some data from the drug  
21 company that suggests in vitro it has activity against  
22 adenoviruses that should be noted, though that was only  
23 tested against adenovirus three and adenovirus seven.  
24 The activity was above the rate that is clinically  
25 achievable without significant myelosuppression. And,

1 unfortunately, there's no clinical data. An important  
2 point to look at is that looking back at the few case  
3 reports that are available in the immunocompromised  
4 population, nearly all of the solid organ transplant  
5 patients that have developed adenovirus infections have  
6 been on a therapeutic dose of mycophenolate, suggesting  
7 that it may not be terribly effective.

8           Ganciclovir. This drug was, as you know, was  
9 developed as an anti CMV agent. It's been tested back  
10 in 1998 against several different sero types in vitro.  
11 It was found actually to be very active against  
12 adenovirus. Unfortunately, despite this, there haven't  
13 been any prospective studies looking at this.

14           There was one case that I could find in the  
15 literature where adenovirus induced hemorrhagic cystitis  
16 responded positively to ganciclovir. Probably the most  
17 important data with regard to ganciclovir comes from a  
18 recent study that was presented at the American  
19 Transplant Congress just a few months ago. In this  
20 study they looked at a group of patients that either  
21 received valganciclovir or no prophylaxis at all. And  
22 they didn't just focus on CMV, they looked at a wide  
23 battery of viruses. One of the viruses that they found  
24 was adenovirus. The interesting thing was that a high  
25 percentage of patients in this population did have

1 adenovirus disease as evidenced by positive PCR in the  
2 blood. Very few of these patients had clinically  
3 evident disease with either hepatitis or any other  
4 significant manifestations, respiratory disease or  
5 whatnot, although many did present with fever. There  
6 was no difference in the frequency. It was about 6  
7 percent in those patients that received valganciclovir  
8 versus those that had received no prophylaxis,  
9 suggesting that ganciclovir are not terribly active and  
10 then, therefore, may not be a valid drug to study in the  
11 future.

12           Now, let's move to the last two groups of  
13 compounds that people have had a fair amount of  
14 experience with. First that is Ribavirin. It's  
15 guanosine analogue where both base and the ribose sugar  
16 are necessary for antiviral activity. It's virustatic.  
17 And the interesting part is that for a number of  
18 different viruses its activity appears to be less  
19 related to its direct antiviral activity but more due to  
20 it's immunomodulatory activity. Unfortunately,  
21 this -- which components of the immune system are being  
22 modulated have not been carefully studied, but there  
23 have been markers of inflammation that are reduced when  
24 ribavirin are given, suggesting this reduction in  
25 inflammation may be contributing to disease

1 manifestations. An oral formulation and inhaled  
2 formulation are FDA approved. I.V. formulation is  
3 investigational. Unfortunately, it's associated with  
4 significant adverse events, most notably anemia  
5 secondary to direct toxicity to the red blood cells. I  
6 think the most important toxicity is that of  
7 teratogenicity. It's been associated with teratogenic  
8 effects for up to six months after the last dose of the  
9 drug was given, which suggests this is a serious  
10 potential liability to anyone who conducts a study in a  
11 population that may be sexually active. Whether or not  
12 they comply with the need to use condoms or abstain from  
13 sex can be a severe limiting factor.

14           There is some in vitro data that were  
15 initially presented -- some additional viruses that have  
16 been added that I'll show you on the next slide where  
17 they basically looked at ribavirin. They did a number  
18 of different sero types that were strains that were  
19 obtained from a reference laboratory and were all tested  
20 on the HEP-2 cell line. Unfortunately, what they found  
21 is that there was absolutely no activity for ribavirin  
22 except for the sero group C of viruses, and these --  
23 some of these were at the upper limits of what was  
24 achievable, suggesting that unless you were affected  
25 with this group that ribavirin is probably not the best

1 choice.

2           They then looked at some clinical isolates  
3 they had from their study they were conducting in  
4 Europe. Again, they have limited numbers. But  
5 important to this group, sero type seven, they had five,  
6 all of which were highly resistant to ribavirin. Again,  
7 they also confirmed that for the Group C there was some  
8 degree of activity.

9           Looking at clinical studies, most of the  
10 clinical studies have involved immunocompromised  
11 patients that have disseminated disease which may not be  
12 the best model for the military. But in one study where  
13 they gave 35 milligrams per kilogram of ribavirin  
14 followed by 25 milligrams per kilogram IVQ-8 for ten  
15 days, there was significant mortality even within the  
16 ribavirin group, which was substantially higher than  
17 cidofovir. Virus was clear -- in those that had  
18 clearance of virus, virus was cleared at a late time  
19 point and dates.

20           Probably the most important study, in my  
21 opinion, looking at ribavirin was published earlier this  
22 year in Clinical Infectious Disease. And what they did  
23 -- again, this was in stem cell transplant recipients  
24 that have disseminated disease that had virus detectable  
25 by serum PCR -- they monitored these patients' blood for

1 PCR viral load while on ribavirin therapy. As you can  
2 see, all four patients -- again, very small  
3 number -- they all had a rise in viral load despite  
4 active therapy, suggesting that ribavirin was not  
5 active. Unfortunately, they didn't clarify which  
6 viruses were present in this. But my guess is they were  
7 not sero Group C. So in conclusion for ribavirin, IC 50  
8 is high for most isolates, and it only appears to be  
9 active in Subgroup C viruses in vitro and may not be  
10 clinically active in vivo. Although in immunocompetent  
11 patients that have normal immune systems that may be  
12 modulated by this drug, there may be some benefit. It's  
13 just not clearly shown in any studies to date.

14           The next drug that has probably had the  
15 clearest evidence of benefit in the stem cell population  
16 is cidofovir, which is a cytosine analogue that inhibits  
17 DNA polymerase. It also is virostatic. It's only  
18 available intravenously and is typically given with  
19 probenecid, which may limit its usefulness since sulpha  
20 allergic patients cannot take probenecid. One  
21 advantage is that the drug stays around for a long  
22 prolonged period of time allowing it to be given weekly.  
23 Unfortunately, it's associated with a very high rate of  
24 renal failure and proteinuria as well as the risk of  
25 neutropenia. In studies of HIV patients, there was an

1 increased risk of intraocular pressure and anterior  
2 uveitis, although this adverse effect has not been  
3 clearly noted in subsequent clinical experience.

4           In vitro data -- again, from Europe -- we can  
5 see that for all species A through F there appears to be  
6 very good activity in vitro with IC 50s that are well  
7 within the achievable clinical range. In clinical  
8 isolates from the same group -- again, I'll focus you on  
9 the sero Group 7 isolates -- they have here all were  
10 within the clinically achievable range.

11           Let's now turn to in vivo models. There have  
12 been several groups, particularly this group from Japan,  
13 who have looked at ocular infection with adenovirus.  
14 And when adenovirus is applied to the eye of rabbits and  
15 the patients -- or the rabbits are given nothing or  
16 intraocular cidofovir, there's a marked reduction in  
17 viral load detectable from the eye in those that are  
18 treated. And that was significant at all time points.

19           In clinical studies -- again, predominantly  
20 from bone marrow transplant population -- different  
21 regimens have been used -- either a high dose weekly or  
22 a low dose three times a week has been associated with a  
23 very high rate of survival in these patients between 70  
24 and 100 percent, suggesting that in this population it  
25 has significant activity. None of these studies have

1 been prospective or controlled. Like the study with  
2 ribavirin this year, there was also a great study in  
3 which stem cell transplant patients that were -- that  
4 developed disseminated adenovirus infection were  
5 monitored if they had positive viral load for adenovirus  
6 over time. As you can see, the arrows are times that  
7 cidofovir is dosed. In many of the patients, there is  
8 clear decline of viral load. These declines were  
9 associated with clinical response. And all patients  
10 that had response to the drug clinically survived their  
11 infection.

12           The concerning thing is this was not a  
13 consistent finding. Although most of the patients had a  
14 decline in viable load, there were a few patients --  
15 three out of the eight -- that did not have significant  
16 declines and continued to have symptoms of their  
17 respiratory disease. Two of these ended up succumbing  
18 to their adenovirus illness.

19           A group of compounds are being developed by a  
20 company here in San Diego called Chimerix which are  
21 lipid ester formulations for cidofovir. These lipid  
22 esters have enhanced activities and have the advantage  
23 of being orally available so they can be delivered much  
24 more easily than the I.V. cidofovir. Likewise, in  
25 animal models it appears there is practically no

1 nephrotoxicity to this drug, which is an additional  
2 benefit. In CMV and orthopox viral infections in animal  
3 models, they have shown clear efficacy that's at least  
4 equal to I.V. cidofovir. In both of these infection  
5 models -- have been associated with a lot less increases  
6 in cramping. Basically, the way they work is they tack  
7 the drug onto a lipid by forming an ester bond in place  
8 of the choline, and this allows it to be absorbed  
9 through the intestinal luminal cells which then cleaves  
10 the drug from the lipid allowing it to be freely  
11 available in the blood stream.

12           These data were provided to me by Dr. Pern  
13 (phonetic), who has done the in vitro studies of lipid  
14 esters of cidofovir. There are three different esters.  
15 The main difference is how long the lipid is that's  
16 connected to the drug. And quite clearly there is about  
17 a two log (sic) or greater increase in activity with  
18 these lipid esters in vitro.

19           So it appears that cidofovir, the IC 50s, is a  
20 achievable for most isolates in vitro. It appears to be  
21 clinically active in vivo. And the lipid ester  
22 formulations may be better tolerated and are fully  
23 available. It is important to note this is just  
24 entering Phase 1 clinical studies in humans. So the  
25 availability for studies in this population would be, at

1 a minimum, one year away.

2           The group is also looking at HPMPA, which is  
3 an adenosine analogue very similar to cidofovir, and has  
4 found, likewise, significant activity with reduced  
5 nephrotoxicity. These studies are also being moved  
6 forward into Phase 1.

7           So what has been my experience? Because all  
8 of the older studies have used multiple cell lines and  
9 multiple different viruses to test adenovirus, I decided  
10 to test -- first off, to test some standardized  
11 adenovirus 3 and 5, which we obtained from HECC outside  
12 of D.C., and test them in a standardized method using a  
13 standardized cell line. We use two different cell  
14 lines. We started by doing studies -- and this is the  
15 data I'll present to you here -- looking at inhibition  
16 of plaque formation. With this, we looked at the  
17 ribavirin, ganciclovir, mycofenolate, and DDC. And  
18 basically we found no significant activity for  
19 adenovirus 3 or 5 within the clinically achievable range  
20 for any drug other than cidofovir. We then had the  
21 fortune of having an adenovirus 4 isolate that was  
22 collected from an Air Force personnel that succumbed  
23 from adenovirus pneumonia. From this, again, we were  
24 able to find that cidofovir was active. But none of the  
25 other drugs were active at clinically achievable ranges.

1 Since then, we've looked at combination therapy to see  
2 if putting two drugs together would have any additional  
3 benefit. We have only found that the addition of  
4 cidofovir with HPMPA has any significant additive  
5 effect, suggesting there is no other clear drug that's  
6 clinically available that could boost the effect of  
7 cidofovir.

8           So what can we say about adenovirus therapy  
9 and its options? First off, adenovirus is a significant  
10 pathogen of clinical importance to the military and  
11 could potentially undermine the overall state of  
12 preparedness of the military since a number of recruits  
13 are getting ill each year and they're being ill for  
14 almost a week, which may limit their ability to be  
15 prepared to enter the battlefield if they need to be  
16 processed very quickly. There are no randomized studies  
17 of available antiviral agents. Ribavirin is of  
18 questionable benefit except in sero Group C cases, but  
19 cidofovir and its lipid esters may be more beneficial.

20           So what directions should be taken to better  
21 address the issue of adenovirus in the military? I  
22 think the most important thing from the data that I've  
23 shown you -- the clearest benefit comes from  
24 vaccination. I know that efforts are being made to  
25 develop and implement a new vaccine since it's highly

1 effective in preventing disease. Unfortunately, that's  
2 not in the near future. And so I think it's appropriate  
3 to consider clinical studies of available compounds.  
4 This is particularly important because you have a high  
5 number of people that are getting ill each year which  
6 would allow you to complete the study in a short period  
7 of time and give you useful information in one year.  
8 Cidofovir shows the most promise. But, unfortunately,  
9 it has significant toxicities. Ribavirin may be an  
10 option if Group C were a common problem, but that does  
11 not appear to be the case in the military. The  
12 development of the new lipid esters in cidofovir, in my  
13 mind, pose the most likely potential drugs to be used in  
14 this population if they prove to be safe in Phase 1  
15 studies and if it's felt to be worthy of putting  
16 patients at risk from potential toxicities from these  
17 new drugs before they're tested in a wider population.

18 So lastly, as we look at the Bullfinch  
19 Hospital, which was the original part of Massachusetts  
20 General Hospital, I'd be glad to take any questions that  
21 you have.

22 DR. OSTROFF: Thanks very much. That was a  
23 wonderful overview and presentation. And I must confess  
24 I was not aware of many of the things that you  
25 mentioned, so it's extremely helpful to hear them.

1                   Regarding the lipid form of cidofovir, does  
2 that also need to be boosted with probenasad, or is that  
3 not yet known?

4                   DR. ISON: It's not yet known, but the  
5 likelihood is that it would not. The main reason why we  
6 use the probenasad is to protect the renal tubuals from  
7 the cidofovir. So it's not really a boosting effect as  
8 much as a protective effect. At least in animals, the  
9 rise in creatinine noted in the lipid ester treated  
10 patients was not significant increase compared to  
11 controls, whereas there was a significant increase in  
12 patients that had -- or sorry -- in the animals that had  
13 received cidofovir.

14                  DR. OSTROFF: Other questions from the group?

15                  DR. BROWN: Maybe you addressed this, but it's  
16 not clear to me that we have the ability to detect, as a  
17 test, for adenovirus, to be able to -- using something  
18 like cidofovir, can we detect the presence of that being  
19 a diagnosis for that virus and then use the drug in a  
20 timely fashion?

21                  DR. ISON: Yes. The detection of adenovirus  
22 is actually very easy. There are several different  
23 techniques. There are rapid detection kits that are  
24 commercially available. There are PCR kits available  
25 and a multiplex PCR that is commercially available.

1 Outside of the military -- I know there are several  
2 people within the military that are working on PCR.  
3 Again, the advantage of the PCR is you may be able to --  
4 give you a specific sero type which may or may not have  
5 implications on what therapeutic options would be  
6 available to the patients above what would be  
7 achievable -- just tell you, yes, there is adenovirus  
8 hexon present.

9 UNIDENTIFIED SPEAKER: Within all the recruit  
10 training camps, our surveillance for respiratory illness  
11 does do PCR techniques first for both adenovirus and  
12 influenza. And, subsequently, culture -- a proportion  
13 of those adenovirus just have the *vivro* virus, but a  
14 variety of PCR techniques are available within the  
15 military.

16 DR. PATRICK: I just want to ask, though this  
17 is impressive, how long and when this is ready how much  
18 is this -- are these going to cost, whatever is best and  
19 around the corner? Realistically, how many years out  
20 for actual practical application of this?

21 DR. ISON: If you look at the standard time  
22 between Phase 1 testing and clinical approval, you will  
23 -- you're probably between three and five years before  
24 it's approved by the FDA. Since this is being developed  
25 predominantly for a therapeutic option for smallpox, the

1 rate at which it passes through the FDA may be  
2 expedited. The second issue is there is a need for an  
3 active compound which may push the FDA to approve this  
4 compound as long as there's no significant toxicity  
5 recognized.

6 DR. PATRICK: Do you have an estimate -- I  
7 mean, what are these things likely to cost?

8 DR. ISON: Cidofovir is exceptionally  
9 expensive. It costs about 2,000 to \$3,000 a dose. So  
10 at least -- so it's not cheap. So I have no idea. I  
11 have not talked with my contacts about what the cost  
12 would be. I think that's not even in their minds yet.

13 DR. OSTROFF: Let me ask you this question:  
14 If next month there was a severely ill recruit that came  
15 into your institution, what would you consider the  
16 available options to be?

17 DR. ISON: I think if you had an individual  
18 that had pneumonia, for example, or significant evidence  
19 of disseminated disease respiratory illness, hepatitis,  
20 something along those lines, I think given the data we  
21 have and the available drugs I would go for cidofovir.  
22 I'd probably go for the higher dose, weekly 5 milligrams  
23 per kilogram with probenesad, and cross my fingers. I  
24 would also encourage that you correct serum samples.  
25 And if you can't run PCR on the serum, that you at least

1 freeze it and get in touch with me to do those PCRs.

2 DR. OSTROFF: I assume you're saying that you  
3 would -- are you saying you would not wait for a  
4 definitive diagnosis for adenovirus before you would  
5 resort to that?

6 DR. ISON: No. Because, unfortunately, if you  
7 look outside the military, what would be the most common  
8 cause to cause respiratory pneumonia, let's say,  
9 particularly depending on the season? Influenza would  
10 be the highest as well. In the military where  
11 adenovirus is much higher, you could make the diagnosis  
12 very quickly if you had evidence to think you had lower  
13 respiratory tract disease. I would think that cidofovir  
14 would be the appropriate therapy. I think that looking  
15 at patients that just have adenovirus upper respiratory  
16 tract disease without significant data, I don't think  
17 you could make the case for treating this patient  
18 because of the toxicity of cidofovir.

19 DR. OSTROFF: Do you know if -- is the lipid  
20 ester form of cidofovir going to be available in  
21 intravenous form, or is it exclusively going to be an  
22 oral?

23 DR. ISON: As far as I'm aware, just being  
24 developed in an oral formulation.

25 DR. ENNIS: I enjoyed your presentation.

1 What's the case fatality rate for adenovirus pneumonia?

2 DR. ISON: In the military there's about two  
3 fatalities per year, somewhere around 600 pneumonias.  
4 So very low. In the immunocompromised population, it's  
5 much higher, around 60 to 70 percent.

6 DR. OSTROFF: If I remember correctly, not all  
7 of the fatalities in the military have been due to  
8 adenovirus pneumonia. I think there have been other  
9 manifestations, including a case of encephalitis. So  
10 it's not an easy question to answer.

11 DR. ENNIS: I guess my reaction is that these  
12 drugs do have pretty significant toxicities. So I think  
13 there will be a lot of testing in patients who are  
14 severely ill and immunocompromised, I think, before  
15 there'll be enough data to probably warrant wide use of  
16 such drugs in otherwise healthy individuals who aren't  
17 likely to die in the near future. I think it's a  
18 toxicity issue.

19 UNIDENTIFIED SPEAKER: This is a more general  
20 question probably than Dr. Ison can answer, but I was  
21 around when adenovirus vaccines were used, and I'm aware  
22 of the fact that Wyeth, I guess, had stopped producing  
23 it. But what is the status of that vaccine in terms of  
24 somebody producing it?

25 DR. OSTROFF: Well, all I'll say is we can go

1 have a beer after the meeting is over. We'll fill you  
2 in on this particular subject.

3 COL. GIBSON: The trips from our last several  
4 meetings would lay that out. The Board has addressed  
5 the vaccine availability issue several times.

6 DR. OSTROFF: Thank you very much. That was a  
7 terrific presentation. Let me just open it up to the  
8 Board to determine whether or not there are any other  
9 issues, questions, or comments that need to be broached  
10 by the Board before we bring the meeting to a close. I  
11 do know that there is another activity scheduled for  
12 this room after we conclude, so I'd like to try to bring  
13 the meeting to closure as quickly as possible.

14 The action items that I have that I'd like to  
15 make some progress on, not necessarily today, but after  
16 we conclude, one of them is to have further discussions  
17 with Dr. Kaplan about how we can be most helpful to  
18 address the issue of the Warren serum repository because  
19 I do think that most of us feel this is a treasure that  
20 we would want to manage cooperatively with Dr. Kaplan in  
21 the best way so we can assure its continued availability  
22 as well as its maximal utilization.

23 And then the second is the chlamydia issue,  
24 which I will be relentless about until I can draft some  
25 sort of a letter to ask the services to come to some

1 consensus on this. And so hopefully we can do that  
2 relatively quickly. I would ask each of the services to  
3 provide to Dr. Gibson, so we can produce a summary  
4 chart, the current status of screening activities. And  
5 I do intend to pursue this vigorously.

6 Are there any other issues or comments?

7 Let me conclude by thanking Colonel Gibson and  
8 his wonderful staff -- Severine, Abby, et cetera -- for  
9 all of the support and assistance as well as the fine  
10 people here in San Diego. Great job, fine weather,  
11 wonderful setting. We're only too happy to come back as  
12 frequently as you would like us to come back. And I  
13 thank all the Board members who were available to stick  
14 it out to the end.

15 Unless Colonel Gibson has any other issues to  
16 discuss, I'm going to bring the meeting to a conclusion.

17 COL. GIBSON: We will be sending out the  
18 invitations to the next meeting very shortly. It's in  
19 March -- the third week in March, Tuesday and Wednesday  
20 -- and look forward to you being there. Keep checking  
21 the AFEB website for updates.

22 DR. OSTROFF: Thanks very much.

23 (Meeting adjourned at 3:30 p.m.)

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