

WINTER MEETING

FOUR POINTS SHERATON  
1325 Miracle Strip Parkway East  
Fort Walton Beach, Florida

FEBRUARY 17, 2004

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## I-N-D-E-X

Opening Remarks .....	3
Welcome .....	3
Ethics Training .....	22
Discussion .....	40
MilVax Update .....	41
Discussion .....	50
Adenovirus Vaccine-Status Update .....	70
Questions to the Board .....	86
Multiple Concurrent Immunizations .....	104
Surveillance for Vaccine Adverse Events-DoD .....	124
Discussion .....	148
Multiple Concurrent Immunizations	
Charles Hackett .....	154
Mark Peakman .....	181
Leah Scott .....	204
Questions to the Board .....	223
Medically Related Deaths-OIF .....	233
and OIF Non-Combat Deaths	
Discussion .....	253
Adjourn .....	292

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

DR. OSTROFF: I would ask everyone to take their seats so that we can get started.

Welcome to the Winter Board Meeting. It's been about five or six months since we were last together, the last meeting being in Connecticut. It's nice to see everybody. I guess if I would recall the previous meeting, it would be like it because we didn't have a lot of things to discuss.

It's nice to see such a terrific turnout for the meeting and I think it's a reflection of the fact that we've all been very busy with lots of very important issues and we're looking forward to continuing to try to do as much as we possibly can.

Let me just welcome a couple of individuals that are here today. First let me welcome Major General Joseph Kelley, who is sitting next to me. General Kelley is the Assistant Surgeon General for Healthcare Operations. This is a very important job and we really appreciate you taking the time out of your very busy schedule to participate in the meeting. His particular division is the focal point for healthcare operations and provides healthcare programs and policy guidance for the 42,000 airmen and 74 different medical facilities in their system. So

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1 that's quite an impressive array of responsibilities  
2 and once again, we thank you for taking the time out  
3 of your schedule.

4 I would also like to thank Lieutenant  
5 General Paul Hester, who is the Commander of the Air  
6 Force Special Operations Command for basically hosting  
7 us here at Fort Walton. I'm sure he's got a fine  
8 program scheduled for us tomorrow, and unfortunately  
9 probably can't do anything about the weather. This is  
10 typical of Florida, but at least it will keep everyone  
11 indoors and participating in the meeting.

12 (Laughter.)

13 DR. OSTROFF: Let me also welcome COL  
14 Wyman, who is also sitting to my right, who is the  
15 Command Surgeon for the Air Forces Special Operations  
16 Command, which I am sure is a very interesting job.

17 And also, I would welcome Lieutenant COL  
18 Woodruff, who is the Command Public Health Officer and  
19 also an old friend. He has done a lot of work, a lot  
20 of legwork to get the activities ready for us and I'm  
21 sure that we look forward to all of that.

22 Ellen Embrey is the Deputy Assistant  
23 Secretary for Health Affairs, is unable to attend this  
24 particular meeting because she has been given the  
25 unfortunate and daunting task of having to deal with

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1 issues related to the recent concerns about sexual  
2 assaults in Iraq, and because of those  
3 responsibilities, is unable to attend and perform her  
4 usual role as the Designated Federal Official, and she  
5 has tasked COL Riddle, sitting to my left, with that  
6 particular responsibility, so let me turn the  
7 microphone over to him.

8 COL. RIDDLE: Thank you, Dr. Ostroff.

9 As the Designated Federal Official for the  
10 AFEB, a Federal Advisory Committee to the Secretary of  
11 Defense, which serves as a continuing scientific  
12 advisory body to the Assistant Secretary of Defense  
13 for Health Affairs and the Surgeon General of the  
14 Military Departments, I hereby call this Winter 2004  
15 meeting to order.

16 The meeting is being transcribed. So as  
17 you speak, if you would please identify yourself to  
18 the transcriptionist so we can accurately capture all  
19 of the comments and discussion here today.

20 COL Wyman, COL Woodruff, please accept my  
21 appreciation for your willingness to host this meeting  
22 and the outstanding support you and your staff have  
23 provided to the AFEB.

24 We have several distinguished guests here,  
25 as far as administrative remarks. To the speakers, I

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1 want to thank you very much for all the hard work you  
2 put into the presentations. We will have all of the  
3 slides up on the website when I return and we should  
4 have transcripts of the meeting in a couple of weeks.

5 Our next Board meeting will be on the 18th  
6 and 19th of May at Fort Detrick in Frederick,  
7 Maryland. Our host there again will be the Armed  
8 Forces Medical Intelligence Center, U.S. Army Medical  
9 Research Institute for Infectious Diseases, which as  
10 you know is pretty standard. At that meeting, we  
11 always have the intelligence brief to review, the  
12 current threat of biological warfare and also the  
13 biological warfare immunization program for the  
14 Department of Defense.

15 Our refreshments today will be in the back  
16 of the room. We'll have refreshments this morning and  
17 this afternoon. For lunch, for all of the speakers  
18 and Board members and PM consultants, we will have a  
19 catered lunch in the area this morning where we had  
20 breakfast. So if you would join us at 12:00 and we  
21 can continue our discussions and collaborations during  
22 that lunch meeting.

23 There are many restaurants in the local  
24 area. Tonight we do have a hosted dinner which is  
25 going to be at a very, very good seafood restaurant,

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1 which is the Old Bay Steamer. We're going to meet in  
2 the lobby at 6:30. If you could, if you're going to  
3 attend the dinner tonight, please let Severine know  
4 before 2:00 this afternoon, so that we can confirm the  
5 reservation. But it is open to everybody, both the  
6 speakers, presenters and folks in the audience and we  
7 certainly welcome you to attend.

8           Thanks to the hard work and diligence of  
9 Severine and the support from the Uniformed Services  
10 University of the Health Sciences, we are able to  
11 offer 14 CME credits for this meeting. To receive the  
12 credits, you need to sign the physician attendance  
13 roster and Severine has that out front, so that she  
14 can prepare the certificates. And also you must  
15 complete the evaluation form. For the folks here at  
16 the table, the evaluation form is in your notebooks.  
17 For others eligible for the CME credit, there are  
18 evaluation forms over on the handout table up here on  
19 the right and we will have those certificates for you  
20 and you can pick those up tomorrow afternoon.

21           If you plan on attending the visit  
22 tomorrow to Hurlburt Field, the Air Force Special  
23 Operations Command, we have 45 slots available. We  
24 have all of the Board members and the PM consultants  
25 already signed up. If you are a Board member or one

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1 of the individuals here at the table, please let  
2 Severine know, but for everybody else, it will be on a  
3 first-come/first-first served basis. So if you can  
4 get in touch with her, we'll take the first 45 folks  
5 on the tour tomorrow and I think we're going to have a  
6 great tour and a great orientation to the Special  
7 Operations Command.

8 Thank you.

9 DR. OSTROFF: Thanks very much.

10 At the risk of not trying to get too far  
11 behind the schedule, since we do have a new Board  
12 member, I would like to get started if we could by  
13 having -- going around the table and having the  
14 persons who are sitting at the table introduce  
15 themselves and your affiliations and then Dr. Shamoo  
16 might want to give us some brief comments about his  
17 background, when we get to you, that would very much  
18 be appreciated.

19 Why don't we start over here.

20 COL. GRABENSTEIN: I'm John Grabenstein,  
21 I'm merely one of the morning speakers.

22 (Laughter.)

23 DR. BROWN: I'm Mark Brown, Department of  
24 Veterans' Affairs.

25 MR. JONES: Dave Jones, Joint Staff,

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2 DR. GARDNER: Pierce Gardner, Fogarty  
3 International Center, National Institutes of Health.

4 DR. CLINE: Barnett Cline, Tulane  
5 University.

6 DR. GRAY: Greg Gray, University of Iowa.

7 DR. FORSTER: Jean Forster, University of  
8 Minnesota.

9 DR. BERG: Bill Berg, Hampton, Virginia  
10 Health Department.

11 DR. CATTANI: Jackie Cattani, University  
12 of South Florida.

13 DR. HERBOLD: John Herbold, University of  
14 Texas, Bureau of Public Health.

15 DR. LAUDER: Tam Lauder, physician, St.  
16 Germain, Wisconsin.

17 DR. BLAZER: Dan Blazer, Duke.

18 COL. GIBSON: Roger Gibson, Office of the  
19 Secretary of Defense.

20 COL. RIDDLE: Rick Riddle, APD.

21 DR. OSTROFF: Steve Ostroff, Centers for  
22 Disease Control, Atlanta.

23 MAJ GENERAL KELLEY: Joe Kelley, Air Force  
24 Healthcare Operations.

25 COL. WYMAN: Dan Wyman, AFSOC SG.

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1 DR. SHAMOO: Adil Shamoo, University of  
2 Maryland School of Medicine, I'm the Ethics  
3 Consultant.

4 DR. SHANAHAN: Dennis Shanahan, Consultant  
5 from Carlsbad, California.

6 DR. POLAND: Greg Poland, we used to say  
7 Mayo Clinic, but as of last month, it's Mayo Clinic  
8 College of Medicine.

9 (Laughter.)

10 DR. PATRICK: Kevin Patrick, University of  
11 California, San Diego.

12 DR. MORRIS: Glenn Morris, University of  
13 Maryland.

14 COL. UNDERWOOD: Paula Underwood,  
15 Preventive Medicine Staff Officer, Army Surgeon  
16 General.

17 COL. WOODWARD: Good morning. Kelly  
18 Woodward, Chief of Preventive Medicine, Air Force  
19 Medical Support Agency.

20 CAPT KILBANE: I'm Ed Kilbane, I'm from  
21 the Bureau of Medicine and Surgery for the U.S. Navy.

22 CDR MCMILLAN: David McMillan, I'm the  
23 Preventive Medicine Officer for the Headquarters, U.S.  
24 Marine Corps.

25 DR. ZAMORSKI: Mark Zamorski.

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1 CAPT. OBRAMS: Iris Obrams.

2 LTC PHILLIPS: I'm Steve Phillips, Program  
3 Director for Preventive Healthcare.

4 DR. HACKETT: John Hackett, Institute of  
5 Allergies and Infectious Diseases, NIH.

6 DR. PEAKMAN: Pete Peakman.

7 DR. OSTROFF: Thanks very much.

8 I'd like to point out that there are a few  
9 Board members who, for various reasons, were unable to  
10 make it to this meeting -- Linda Alexander, David  
11 Atkins, Grace LeMaster and Dr. Malmud. We miss their  
12 presence.

13 I would be remiss if I didn't point out  
14 that we very much miss the presence of another Board  
15 member, Dr. Shope, who passed away at the beginning of  
16 this year. For those of us who had an opportunity to  
17 work with him over the years, it is a really  
18 tremendous loss. As I'm sure many of you know, he was  
19 ill for sometime, but always made it a priority right  
20 up until almost the very end to participate in matters  
21 relating to the Board. His last meeting that he  
22 attended was the meeting that we held last spring. He  
23 very much wanted to attend the meeting in August but  
24 he wasn't well enough. And for those of you who  
25 participated in the smallpox vaccine work, as you

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1 know, he participated telephonically almost until the  
2 very end.

3 And what I'd like to do -- Rick is going  
4 to make a couple of comments and then I'd like to have  
5 a moment of silence to just remember him.

6 COL RIDDLE: On Monday, 19 January 2004,  
7 the world lost a great scientist, the Armed Forces  
8 Epidemiological Board a distinguished member, and many  
9 of us lost a great friend, Dr. Robert E. Shope. Dr.  
10 Shope had suffered from idiopathic pulmonary fibrosis  
11 for a decade, and finally succumbed, but only after  
12 battling heroically.

13 Dr. Shope was the son of Dr. Richard  
14 Shope, also a former member of AFEB, who discovered  
15 Rabbit fibroma virus and who worked with Peyton Rouse  
16 in the discovery of the first papovavirus. Dr. Shope  
17 served on the AFEB. Growing up in an environment with  
18 Albert Einstein as a neighbor in Princeton, he  
19 naturally gravitated to medicine, attending Cornell  
20 University for a B.A. in zoology and then an M.D. in  
21 1954. At the time of his death, Dr. Shope was  
22 Professor of Microbiology and Immunology at the  
23 University of Texas Medical Branch at Galveston. He  
24 was also serving as a Professor of Preventive Medicine  
25 and Community Health, Sealy Centers for Structural

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1 Biology, Environmental Health and Medicine and Vaccine  
2 Development and was the John S. Dunn Distinguished  
3 Professor, but was specifically located at the World  
4 Health Organization Center for Tropical Diseases,  
5 Center for BioDefense and Emerging Infectious Diseases  
6 in the Department of Pathology.

7 His many accomplishments have been  
8 outlined in a eulogy which we have posted on the Armed  
9 Forces Epidemiological Board website. As important as  
10 his accomplishments was the quality of the  
11 relationships he developed with both students and  
12 colleagues. He was unfailingly collegial with  
13 collaborators and endlessly patient with students. He  
14 will be tremendously missed.

15 DR. OSTROFF: With that, could we have a  
16 moment of silence?

17 (Moment of silence.)

18 DR. OSTROFF: Thanks very much. He will  
19 be dearly missed by all of us.

20 I would also like to point out that this  
21 is definitely a meeting of partings, because we have  
22 another very important person and this will be his  
23 last meeting and that is the person sitting to my  
24 left. Rick Riddle has been the Executive Secretary  
25 during my particular tenure as the Board President and

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1 I think all of us are extremely appreciative of the  
2 really tremendous job that Rick has done. I think  
3 without question, that over the recent history of the  
4 Board, the last couple of years have been amongst the  
5 most challenging and productive that we have had in  
6 quite awhile and I think that by and large, we owe it  
7 to the fine work that COL Riddle has done in  
8 challenging us and keeping us on our toes, keeping us  
9 as busy as possible and I really think that all of us  
10 will very dearly miss him.

11 I do have here a little poster that I've  
12 had made to show our appreciation for Rick's tenure on  
13 the AFEB as Executive Secretary. And if possible,  
14 what I'd like to try and do is pass it around to all  
15 the various Board members to put their signature on  
16 the poster and then what we will do is have it framed  
17 so that you can take it on to your next assignment.

18 In addition to that, I had a really  
19 difficult time trying to figure out what an  
20 appropriate gift would be for you. I contacted  
21 various folks up in Washington, including several who  
22 have been sitting around the table, trying to figure  
23 out what exactly would be the most appropriate gift to  
24 give you at last meeting. Several of them snuck into  
25 your office looking for ideas. Then we contacted your

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1 wife and she said, you know, the house is full of  
2 Falcon stuff and so I kind of really tried to figure  
3 out what an appropriate gift would be.

4 As some of you know, last week, I went to  
5 South Africa and I promised that while I was there, I  
6 would try to make an effort to find something really  
7 nice and special for Rick. And as you know, there's  
8 lots of different shops that you can go into that have  
9 all those masks and shields and all kinds of things,  
10 and I was really looking for something very special  
11 and I just happened upon one afternoon when we had a  
12 chance to sort of meander around some of the back  
13 country outside of Cape Town, a wonderful health  
14 stand. There were all kinds of exotic animals like  
15 beaver hides and python skins and all kinds of things  
16 like that and sitting out in front was this grizzled  
17 old sort of classic great white African hunter, right  
18 out of central casting, and I said let's stop the car.

19 We got out and he was telling me all about these  
20 fabulously exotic things that he had, most of them  
21 which were probably not exportable. I said I wasn't  
22 really comfortable taking some of those things with me  
23 and then he brought out this very interesting little  
24 rug that he had which is from something called an  
25 Anguna cow. He explained to me that this particular

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1 animal was a domesticated cow and he didn't need an  
2 export permit for it and it was really a marvelous  
3 animal, the traditional cow in the southern part of  
4 Africa and it's the one that the bushmen traditionally  
5 herded and had several qualities which made it  
6 particularly appropriate for the harsh climate of the  
7 southern part of Africa.

8 I went onto a web page and got some  
9 information before I came down here on the Anguna cow,  
10 because I didn't know very much about it, and amongst  
11 the things in the article that I found, it said they  
12 had a docile and calm temperament, they were a  
13 selective grazer and browser, they were tolerant to  
14 extreme and hostile conditions and had inherent  
15 hardiness, performed very well in a highly challenging  
16 environment, survived with minimal care, oversight and  
17 supervision and finally were low maintenance and high  
18 output.

19 (Laughter.)

20 DR. OSTROFF: And I thought, what an  
21 appropriate gift for him. So here is your Anguna  
22 cowhide.

23 (Laughter and applause.)

24 DR. OSTROFF: Now you'll have something  
25 nice to put in your office.

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1           Why don't we go ahead while Rick is trying  
2 to figure out how to open it -- now that's a special  
3 gift.

4           (Laughter.)

5           DR. OSTROFF: Why don't we go ahead to our  
6 first presentation. Oh, I'm sorry, we have a  
7 presentation to make to COL Woodruff.

8           COL RIDDLE: I can't not say a few words.  
9 To begin with, I don't think that there could be a  
10 better job in the Department of Defense than the job  
11 that I've had, to be able to interact and to have  
12 colleagues that I've had during my tenure on the AFEB  
13 and to develop the friendships I have developed -- to  
14 sit at the table and have discussions with the people  
15 that I've had the opportunity to sit at the table and  
16 have discussions with, and to do the things that we've  
17 really been able to do over the last two or three  
18 years. I thank you very, very, very much for that  
19 opportunity. And again, it's a once in a lifetime  
20 opportunity and as many of you may already know, COL-  
21 Select Roger Gibson has been named as my replacement,  
22 I passed the baton. The Preventive Medicine Officer  
23 felt that Roger could do the very best at maintaining  
24 the current vector the Board is on and I  
25 wholeheartedly agree with that and I think the

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1 transition will be smooth. Roger will enjoy the job  
2 and you all will enjoy working with Roger.

3 From the bottom of my heart, I really,  
4 really do thank you and thank you, Dr. Ostroff, it has  
5 been a once-in-a-lifetime opportunity.

6 (Applause.)

7 DR. OSTROFF: Roger, you have big shoes to  
8 fill.

9 COL GIBSON: My goal is to keep you as  
10 busy and engaged as Rick did.

11 DR. OSTROFF: And let me present the  
12 certificate of appreciation to COL Tim Woodruff for  
13 his leadership, excellent organizational skills and  
14 outstanding professional knowledge and willingness to  
15 assist and cooperate in all issues surrounding the  
16 AFEB Winter 2004 Meeting at Air Force Special  
17 Operations Command, Fort Walton Beach, Florida. We  
18 have a certificate for you and we also have a very  
19 nice plaque to commemorate the occasion. Thanks very  
20 much for hosting us.

21 (Applause.)

22 DR. OSTROFF: And one more special thing.  
23 We now have an AFEB coin, which really is beautifully  
24 done, another fine accomplishment of COL Riddle. And  
25 you are the first recipient.

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1 (Applause.)

2 DR. OSTROFF: With that, unfortunately  
3 we're about 15 minutes behind schedule, so I'm going  
4 to ask COL Wyman, who I think is the first presenter.

5 COL WYMAN: Distinguished Board members  
6 and guests, on behalf of Lieutenant General Hester,  
7 the Commander of AFSOC and the men and women, the  
8 airmen in the Air Force Special Operations Command,  
9 welcome and thank you for all the great work that you  
10 guys do, the work that you've done in the past and the  
11 work that you will do for us in the future.

12 The Air Force has a label for what you  
13 guys do and we call it force health protection. Not  
14 real glamorous, not like our cool surgeons down range  
15 doing the things that makes the press, save the lives  
16 candidly right there, but obviously as you guys know,  
17 force health protection is critical to the success of  
18 the mission. Every commander understands that.

19 The results have been phenomenal and  
20 again, I'm sure you will discuss -- have already  
21 discussed -- the DMBI from this latest war, it's just  
22 better and better. Probably not zero, probably never  
23 going to be zero, but the closer to zero we get, the  
24 better off we are.

25 I just wanted to take a couple of minutes

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1 -- I promise I'll try to get you back on schedule here  
2 -- the discussions that you guys are going to have, I  
3 guess, yesterday, today and tomorrow, the science part  
4 is probably the easy part. For me, as a deployed  
5 warrior and now as a command surgeon for a command  
6 that obviously deploys units out there that go out for  
7 three to four months in a forward location, come back  
8 home for about two months and then go back out again.

9 We have one squadron that's doing that now on a  
10 constant basis. Both bases are down range and in the  
11 fight. So force health protection is obviously huge  
12 for them.

13 And as I was saying, the science part is  
14 probably pretty easy for you guys, it's the  
15 implementation and the application that's key.  
16 Anything you guys can do to make this -- this probably  
17 won't be politically sensitive, I'll use the blue  
18 uniform -- airman proof, army proof, you know, soldier  
19 proof, sailor proof, marine proof -- anything you can  
20 do to do that helps us.

21 Our commanders out there need to  
22 understand what this Board brings forward. It's  
23 probably not the rocket science, the epidemiology that  
24 all goes into every decision that you make, but our  
25 commanders, our airmen, soldiers, sailors and marines

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1 need to understand that that shot they're getting in  
2 their arm, that pill they're taking, is vital to the  
3 success of their -- it's obviously vital to their  
4 health and then to the success of the mission.

5 I'm not sure how much you guys have  
6 discussed a couple of endeavors recently, one with the  
7 Marine Corps in North Africa. That message is not  
8 always conveyed. So I urge you -- again, I thank you  
9 for what you do and I urge you, as you make your  
10 decision, remember the grunts. We in the Air Force  
11 have our grunts, they're called special operators, the  
12 guys in the forward edge of that battle, got his boots  
13 on the ground, this is a typical uniform of an AFSOC  
14 warrior. We are down in the dirt with the Army, with  
15 the Navy, with the Marines. Even our flying platforms  
16 are forward in areas where disease and critters run  
17 rampant.

18 And so I urge you, as you make your  
19 decisions, remember the soldier and try to make these  
20 implementations as soldier proof as you can.

21 Again, I thank you for your time, welcome  
22 you to -- it will be sunny here, maybe not as warm as  
23 you want. Come on down in about five months and it'll  
24 be warm enough, I guarantee. The Emerald Coast is  
25 beautiful, it's been my home now for a couple of

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1 years. Enjoy your stay here. For those of you who  
2 come up tomorrow, you'll really see what it's all  
3 about. We're flying some 50-year-old helicopters, 50-  
4 year-old airplanes doing some incredible stuff.  
5 You'll see some of that. I don't want to steal all of  
6 Tim's thunder, he's got a presentation for you  
7 tomorrow, some of the things that your medics in  
8 AFSOC, but all your SOCs, and CSAR, Combat Search and  
9 Rescue which AFSOC's all about these days, are doing  
10 some incredible things in some incredible places. You  
11 get a phone call today and they're in places I can't  
12 pronounce and it'll be up to the decisions of this  
13 Board to ensure that they are fit to fight, fit to  
14 fight tonight and that force health protection is not  
15 a buzz word but something that they love and the  
16 commanders understand.

17 So thank you for your time and welcome to  
18 Florida.

19 DR. OSTROFF: COL Wyman, thanks very much.

20 Speaking for all of us, we appreciate everything that  
21 you and the fine folks at Air Force Special Operations  
22 Command do for not only us but for the entire country.

23 And thanks for hosting us.

24 Our next presentation is also one that we  
25 have to have on an annual basis and it's our ethics

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1 training, and we have with us Mr. Ron Buchholz from  
2 the Department of the Army Office of the Judge  
3 Advocate General, Standards of Conduct Office, which  
4 is a pretty big title. He's going to present our  
5 annual ethics training.

6 MR. BUCHHOLZ: Good morning. I don't  
7 often get to address a distinguished group as this.  
8 I'm also a retired Army JAG Colonel and my only  
9 experience with the medical community throughout my  
10 career has been late '80s time frame, I was the  
11 putative subject matter expert in the legal community  
12 at least for the treatment and disposition of HIV  
13 soldiers. I think I'm familiar with the term  
14 epidemiology, but that was a long time ago.

15 Again, I guess this is your mandatory  
16 block of instruction. I will try to keep you on  
17 schedule here. I suppose you want to get this out of  
18 the way, so you can get into the meat of your  
19 conference. I'll try not to bore you to tears.

20 I do welcome the opportunity to come here.  
21 Any time I can talk to folks about ethics, I view my  
22 role in this thing as trying to be helpful. Hopefully  
23 I can be as helpful to you in the ethics environment  
24 as you are to the military in the area of what you do  
25 in the medical community. My phone number and e-mail

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1 is up there. You'll get the slides, please don't  
2 hesitate to write me, e-mail me, call me on the  
3 telephone. I take calls all day long. I don't know  
4 that anybody in this room necessarily has a big  
5 problem in this area, it's my understanding y'all  
6 serve without compensation, you deserve a bigatta boy  
7 for that, but there is obviously a potential for  
8 conflicts of interest and if I can help you walk  
9 through that mine field at all, especially those that  
10 have some outside connections that might carry over  
11 into something you do with the Board, that's what I'm  
12 there to sort out. Obviously I can do a lot more to  
13 prevent a situation than if something has gone astray.

14 DR. OSTROFF: Let me just point out that  
15 your presentation is in Tab 2 of the briefing book.

16 MR. BUCHHOLZ: Okay.

17 As far as agendas, I'm going to talk about  
18 your status as special government employees, your  
19 legal status, your requirements to file financial  
20 disclosure reports, situations under which it might be  
21 a good idea to disqualify yourself from acting in a  
22 particular subject matter in the course of your duties  
23 on the Board just to prevent a conflict of interest  
24 from arising, and a little bit about gifts from  
25 outside sources, since you may be in a situation where

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1 some gratuities might come your way.

2 As has been mentioned, the Armed Forces  
3 Epidemiological Board is a Federal Advisory Committee  
4 Act Board, created under that statute as the specific  
5 authority that allows federal government agencies  
6 generally to have these kinds of organizations.

7 Board members are considered special  
8 government employees, and as you can see, you are an  
9 individual who serves with or without compensation. I  
10 guess we do have some out there that serve with  
11 compensation. Not to exceed 130 days during any  
12 period of 365 consecutive days. Now that means as  
13 long as you perform some kind of duty in your capacity  
14 as a Board member on any given day, whether it's an  
15 hour or whatever, that's considered a day of duty. I  
16 don't know that anybody on the Board has a problem  
17 exceeding the 130 days. I know you've got annual  
18 meetings throughout the year, but anyway, if you think  
19 for whatever reason you might get over that 130 days,  
20 please give me a call.

21 There's also a regulatory basis for the  
22 Board. As almost everything important that happens in  
23 the Department of Defense, we've got a regulation that  
24 covers it. I believe your appointments are consistent  
25 with the requirements of up to four years. There's

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1 also an Army regulation. I didn't know that this  
2 regulation existed until I started doing the research  
3 for this presentation. It's a little long in the  
4 tooth, but it is relevant because the Army has  
5 executive agency for the Board.

6 Now you may have read about Mr. Pearle's  
7 problems not too long ago in his capacity on the  
8 Defense Policy Board, he ran into a potential conflict  
9 of interest because prior to serving in that capacity,  
10 he was also getting a significant retainer from a  
11 company called Global Crossings which was hiring him  
12 to try to influence the Department of Defense to look  
13 favorably on their acquisition by a foreign company.  
14 Well, the media got ahold of that and next thing you  
15 know, Richard Pearle has to resign from his position  
16 on the Defense Policy Review Board.

17 So again, those are the kinds of things.  
18 I can only speculate on the opportunities y'all might  
19 have in your capacities representing various  
20 institutions of higher learning or companies that do  
21 business providing medical services or  
22 pharmaceuticals, et cetera. But that's what I'm here  
23 for, I'm here to prevent a Richard Pearle situation  
24 from happening on the Board.

25 Okay, financial disclosure. Why do we go

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1 through that drill of asking you to do a financial  
2 disclosure report annually? It's to identify and  
3 avoid potential conflicts of interest. When you  
4 submit the reports, the Executive Secretary looks at  
5 them, he forwards them to me, I take a look at them  
6 and if something pops up, we might come back to you  
7 and ask a few questions, and then at that point we  
8 might ask you to do a disqualification statement  
9 because of that potential.

10 Most of you file what's called an Office  
11 of Government Ethics Form 450. It is a confidential  
12 report, they don't get released outside the agency,  
13 not even under a Freedom of Information Act request,  
14 which is a little bit different than folks who file a  
15 public financial disclosure report which is called an  
16 SF -- standard form -- 278. Generally, those are  
17 special government employees that would be paid at a  
18 rate that exceeds the level that a member of the  
19 senior executive service or an officer of flag rank  
20 would receive. Now those are significant in the sense  
21 that, one, there's a great deal more detail required  
22 on a 278, you're required to disclose the amounts of  
23 financial interest that you have, within ranges, and  
24 they're also publicly releasable. My office has only  
25 responded to two requests for release of public forms

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1 since I've been there in the July-August time frame,  
2 but both were situations where there was some media  
3 attention. One general officer who got himself in a  
4 little bit of trouble by speaking in uniform about  
5 some religious matters, and a Presidential candidate.

6 (Laughter.)

7 MR. BUCHHOLZ: So anyway, going back to  
8 the 450. They stay in my office, they don't go  
9 anywhere else. As I said, it should be completed  
10 before assumption of duties, that's so we can examine  
11 the situation prior to the time of your appointment.  
12 Hopefully that's happening. And then an annual  
13 requirement thereafter.

14 Now usually everybody within the  
15 Department of Defense files those things no later than  
16 to 30th of November. I recently received some  
17 guidance from the Office of Government Ethics that  
18 suggests that we do it on an annual basis either on  
19 the anniversary of one's appointment or some arbitrary  
20 date like May 15, which is the date that the 278 is  
21 due, and it just helps to coordinate all that. I will  
22 work with COL Riddle or his successor on how we're  
23 going to do that. Bottom line is we'll make it as  
24 unobtrusive and as easy for y'all as possible.

25 Okay, what are we going to look for?

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1 We're going to look for interests in what are known as  
2 prohibited sources. That's just a fancy term in the  
3 joint ethics regulations for an entity that does  
4 business or seeks to do business or is receiving  
5 grants from DoD. Could be an entity with whom you're  
6 employed or by whom you're employed either in a  
7 consulting relationship or you're a physician on the  
8 staff, whatever. Could be an ownership in stock or  
9 other equity in the organization. Now not every  
10 ownership of some financial interest like stock is  
11 going to disqualify you from participating in matters  
12 before this Board. There are certain levels that are  
13 called de minimis exceptions. The first of that sort  
14 is a \$15,000 limitation. So in other words, even if  
15 you own \$14,999 worth of stock in a company whose  
16 product is being considered by the Board for use  
17 throughout Department of Defense and is again a  
18 particular matter, not a buzz work, that you all are  
19 involved in, you could still participate in that kind  
20 of recommendation.

21 As far as filling out the 450, they're a  
22 nuisance, a lot of people don't like to do it, a lot  
23 of people resent having to disclose anything about  
24 their financial holdings, but it's a lot less painful  
25 when you remember that, first of all, there's no

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1 dollar amounts on an OGE Form 450. If I see a holding  
2 in a stock that might look like a stock in a  
3 pharmaceutical company or something of that nature, I  
4 will call you or write you and ask you what is the  
5 nature of your holding and whether it exceeds these  
6 so-called dollar amounts, and then we go through the  
7 analysis and determine whether you need to disqualify  
8 yourself.

9 I do ask when you fill it out though that  
10 instead of just putting down -- I actually had an  
11 employee do this, she just put down stocks, bonds,  
12 mutual funds. This was another employee in DoD that  
13 wasn't happy with her supervisor asking her to fill  
14 out this form. We do need the name of the company in  
15 which you own stock, we need the complete name of the  
16 mutual fund company. As it says, Fidelity is not good  
17 enough, Fidelity has about 30 funds or more, we need  
18 to know if it's Magellan or if it's Growth and Income  
19 or something like that. Why? Most of the time a  
20 mutual fund is not a problem. They're widely  
21 diversified, you don't control what's bought and sold  
22 as part of the mutual fund. However, if it's a sector  
23 fund, something say that concentrates in  
24 pharmaceuticals, you know, health services, things of  
25 that nature, it might become relevant for what you

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1 folks do. At that point, we would then inquire  
2 because again, if it's another one of those amounts  
3 that doesn't exceed that level, you're going to be  
4 okay, but we at least have to ask the question. But  
5 that's why we need the individual name of the fund.

6 You may attach a brokerage statement that  
7 shows you are doing fairly well and would rather not  
8 have to completely copy down everything you own onto a  
9 450. Take your brokerage statement, X out all the  
10 personal information like home address and social  
11 security number, account numbers, all that, and we'll  
12 do it that way, try to make it as easy as possible,  
13 and also the dollar amounts. Again, we're generally  
14 not interested in the dollar amounts of the  
15 investments.

16 Okay. Disqualification. Why do we talk  
17 about disqualification? Again, we're talking about a  
18 criminal statute here. Unfortunately once you become  
19 a so-called special government employee, you're bound  
20 by these federal criminal statutes that says you  
21 cannot participate personally and substantially in an  
22 official capacity, in other words, as part of the  
23 Board, in a particular matter in which you've got a  
24 financial interest. Now again, there's a bunch of  
25 buzz words in there -- personally, substantially,

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1 particular matter. We have to define what that  
2 particular matter is sometimes, but once we do that,  
3 then we can determine whether there's a potential  
4 problem. And of course, it has to have a direct a  
5 predictable effect on the financial interest. So  
6 again, if you've got \$14,999 worth of stock in X  
7 pharmaceutical company, it's not going to have, by  
8 definition, a direct and predictable effect. So we  
9 can deal with the problem through that sort of  
10 analysis.

11 So basically we're -- now this is  
12 something used by the Senate Armed Services Committee.

13 If you're a three or four-star flag officer being  
14 nominated for a position, the Senate Armed Services  
15 Committee will not let you serve unless you divest  
16 yourself of the stock in any of the top 10 DoD  
17 contractors, for example. So if in fact, we ever get  
18 to the point where we determine that y'all might have  
19 to divest yourself of some financial interest, be  
20 advised that hopefully it's not going to be a money  
21 losing venture, you will get a certificate that will  
22 allow you special treatment for tax purposes.

23 Generally, a potential conflict of  
24 interest can be resolved by just having you execute a  
25 disqualification statement. A copy comes to me, a

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1 copy would go to the Executive Secretary and to the  
2 President, just basically advising them that you do  
3 have a financial interest that may be potentially  
4 disqualifying and, therefore, you can't participate in  
5 a particular matter that would affect that particular  
6 financial interest. Again, low likelihood that that  
7 would happen, but again, that's the remedy generally  
8 for those kinds of situations.

9 There's some blanket exceptions out there.

10 I mentioned them before, you can -- generally it's a  
11 widely diversified mutual fund, they increased the  
12 levels recently from 5000 to 15,000. That's  
13 realistic. If you've got \$5000 worth of stock in a  
14 company like Cola-Cola, that's really not going to  
15 matter whether or not you can influence that in any  
16 fashion.

17 Okay, going on to gifts. If you are in a  
18 situation where a particular company -- and this may  
19 occur -- as you read the stories in the media at  
20 least, there's accusations that folks in the medical  
21 community are often being plied with gifts from  
22 pharmaceutical companies and things of that nature, to  
23 get them to try their company's products. If that is  
24 a situation that's related to the workings of the  
25 Board, again, that company would be considered to be a

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1       privated source, if it's trying to influence what the  
2       Board recommends with regard to a particular product  
3       or service that is being offered.

4               A gift may be prohibited if it's offered  
5       because of your rank or your position. So in other  
6       words, if someone approaches you, knowing that you're  
7       a member of the Armed Forces Epidemiological Board, if  
8       they know who you are, and again, regardless of the  
9       dollar amount, again, they're trying to influence you  
10      in the course of your official business with the  
11      government and that could be a problem.

12             There are certain things that are not  
13      gifts, like the coffee and pastry and things like that  
14      that are being served here. If you go to a conference  
15      or seminar being sponsored by a contractor, you can  
16      eat their doughnuts and drink their coffee as well.  
17      Plaques and trophies, that comes in under the  
18      exception that we call the cheap and worthless  
19      exception --

20             (Laughter.)

21             MR. BUCHHOLZ: Maybe there's some residual  
22      value in the metal used for the plaque or whatever,  
23      but I mean other than hanging on your wall, it has no  
24      intrinsic value.

25             You can accept things from folks that you

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1 know that are offering you things because of your  
2 personal relationship and not your official  
3 relationship.

4 And other than that, if it's worth \$20.00  
5 or less, you can accept it as long as you don't accept  
6 more than \$50.00 from the same source in any given  
7 year.

8 Now I suppose there's always the situation  
9 where someone might want to take you to McDonald's for  
10 lunch 10 times a year and that's under 50 bucks  
11 probably, but someone might suggest that if you're  
12 seen in the company of this particular pharmaceutical  
13 company rep or whatever, they're going to think that  
14 they've got their hands in your pocket. So there  
15 always the appearance of impropriety issue that you  
16 should consider.

17 Widely attended gathering -- that's a real  
18 good one for you folks that tend to go to a lot of  
19 professional type conferences or seminars. If you're  
20 invited to speak at one, generally you can accept the  
21 invitation, you can accept the conference fee, you can  
22 accept other items that come with it, provided we can  
23 classify it as one of these widely attended  
24 gatherings. A lot of senior military people take  
25 advantage of that, because again, they're being asked

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1 to come to make a presentation and as long as it's not  
2 being sponsored by say one DoD contractor which is  
3 obviously just trying to get their status as a draw to  
4 their conference, again, this is a way to accept  
5 sometimes a gift worth hundreds of dollars. You know,  
6 some of these conferences are well over \$500 a day.

7 Any questions so far?

8 (No response.)

9 MR. BUCHHOLZ: Hey, that's good. If we  
10 could just go on. I just wanted to finish up with a  
11 little discussion here of the 14 principles which are  
12 the basis for all of the ethics rules that apply to us  
13 as either current government employees or special  
14 government employees. Again, don't worry about the  
15 legal mumbo-jumbo on the top. Suffice it to say that  
16 this all comes from an Executive Order and these  
17 rules, these 14 principles, provide the basis for all  
18 of these federal rules and regulations and the joint  
19 ethics regulation that bind all of us in DoD.

20 As you can see, the purpose of them is to  
21 maintain generally the trust and confidence of the  
22 American people in what we do for the federal  
23 government. And essentially what we do, we're going  
24 to put above personal gain.

25 Number two, you can see basically that's

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1 the principle that's at the root of most of what we're  
2 talking about today, and that is we will not hold  
3 financial interests that conflict with the  
4 conscientious performance of our duty.

5 Number three, that's something else that  
6 might apply to folks on this Board. You may gain  
7 access to information that is not public information.

8 Maybe not classified, but it could be very sensitive,  
9 could be something that we would not release under the  
10 Freedom of Information Act. To the extent that you  
11 become party to that information, it is also protected  
12 by federal criminal statutes. I don't say that to  
13 strike the fear of God into you or intimidate you, but  
14 there again have been people that have run afoul of  
15 that and gotten into some difficulty.

16 Number four is the gift prohibition we've  
17 been talking about.

18 Number five, I don't think that's a  
19 problem for folks in this room, because in my opinion,  
20 you're serving above and beyond the call, you're  
21 putting in an honest day's effort for an honest day's  
22 pay, which you're not receiving, so --

23 (Laughter.)

24 MR. BUCHHOLZ: -- you've got five locked  
25 down.

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1           Number six applies to people that have the  
2 authority to bind the government -- well, actually it  
3 applies to all of us in the sense that we do have some  
4 people out there that unfortunately commit the  
5 government to buy goods and services when they don't  
6 have the authority, and oh, by the way, if we don't  
7 ratify that, that come out of your pocket. So that's  
8 just kind of a suggestion to make sure that you don't  
9 exceed the limits of your authority.

10           Number seven is a repeat of basically  
11 number two. We're not to use public office for private  
12 gain.

13           Number eight covers situations where when  
14 you're dealing with non-federal entities, private  
15 organizations. We're not going to give preferential  
16 treatment to one versus the other. That shouldn't be  
17 a big problem for you folks. It is sometimes in the  
18 military where folks get into professional  
19 organizations and things start to happen.

20           Nine is just an exhortation to be diligent  
21 conservators of our government resources and, again,  
22 not use them for personal gain.

23           Okay, ten talks a little bit about what's  
24 at the root of why we do financial disclosure as far  
25 as our outside employment and activities so that they

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1 don't conflict with what we do for the government.

2           Number eleven is a responsibility that we  
3 all have to -- if we see something that is unethical,  
4 illegal, immoral, that we do something about it,  
5 report it to the Inspector General, to our supervisor,  
6 whatever.

7           Number twelve is interesting because it  
8 goes well beyond necessarily what's related to our  
9 jobs but just talks about otherwise taking care of our  
10 responsibilities as citizens, to include paying our  
11 taxes.

12           Thirteen deals with equal opportunity;  
13 again, a little bit different slant than the rest of  
14 the ethics rules, but also a good idea.

15           And number fourteen is a catch-all, and  
16 that's where again, if I could make this observation,  
17 I doubt that there will be an actual conflict of  
18 interest that will arise between what you do in your  
19 outside activities. If there is, we are going to try  
20 to prevent them. But also, you're cautioned that  
21 there may be situations that arise -- maybe not so  
22 much an outside interest that you have, but maybe an  
23 outside interest in what is known as a covered  
24 relationship -- your spouse, a child, a close family  
25 member, where if someone else saw the relationship

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1 might think oh, isn't that interesting, this  
2 individual's brother, sister, wife, et cetera has this  
3 financial interest, and oh, by the way, this guy is in  
4 a position on this Board to influence that. So to the  
5 extent that there is this appearance of impropriety,  
6 we also must deal with that.

7 And I think that's it.

8 DR. OSTROFF: Thanks very much. Let me  
9 ask if there are any questions or comments from the  
10 members of the Board.

11 (No response.)

12 DR. OSTROFF: Seeing none --

13 MR. BUCHHOLZ: If I may, I also have a  
14 couple of resource materials that, if you'd like, I  
15 can certainly provide a copy to you at some point.  
16 There is an ethics guide for consultants and advisory  
17 committee members at Department of Defense, this is a  
18 DoD publication, very, very good, kind of summarizes a  
19 lot of what I've been talking about. There's also a  
20 packet of guidance for the Designated Federal Officer.

21

22 And there's also some guidance -- one of  
23 the topics we generally mention at ethics briefings  
24 this year, being an election year, are political  
25 activities. Don't know if anybody in this room has a

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1 particular interest in politics or in the campaigns  
2 this year, but in case you are, it's my understanding  
3 that DoD's rules on political activities do apply to  
4 special government employees also. So if you are  
5 interested in what those might be, I can give you a  
6 copy of DoD's guidance -- some do's and don'ts about  
7 the extent to which you can participate. And it's a  
8 fairly extensive set of guidance. There's a lot you  
9 can do and some things you can't, but anyway, I've got  
10 those materials with me if anybody is interested.

11 Thank you.

12 DR. OSTROFF: Thanks very much.

13 I think what we'll do is move on to the  
14 next presentation. The morning and a large part of  
15 the day is filled with issues related to vaccines and  
16 immunizations pertinent to one of the questions before  
17 the Board. So we're going to start out with an update  
18 from COL Grabenstein, who is going to talk about the  
19 current status of vaccination programs, a subject  
20 which has very much been in the news over the last  
21 couple of months, with the lawsuit related to the  
22 anthrax vaccination program. We look forward to your  
23 presentation.

24 COL GRABENSTEIN: Thank you, sir.

25 Appreciate the opportunity to come back to join you.

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1 DR. OSTROFF: And let me just point out  
2 that his materials are not in the briefing book.  
3 However, they should be at your table. If anybody  
4 doesn't have them, let me know. Should be underneath  
5 the binder.

6 COL GRABENSTEIN: My compliments also to  
7 COL Riddle for his tenure with the Board. Dr.  
8 Ostroff, you forgot to mention that that animal is a  
9 fertility symbol there in South Africa.

10 (Laughter.)

11 COL GRABENSTEIN: I'm not sure that you've  
12 alerted his wife to that.

13 (Laughter.)

14 COL GRABENSTEIN: It's a pleasure to come  
15 back and give you a quick update.

16 In all that we do, as you all understand  
17 very, very well, what we are doing this for is not  
18 ourselves but for the troops. And wisely, as the  
19 editors of Time magazine noticed, the contributions of  
20 good, simple folks and named the soldiers, sailors,  
21 airmen, marines, coast guardsmen Person of the Year.  
22 So this is just a reminder of their contributions and  
23 a graphic depiction of our mission statement.

24 This is my ninth presentation to the Board  
25 on military vaccination programs. This is the first

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1 where I will sum up the entire anthrax vaccination  
2 program on one slide.

3 (Laughter.)

4 COL GRABENSTEIN: Basically, on December  
5 22 -- well, let me go back -- on March 17, 2003,  
6 President Bush gave Saddam Hussein 48 hours to leave  
7 Baghdad.

8 On the following morning, four John Does  
9 and two Jane Does filed suit in U.S. District Court  
10 alleging that anthrax vaccine is illegal, that the  
11 vaccination program is illegal, not of appropriate  
12 standing with regard to the Food, Drug and Cosmetic  
13 Act. A hearing was held in May. The judge waited  
14 until -- on the 22nd of December, the Judge issued an  
15 injunction against the program, stating that the  
16 Department of Defense was treating service members as  
17 guinea pigs and that any anthrax vaccinations must be  
18 conducted with informed consent.

19 This was contrary to DoD's arguments, of  
20 course, as well as the Food & Drug Administration's.  
21 And one of the key bases for the Judge's decision was  
22 that the Food & Drug Administration had never  
23 finalized the 1985 proposed rule, and therefore, the  
24 FDA had made no final statement with regard to the  
25 vaccine's status. This, despite FDA's statements to

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1 Congressmen, in response to citizens' petitions and  
2 the like.

3 So on December 30, the FDA issued that  
4 final rule, which had been in percolation for about a  
5 year or two, and so on December 31, we got something  
6 we don't usually get, which was 24 consecutive hours  
7 of good publicity. But these are the newspaper  
8 headlines when the FDA lifted -- or issued that rule.

9 Then the Judge lifted his injunction and we were back  
10 in business.

11 So from March of '98 through February of  
12 '04, we have now given 3.9 million vaccinations to  
13 almost 1.1 million people. And that's where the  
14 program stands.

15 The litigation continues. The current  
16 claim of the plaintiffs is that the final rule is  
17 invalid and that argument will be heard in May of '04.

18 So no doubt, there is more to come on this issue.

19 Any questions on anthrax? The bulk of the  
20 rest of my talk is on smallpox.

21 (No response.)

22 COL GRABENSTEIN: This is just an update.

23 This is one of the efforts that the Army is using to  
24 keep people up to date with the vaccination schedule.

25 I just thought I'd show this to you in terms of our

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1 ability, using technology, to customize messages to  
2 individual service members. The box that's marked A  
3 is -- well, the Army has an information portal called  
4 Army Knowledge Online, AKO. The other services have  
5 something similar, each of them.

6 Box A is what shows up when I log in.  
7 Between my dose 5 -- after I got dose 5, but before I  
8 got dose 6, telling me that dose 6 was due on the 10th  
9 of January. I let myself go overdue so I could  
10 capture the next graphic which is box B that says  
11 you're currently overdue for your next anthrax  
12 vaccination, your due date was the 10th of January.  
13 Please contact your primary care provider to schedule  
14 the vaccination. So customized messages to promote  
15 adherence to the schedule.

16 Adverse events after smallpox vaccination  
17 -- we now are at the point of having screened about  
18 665,000 people, vaccinated 581,000 of them. The  
19 balance of the numbers on the chart are the same as I  
20 showed you at the last meeting, about two-thirds  
21 primary, about 88 percent male and with low levels of  
22 use of sick leave post-vaccination.

23 These are the more note-worthy or  
24 clinically significant adverse events. The  
25 generalized vaccine account has risen -- actually

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1 these are all very much like what I showed last time  
2 only rising in relatively small numbers. Generalized  
3 vaccinia, you have 36, mostly treated as outpatients.

4 Inadvertent infection of the skin or eye of the self  
5 or of contacts, the four values that you see there.  
6 The contact transfer cases were summarized in last  
7 Friday's issue of the morbidity and mortality weekly  
8 report which identified two cases of tertiary  
9 transfer. One case from a soldier to his wife to a  
10 breast-feeding child and one triple case of a  
11 vaccinated marine to another marine to another marine  
12 who had no contact with the first one, in a serial  
13 wrestling event.

14 (Laughter.)

15 COL GRABENSTEIN: The principal risk is  
16 that of sharing your bed with somebody who has been  
17 vaccinated. Essentially failure to bandage, not  
18 failure of bandage. Most of the 31 are spouses and  
19 adult intimate contacts or sports partners. Again,  
20 remarkably and significantly, we've had zero  
21 transmissions in not just healthcare settings where we  
22 use the semipermeable membrane dressings, but also in  
23 any workplace setting -- not on ships, not in  
24 aircraft, not in tanks, not on derricks. Yes, on  
25 basketball courts and in wrestling rinks or whatever

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1 the word is -- arenas.

2 No new uses of vaccine immunoglobulin,  
3 still two. We had modeled that we would need 58  
4 courses by now and we've used only two.

5 Eczema vaccinatum, zero and no progressive  
6 vaccinia, a tribute to the effectiveness of the  
7 screening process on five continents and several dozen  
8 ships at sea.

9 No new cases of encephalitis. The mild  
10 pericarditis count is now at 72, 68 probable, four  
11 confirmed.

12 And with thanks to the Board for their  
13 contributions of Dr. Poland, Dr. Gray, Dr. Shope and  
14 others in the every Friday conference call in  
15 collaboration with the Advisory Committee on  
16 Immunization Practices for review of many of these  
17 cases, including several death cases.

18 The unrelated cases are of some heart  
19 attacks, atherosclerotic coronary vascular disease,  
20 drug overdose, hyperthermia case and classified as  
21 unrelated to smallpox vaccination. Regrettably, one  
22 case of a 22-year old Army Reservist, who developed a  
23 lupus-like illness in the weeks after vaccination and  
24 the panels have concluded that vaccination should be  
25 considered a possible cause of her illness, not a

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1 definitive cause, and motivates some of the further  
2 discussion that we will under go today.

3 Part of the concern in her case was that  
4 she had received five vaccinations in her  
5 mobilization. Actually two panels reviewed her case,  
6 the AFEB work group as well as a panel developed or  
7 staffed or named by the Health Resources and Services  
8 Administration. Both groups used different words, but  
9 came up with the same conclusion about the possible  
10 nature of the relationship.

11 Unfortunately, among the five vaccinations  
12 she received, there is no physical evidence to assert  
13 that any one of the vaccines that she received  
14 triggered the illness, which raises some of the  
15 question we will talk about later.

16 I showed you at the last meeting some of  
17 the work we had done in terms of evaluating the  
18 evolution of smallpox vaccine responses over the four  
19 weeks post-vaccination, and the last time I showed you  
20 the data lumped with primary vaccinees and re-  
21 vaccinees grouped together. This shows it now  
22 stratified and split, so that you see that the  
23 dynamics of the vaccine response are quite different.

24 We knew this, but we didn't know how to chart it out.

25 This top line of diamonds is itching and then the

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1 bold blue is leaking from the vaccination site. In  
2 other words, exudate absorbed by the bandage. You see  
3 that with the primary vaccinees. And then third is  
4 bandage rash, which is not an uncommon response as we  
5 worked on keeping the vaccination site covered to  
6 minimize our contract transfer cases.

7 And similarly, systemic events after  
8 smallpox vaccination stratified -- swollen lymph  
9 nodes, quite remarkably different between initial  
10 vaccinees and re-vaccinees. The purple is headache,  
11 the orange is muscle ache, the green is -- I guess  
12 that's olive -- joint ache, and then the balance.  
13 These are all self-reported, not clinically confirmed.

14 This shows what we know to be true but had  
15 not been able to quantify previously. This is the  
16 date that the new skin manifestation manifests,  
17 stratified by primary vaccinees and re-vaccinees,  
18 showing that re-vaccinees respond faster to smallpox  
19 vaccination -- or manifest faster than re-vaccinees.  
20 This is the onset of the macule, the papule, the  
21 vesicle, the pustule and then the scab formation and  
22 falling off. And remember that we had -- it doesn't  
23 show on this one quite as well, but we had -- the  
24 received wisdom from the ages was that the scab falls  
25 off between days 14 and 21 and our modern experience

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1 is that it is considerably delayed for about half of  
2 the recipients, even out to day 28, probably also an  
3 effect of bandaging.

4 I'll close with this slide, just showing  
5 the intensive effort we have put in with respect to  
6 education, both of the individual vaccinee as well as  
7 healthcare providers. I would be remiss not to  
8 congratulate the individual medics and nurses and  
9 physicians and other healthcare workers in so many  
10 places literally around the globe who in the midst of  
11 going to war learned smallpoxology in order to safely  
12 give this vaccine and the level of skill and care  
13 delivered, the appropriate precautions observed under  
14 remarkable circumstances can't be lauded enough. This  
15 is not a question of headquarters did a good job, this  
16 is the field doing a good job.

17 And I'll stop there and be happy to take  
18 any questions.

19 DR. OSTROFF: COL Grabenstein, thanks very  
20 much. Let me open it up to questions and discussions.

21 I'll start with a couple of questions for you.

22 I must confess I was a little surprised to  
23 learn about the litigation involving the anthrax. If  
24 the suit was filed basically the day after the war was  
25 about to start, it flew under everybody's radar screen

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1 and didn't seem to get a lot of attention at the time.

2 I guess it raises the question, do you have any sense  
3 for how many service members are being discharged  
4 because they are refusing to receive this vaccine and  
5 is it your sense that this is more or less the same  
6 than it was with the first vaccination campaign?  
7 Because I think most of us had been under the  
8 impression that after many of the recent events,  
9 including 9/11 and the anthrax episode, et cetera,  
10 that the vaccine was quite a bit more acceptable to  
11 most service members than it was with the first effort  
12 that went on in the 1990s.

13 And then the second question I have is can  
14 you talk a little bit about the supply of the vaccine,  
15 because that was also a major problem in the past.

16 COL GRABENSTEIN: The supply question is  
17 simpler to answer, so I'll do that first. Phycor has  
18 been producing steadily since January of 2002 and we  
19 actually have at the moment a six digit number of  
20 doses that are FDA released and on hand, able to be  
21 used. So our policies are not constrained by supply.

22 It's not an infinite quantity, it's a finite  
23 quantity, but at this point, we could -- you know, we  
24 are able to provide vaccine to other government  
25 agencies if they request, subject to various economy

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1 act of transfer issues or to either continuance or  
2 expansion of duty policies as the civilian decision  
3 makers direct us.

4 With regard to separations related to  
5 refusals, there is a very marked dichotomy, before and  
6 after the lethal anthrax attacks of fall 2001. Prior  
7 to that, during essentially '98, '99, 2000, there were  
8 some 400 or so UCMJ, Uniform Code of Military Justice,  
9 actions related to refusal of anthrax vaccination.  
10 Subsequent to the lethal attacks there have been  
11 essentially 10, or at least that's the order of  
12 magnitude -- you know, whether it's eight or twelve,  
13 it's something along those lines. And so the number  
14 of people refusing vaccines are extremely few.  
15 Nonetheless, there is a -- I think it is literally an  
16 exact description to call them zealots who are deeply  
17 resistant to the vaccine and object to the vaccine and  
18 have used every avenue available to them to try to  
19 stop the vaccination program, the anthrax vaccination  
20 program. And in this case, it was U.S. District  
21 Court.

22 UNIDENTIFIED SPEAKER: What can you tell us  
23 about new anthrax vaccines that were in the pipeline?

24 COL GRABENSTEIN: There are at least three  
25 different efforts to create a next generation anthrax

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1 vaccine based on recombinant protective antigen or  
2 RPA, and two are under contract with HHS, one under  
3 contract with DoD. They are just beginning their  
4 phase one studies so the total number of humans that  
5 this product has been in is either in the dozens or in  
6 the hundreds, in contrast to the million that the  
7 current vaccine has been in. In terms of licensing,  
8 there is still three to four to six to eight years  
9 off, in terms of licensing with the FDA.

10 UNIDENTIFIED SPEAKER: John, can you give  
11 us a couple of insights -- the injunction of the Judge  
12 was filed within two days of the announcement of the  
13 FDA. Obviously you didn't generate new data during  
14 that time. That's a world's record. Tell us how you  
15 did that.

16 COL GRABENSTEIN: What isn't apparent from  
17 the newspapers is all the work that was going on in  
18 the background. Basically these proposed final rules  
19 from the '80s -- there is another proposed final rule  
20 for viral vaccines that has not been finalized either  
21 and in my words, the FDA thought it had better things  
22 to do than finish -- you know, with limited resources  
23 -- had more important things to do than to finish out  
24 these rules.

25 As the anthrax vaccine criticism continued

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1 for so many years, the FDA began working on finalizing  
2 the rules. If you've read the rule, it's not just  
3 about anthrax, it's about -- several pages on  
4 pertussis products and the adverse event reporting and  
5 maybe a third of the rule is about anthrax, but the  
6 other two-thirds is about other issues and vaccines.

7 And I can tell from questions that various  
8 FDA staffers were asking me, they had been working on  
9 the rule for at least a year, more like maybe two, in  
10 the background, and this was a situation where the  
11 Judge put in the injunction, somebody high in the FDA  
12 leadership called downstairs to find out where the  
13 proposed rule was and all they had to do was dot some  
14 I's, cross some T's and take it down to the Federal  
15 Register, and so a week later they were able to  
16 essentially provide the final copy to the Federal  
17 Register folks and then it was a further week later  
18 that it was actually printed in the Federal Register.

19 But despite assertions to the contrary, this was not  
20 a midnight, quick, hurry up and draft a document to  
21 placate the Judge. This was a -- you know, in typical  
22 FDA fashion, a sound piece of -- a sound document that  
23 had been percolating for quite some time.

24 COL GIBSON: This is COL Gibson. I just  
25 remind you that we are transcribing, so if you would

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1 give your names before you talk.

2 DR. OSTROFF: And before I go to Dr. Berg  
3 -- you know, if you knew that the lawsuit had been  
4 filed back in May and that this was one of the major  
5 bases of their argument, why wasn't something done to  
6 get them to move to the final rule long before the  
7 Judge actually issued this ruling? Because certainly  
8 the perception now is that somebody pressured FDA to  
9 do something.

10 COL GRABENSTEIN: You're asking me why FDA  
11 proceeded at the pace it proceeded. You have to ask  
12 the FDA that question. You know, it was moving. I  
13 don't have an answer for you.

14 DR. BERG: Bill Berg. John, these graphs  
15 of the adverse reactions and side effects are very  
16 nice. What is the denominator and how did you get  
17 them?

18 COL GRABENSTEIN: I think the explicit  
19 denominator is on the next to the last one. That data  
20 is 156 primary vaccinees and 345 re-vaccinees. The  
21 side effect numbers may have been -- are a larger  
22 denominator because we didn't need to correlate with  
23 another data source, so it gets to roughly 1000, about  
24 800 people I think in total.

25 The data was collected by having them

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1 either telephone in or use a website to select from a  
2 fixed list of symptom codes or physical descriptions  
3 of the vaccination that we provided -- pictures of a  
4 macula, papule, vesicle, pustule, to orient them, to  
5 help them choose what to call their own vaccination  
6 site. So this was an effort to see if in a mass  
7 smallpox vaccination program, if you had to vaccinate  
8 a city of 100,000, if you could keep 90,000 of them  
9 from having to come back to the clinic to have their  
10 tape read and just bring in the equivocal ones to get  
11 a professional reading.

12 DR. OSTROFF: Dr. Gray and then Dr. Brown.

13 DR. GRAY: This is Greg Gray. John, I  
14 know some months ago, you were wrestling with the  
15 management of these post-morbidity data and were  
16 having trouble finding the personnel to chronicle  
17 this. You've got 1000, when do you think you'll be  
18 able to do the 580,000 or are you kind of not going to  
19 do that?

20 COL GRABENSTEIN: Are you referring to the  
21 graphs?

22 DR. GRAY: Right, the chest pain, eye  
23 infection --

24 COL GRABENSTEIN: Oh. This is about as  
25 far as it's going to go essentially. Well, that's too

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1 cavalier. We aren't going to expand and collect more  
2 data by this medium, by -- it's from a contractor  
3 called Vocciva -- in terms of this web-based,  
4 telephone-based data collection.

5 We are pursuing the chest pain axis in a  
6 prospective fashion in collaboration with CDC, Dr.  
7 Engler may speak to this when she comes to the podium,  
8 to do serial ECGs and serial cardiac enzymes and a  
9 variety of other interventions in a cohort of a few  
10 hundred people to see what there might be in terms of  
11 subclinical morbidity with respect to cardiac adverse  
12 events using smallpox vaccine and an influenza vaccine  
13 as a control population. So that still is coming.

14 I'm not sure I've answered your question  
15 though.

16 DR. GRAY: I thought you were collecting  
17 data somehow by other means regarding the morbidity,  
18 besides this special subcontractor studies. You were  
19 going to eventually bring this into a large data set  
20 where we would have smaller confidence intervals, if  
21 you will, regarding these symptoms.

22 COL GRABENSTEIN: No, I don't --

23 DR. GRAY: This is it, 1000. Okay.

24 DR. OSTROFF: Dr. Brown and then Dr.  
25 Herbold.

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1 DR. BROWN: Mark Brown, VA. My question  
2 is what you're calling re-vaccinees, is that  
3 population where the first vaccination didn't take or  
4 is that a population --

5 COL GRABENSTEIN: This is a vaccination  
6 prior in life.

7 DR. BROWN: Before 1970 or whatever.

8 COL GRABENSTEIN: Well, for the military,  
9 prior to 1984 and 1990. My last active duty, prior to  
10 2000, my previous vaccination was in 1983. So the  
11 initial vaccinees is the first time in your life, re-  
12 vaccinees is some time prior to 2002.

13 DR. BROWN: Has anybody speculated about  
14 what this means?

15 COL GRABENSTEIN: It's what's known with  
16 smallpox vaccination. Other than initial vaccinees in  
17 the '60s and '70s were typically infants, children as  
18 opposed to adults. But essentially this is the first  
19 time this level of detail in a kinetic fashion has  
20 been reported, to my knowledge.

21 DR. OSTROFF: John and then Kevin.

22 DR. HERBOLD: John Herbold. If I can just  
23 hitchhike on Greg Gray's comment and shift from a  
24 military population to vaccinating a maybe not-so-  
25 well-screened civilian population in the case of a

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1 bioterrorism event, the complex of clinical signs of  
2 muscle ache and joint ache and headache are at 25  
3 percent are substantial. So I'm hoping that we can  
4 maybe help get some more morbidity data so that we can  
5 look at how this would play out in a mass vaccination  
6 of civilians.

7 COL GRABENSTEIN: I'm not sure how you two  
8 are using the word morbidity.

9 In the previous slide I showed that also,  
10 which is three percent or half a percent needing sick  
11 leave. But, you know, this is self-reported data,  
12 this is essentially absence or presence data. So I  
13 don't consider any of these numbers particularly  
14 surprising, given what we have known about smallpox  
15 vaccinations.

16 DR. OSTROFF: Kevin.

17 DR. PATRICK: Kevin Patrick. I'm  
18 particularly interested in this, this is great, this  
19 website, going back to the anthrax, the reminder  
20 system. And I'm wondering, number one, was that  
21 evaluated? How well did that work? Did a lot of  
22 folks use it? If so, who? If not, how to get more  
23 people onto this. Was this pushed out to people, did  
24 they have to go --

25 COL GRABENSTEIN: You're referring to the

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1 AKO site?

2 DR. PATRICK: Yes.

3 COL GRABENSTEIN: Any time you go to read  
4 your e-mail -- anybody who has a us.army.mil e-mail  
5 address has to go to this portal to read their e-mail,  
6 so it's essentially like putting up a billboard on the  
7 side of the road. It's a visual cue that --  
8 relatively passive. We've not evaluated its effect in  
9 terms of motivating folks to come in.

10 DR. PATRICK: That's my point. I think  
11 evaluating the effect of this would be a very  
12 important thing to do because this does fit with the  
13 way we're handling other types of health interventions  
14 these days and you should be encouraged -- and this is  
15 great that this was used. And it also relates -- if I  
16 could piggyback to what Greg was saying -- not only in  
17 terms of ensuring the fidelity of whether or not  
18 people get the vaccine, but also reporting adverse  
19 events. And Vociva is an AVR, active voice response,  
20 plus web-based system, but I have the notion that some  
21 combinations of that might actually help get out to  
22 the point that Greg is talking about, getting better  
23 confidence intervals around the side effects if you  
24 improve your sampling strategies. So this is  
25 something that I believe merits attention in and of

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1       itself.

2                   DR. OSTROFF:   Glenn.

3                   DR. MORRIS:    Let me come back to my  
4       questions about development of new anthrax vaccines.  
5       I know one of the focuses here for awhile has been  
6       trying to do some fast tracking in terms of some newer  
7       vaccine candidates and some of the problems that have  
8       existed with it -- some of the concerns that have been  
9       expressed about the anthrax vaccine.  You're talking a  
10      four to eight year time period before licensure.  Can  
11      you give us a feel for whether indeed there has been  
12      any fast tracking of these?  I mean it seems like  
13      we've still got -- we've been working on this for a  
14      long time and we've still got a long way to go.

15                  COL GRABENSTEIN:  Remember, it's not up to  
16      the Department of Defense when it gets licensed, it's  
17      not up to NIH when it gets licensed, it's up to the  
18      FDA when it gets licensed.  So what are the minimum  
19      essential requirements to get licensed?  And it's  
20      phase one studies of a few dozen, phase two studies of  
21      a few hundred, and phase three studies of a few  
22      thousand people.  And they have to be done serially  
23      and yes, they can be compressed and yes, HHS  
24      headquarters is talking about purchase of RPA vaccines  
25      for the strategic national stockpile, but, you know,

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1 can we turn on a dime and get this stuff licensed in a  
2 year? The FDA has not -- well, I'm not in the  
3 meetings where this is discussed, this is outside of  
4 my personal experience, but I've not heard that the  
5 FDA is willing to waive its requirements with respect  
6 to licensing of products for human use.

7 The other piece that must attend licensing  
8 of any RPA vaccine will be a clinical correlant of  
9 immunity, how much antibody is enough, how much  
10 antibody is protective. We won't have that until we  
11 have the monkey challenge data and that's a year or  
12 two or so away, as I understand it.

13 DR. MORRIS: I guess my question is what  
14 role does the military play at this point in this  
15 process?

16 COL GRABENSTEIN: We are the source of  
17 funds to a prime system contractor to go perform the  
18 trials, to assemble the data, submit them to the FDA.

19 DR. MORRIS: So you are actually driving  
20 the process in the sense that you're paying for it.

21 COL GRABENSTEIN: Yes.

22 DR. MORRIS: Can you give us a feel for  
23 what the funding levels have been in this particular  
24 process?

25 COL GRABENSTEIN: I don't know. Surely

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1 they're publicly available, we can get them and get  
2 them back to the Board.

3 DR. MORRIS: I'm still just trying to get  
4 a feel for whether there has been a strenuous effort  
5 to move this forward. A lot of this is driven by  
6 funding and obviously if the funding is not there, it  
7 will continue to go at a reasonable measured pace.  
8 The question is that sort of where we're headed or has  
9 there been additional funds committed to the process?

10 COL GRABENSTEIN: Others in the room may  
11 know the data better than I, but the vast majority of  
12 the money has not gone to the DoD, the vast majority  
13 of the new money has gone to NIH and as far as I  
14 understand it, there is not much of a plus-up to the  
15 DoD R&D -- research and development -- budget.

16 DR. POLAND: Greg Poland. I think your  
17 last point, John, is true. We've been involved in I  
18 think all the anthrax vaccine trials and the  
19 limitation I don't think has been so much money as it  
20 has been simply the time that it takes to do these.  
21 For example, for the currently licensed vaccine, we're  
22 involved in a clinical trial that's run by CDC looking  
23 at giving it IM rather than subcu, and the collection  
24 of that data will take four years alone. We're also  
25 involved in Basgins RPA vaccine trial which is just

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1 getting ready to start and just the first group of  
2 people through that phase one will take a little over  
3 a year.

4 So I don't think it has anything to do  
5 with so much the dollar funding of it as it does  
6 simply the time that it takes to organize and run  
7 these trials. In terms of fast tracking, remember  
8 that the FDA by law has to go through the usual  
9 routine for licensing any biologic that's going to be  
10 administered to humans unless there's an Executive  
11 Order to the contrary. The President and the  
12 President alone does have the authority to abrogate  
13 those recommendations, should there be a state of  
14 emergency. But short of that, it's a multi-year  
15 process. Maybe some perspective would be the  
16 development and eventual licensure of Veracelevrex  
17 (ph.) which took 20 years.

18 DR. OSTROFF: Thanks.

19 John, let me ask you one last question  
20 which is kind of shifting the subject a little bit,  
21 but it's one that we had some discussions about over  
22 the last several months. We've just come through a  
23 fairly difficult influenza season and I'm wondering if  
24 you can comment about whether or not there were any  
25 particular supply issues related to flu vaccine and

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1 then, once again, knowing that we now have  
2 difficulties related to avian influenza and the  
3 potential is certainly there for some challenges to  
4 the vaccine supply next year if we have to start  
5 producing vaccines against avian influenza, whether or  
6 not you could comment about the issue that I raised  
7 before, which is whether there's been any  
8 consideration regarding purchase of Flu Mist vaccine.

9 COL GRABENSTEIN: The Department of  
10 Defense purchased roughly three million doses of  
11 influenza vaccine in 2003, which is essentially the  
12 same as previous recent year's levels. As the  
13 newspaper articles about childhood deaths and what-  
14 have-you, the headline in the USA Today took hold and  
15 the media grabbed onto the topic, we had increased  
16 demand from non-active duty beneficiaries, family  
17 members and retirees. This tended to draw down  
18 vaccine supply in several locations, so at about the  
19 same time I got telephone calls from HHS asking if HHS  
20 could have DoD's unused vaccine, we were going out  
21 looking to see if we could buy some more. So we were  
22 competing in the same marketplace for a greatly  
23 diminished residual supply.

24 At about the same time roughly speaking,  
25 Wyeth and MedImmune offered a lower price than their

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1 original federal contract price for Flu Mist. Several  
2 places did buy some, but I don't have any quantities  
3 to give you, nor do I have any reports back on  
4 satisfaction or preference among the products. The  
5 service PM reps may fill in if they know something  
6 that I don't.

7 COL UNDERWOOD: This is COL Underwood. In  
8 the Army, we -- again, just to reiterate what John has  
9 said -- we were concerned that we wouldn't have enough  
10 vaccine, so we had requested some Flu Mist, they  
11 reserved an amount for us in case we needed to dip  
12 into that. Approximately -- we did, various posts, a  
13 couple of posts ordered about 500 doses, but in the  
14 end, given the fact that we wanted to ensure we had  
15 enough vaccine for those individuals who were immuno-  
16 compromised or otherwise at high risk, and then  
17 sufficient vaccine to cover for our Reserve population  
18 and deployers up until the end of the shelf life of  
19 the inactivated vaccine. The bottom line is we have  
20 enough inactivated vaccine and we want to use all of  
21 that and we are no longer dipping into the reserve of  
22 the Flu Mist vaccine.

23 DR. GARDNER: Pierce Gardner. At the time  
24 that we really looked like we had a terrible, terrible  
25 shortage of the regular inactivated vaccine, it seemed

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1 to me that one of the strategies that was never  
2 implemented, but made sense to me at least, was in the  
3 5 to 50 year olds, those vaccines were okay, to  
4 preferentially use the Flu Mist and allow the killed  
5 vaccine to be used in all the other people for whom  
6 the Flu Mist wasn't available. And in fact, the  
7 military would have been an excellent group, almost  
8 all would fit into that category.

9 I'm glad to hear at least that was thought  
10 about to some extent. It would provide -- one of the  
11 great defects in our knowledge I think is any head-to-  
12 head comparison of the two vaccines. It just never  
13 was done and it's an important issue to know whether  
14 these biologic differences actually make any on-the-  
15 ground difference.

16 So if there are settings in which both  
17 vaccines were used, it would be an interesting  
18 opportunity to try to do some follow up to see if  
19 there in fact were any differences in infection  
20 levels.

21 COL GRABENSTEIN: I agree. One of the  
22 things that was also noteworthy was that Christmas  
23 seemed to break people's attention to the story and so  
24 we did not see sustained high demand through January,  
25 which took away a lot of the problem, in some

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1 respects. Had the cases and the attack rate and,  
2 therefore, media attention, continued, it would be a  
3 different story.

4 DR. OSTROFF: Kelly Woodward.

5 COL WOODWARD: If I could comment on Flu  
6 Mist. In the Air Force, by the time the shortage  
7 became apparent, we had I think vaccinated I think  
8 roughly 93 percent of our active duty, so we didn't  
9 see -- we had sufficient supply scattered across the  
10 Air Force to cover our military personnel and  
11 carefully massaged the supply to cover the high risk  
12 population, following the CDC's lead. Flu Mist, not  
13 only for cost reasons, but because of the added  
14 complexity of medical screening that went along with  
15 it, particularly in the throes of the busy vaccination  
16 time, throwing that in the mix by preference was  
17 undesirable for us and not necessary.

18 DR. OSTROFF: All I can say before we  
19 bring it to a close is that I would strongly urge you  
20 to think proactively about next season. It's a great  
21 vaccine and if there can be any potential cost  
22 equivalency, yours is the largest vaccination campaign  
23 among targeted individuals for whom that vaccine is  
24 licensed and it certainly would free up a lot of  
25 inactivated product for higher risk individuals.

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1 COL GRABENSTEIN: The price premium is  
2 still pretty substantial -- for what that's worth.

3 DR. OSTROFF: Last comment.

4 COL GIBSON: Just before we break, there's  
5 a group of us folks who are military folks who are  
6 looking at this for a potential study. We're going to  
7 meet during the lunch hour in this little conference  
8 room next door. So at that time, grab your lunch, I  
9 just wanted to give you a warning before we get that  
10 close to lunch in case you're making other plans.

11 COL GRABENSTEIN: If I could make one last  
12 comment. I did not bring enough of these, but I  
13 distributed to most of the seats at the table a  
14 wrinkled but relatively comprehensive summary of each  
15 vaccine by various population groups that we're  
16 beginning to distribute and if anybody has any  
17 comments about this, I'd be happy to take them.

18 DR. OSTROFF: As always, COL Grabenstein,  
19 thanks for your tremendous work and for keeping us  
20 apprised of everything going on on the vaccine front.

21 I think what we'll do is we'll take our  
22 15-minute break now so that we can try to keep on  
23 schedule, because I think that the presentations that  
24 follow the break are going to be somewhat challenging  
25 and possibly a bit frustrating. So let's try to get

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1 back exactly at five of ten.

2 (A short recess was taken.)

3 DR. OSTROFF: Our next presentation is by  
4 another old friend, Dr. Charles Hoke, who is now the  
5 Chief Scientist, Anteon Medical Advisor, Medical  
6 Systems Program at U.S. Army Medical Research and  
7 Materiel Command.

8 COL Hoke has the opportunity to brief us  
9 on the status of a topic that has been of longstanding  
10 interest and concern to the Board, which is the  
11 restoration of the adenovirus vaccine. I had asked  
12 for us to receive an update on where things stand and  
13 it's particularly pertinent based on what has  
14 transpired over the last several months with some  
15 additional fatalities, and again, the Board is really  
16 extremely concerned about the loss of this vaccine and  
17 efforts to make sure that we can restore it as rapidly  
18 as possible, so we look forward to your presentation.

19 COL HOKE: Thank you, Dr. Ostroff and  
20 members of the Board, it's a pleasure to be here.

21 COL Riddle has asked me not to spend too  
22 much time on telling you what you already know, so  
23 I'll go through the first slides fairly quickly.

24 But just to tell you what I wanted to  
25 cover, I wanted to give just a little historical

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1 review, talk about your recommendations and some of  
2 the IOM, give you a little update on the  
3 epidemiological situation with adenovirus in basic  
4 training and then tell you what's gone on with the  
5 capability restoration.

6 As you know, acute respiratory disease in  
7 recruits was actually a significant problem of  
8 longstanding, but in the '50s and '60s work identified  
9 adenoviruses as an important player. An NIH/DoD  
10 effort established a vaccine, the vaccine was  
11 manufactured for the DoD by Wyeth. It was used in  
12 recruits from the '70s onward. After many warnings,  
13 Wyeth halted manufacturing in 1996.

14 The AFEB has weighed in on this issue 17  
15 times, according to your website. When one searches  
16 on adenovirus vaccine, this is --

17 VOICE: This will be 18.

18 (Laughter.)

19 COL HOKE: This will be 18.

20 The theme in the next slide -- I can  
21 hardly read this because I just cut and pasted it, but  
22 you can see it says the single greatest priority is to  
23 re-establish a stable supply of adenovirus vaccine and  
24 that every reasonable effort be made to assure  
25 availability of oral vaccine and the impact of

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1 adenovirus on our military recruits is such that a  
2 vaccine needs to be established or replaced.

3           And the next slide, the Institute of  
4 Medicine was asked to look at military vaccines and  
5 published a book Protecting our Forces, which was in  
6 the read-aheads for the meeting. In the middle of  
7 their deliberations, they realized that adenovirus  
8 vaccine was falling off the tracks and they sent a  
9 letter to the Commanding General of the Medical  
10 Research & Materiel Command that said that the  
11 Committee recommended a much greater sense of urgency  
12 be placed on reacquiring an effective adenovirus  
13 vaccine; that a significantly larger and long-term  
14 commitment be made to restore and maintain the ongoing  
15 availability of adenovirus vaccine; and that the DoD  
16 not only evaluate the causes underlying this serious  
17 procurement system failure, but also make a clear  
18 commitment to the changes necessary to prevent similar  
19 breakdowns in the future. These are really pointed  
20 recommendations.

21           The current epidemiological situation was  
22 provided to me by people at the Naval Health Research  
23 Center and the Air Force Institute of Occupational  
24 Health and the Armed Forces Institute of Pathology.

25           This data from the NHRC website, from

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1 Commander Kevin Russell, shows -- it looks a little  
2 chaotic, but what it really shows is continuous  
3 isolations of adenoviruses, almost all adeno 4, at  
4 levels substantially above those observed during the  
5 period of time during which adenovirus vaccine was  
6 used.

7 This graph, which shows the febrile  
8 respiratory illness rates and adenovirus morbidity  
9 among symptomatic trainees at eight military training  
10 centers, shows a gradual increase in the monthly  
11 numbers of adenovirus cases in the green bars and the  
12 blue lines show a gradual increasing number of  
13 adenovirus isolations over that period of time as  
14 well.

15 The next slide shows the overall isolation  
16 proportions of adenovirus from specimens from recruits  
17 with respiratory disease, and obviously the adenovirus  
18 part of the pie is the great preponderance. And you  
19 might ask yourself well what might this have looked  
20 like during a similar period when the vaccine was  
21 available. And what it would have looked like would  
22 have been a much smaller number overall and virtually  
23 no adenovirus isolations, or very, very few when the  
24 vaccine was being used. So this tells you what a  
25 dramatic part of the overall respiratory illness

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1 burden is caused by adenoviruses.

2 Next slide -- I think I'll skip this and  
3 the next one and go on to the next one.

4 The Air Force provided data here that  
5 shows the number of specimens submitted from patients  
6 with respiratory illness. You can see that in the  
7 years covered, the number went up dramatically after  
8 1999 to 3000 and the percentage of specimens that were  
9 positive for adenovirus went up as well as the total  
10 number that were positive. So this is really a  
11 remarkable increase in the number of adenovirus  
12 isolations in the population sampled.

13 Now there have been eight fatal adenovirus  
14 infections in recruits. This goes back a long time,  
15 this isn't eight recent ones. And these are the  
16 citations for them. The first citation is of three  
17 cases due to adeno 7 from 1972, so that's long ago.

18 Then from Commander Ryan, two cases were  
19 reported in the MMWR in 2000.

20 And cases that are currently under  
21 investigation are three cases that were reported to me  
22 by CDR Russell and MAJ Pearse at the AFIP. These are  
23 from September, November and December of 2003, so just  
24 a couple of months ago, associated with adenovirus  
25 either PCR positive or culture positivity in cases B and

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1 C. So that there is rather clear evidence that these  
2 recruits died with and probably of adenovirus  
3 associated disease and the serotypes that are in the  
4 two vaccines.

5 So in summary then, of the epidemiological  
6 situation, the rates of febrile respiratory illness on  
7 basic training posts continue to be above levels  
8 observed when adenovirus vaccine was available.  
9 Isolates are made in large numbers year round but more  
10 especially associated with times during which recruit  
11 camps are fullest. Occasional fatalities have  
12 occurred with three recently at the end of 2003 and  
13 isolates have been obtained from recruits in all  
14 services.

15 The return of adenovirus disease to  
16 recruit camps following withdrawal of licensed  
17 adenovirus vaccine is a profound epidemiological  
18 demonstration. Really, it's that a vaccine is  
19 effective, but I think also that a vaccine is needed.

20 Now I want to tell you now about the  
21 vaccine restoration effort and I want to take just a  
22 moment to talk to you about the military, both DoD and  
23 Army, acquisition system. Now medical scientists'  
24 eyes usually glaze over right about now when we start  
25 talking about acquisitions, but I want to just tell

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1 you some features of the system that I think are  
2 applicable to vaccines as well as tanks and guns.

3 The concept is fairly simple. You start  
4 with a requirement for an item with a capital R, and  
5 then you start off on a program and you give someone  
6 the responsibility to make decisions at certain points  
7 and these points are called milestones. And the guy  
8 who makes those decisions, the person who makes those  
9 decisions, is called the milestone decision authority.

10 It's usually a general who is given the acquisition  
11 responsibility for this capability. These are all  
12 sort of abstract words that are in this regulation.

13 So these milestones are A, B and C. and  
14 what's the process? Well, the process is pretty  
15 logical, you start with a requirement and then you  
16 refine the concept, develop the technology, put the  
17 system together and demonstrate it, then produce it  
18 and deploy it. So it's very common sense. Now there  
19 are some documents that you need as you go along and  
20 they're called initial capability documents or  
21 capability development document and a capability  
22 production document. These are the way that DoD tells  
23 you that you're starting off in the right direction  
24 and you're still going in the right direction.

25 Now adenovirus vaccine comes to us as a

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1 rather advanced technology. The basic work has been  
2 done, so we're talking about what's called a  
3 technology insertion. We need to start kind of at the  
4 phase before you start producing it. We don't need to  
5 invent it again, it needs to be produced and licensed  
6 and fielded.

7 And so if you're starting right here, you  
8 might expect that we would need a capabilities  
9 production document to formalize this process and to  
10 establish for subsequent people that we're actually  
11 working on something that the DoD told us to do. You  
12 know, we're frequently asked a question who told you  
13 to do that.

14 So at this point, we don't actually have  
15 the formal document. The system is in a state of re-  
16 examination and the process for getting these  
17 documents is being formalized, but we don't have such  
18 a thing for adenovirus vaccine at this point.

19 Nevertheless, we've moved ahead with  
20 Defense Health programming funding and we have  
21 developed a schedule. And in the acquisition lingo  
22 the three parameters are cost, performance and  
23 schedule. Of course, everybody wants things free,  
24 perfect and now. Those are the optimal parameters,  
25 but cost, performance and schedule. And so I'm going

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1 to tell you a little bit at least about the schedule  
2 and performance.

3 The schedule is shown on this scan chart  
4 and this has been worked out with the selected  
5 manufacturer and the product manager at USONDA, the  
6 Medical Materiel Development Activity, and it calls  
7 for activities having to do with building the plant  
8 and establishing the tableting capability, then  
9 producing material for a phase one clinical trial,  
10 phase one clinical trial being conducted and then  
11 materials for phase two and materials -- and  
12 conducting the phase two, materials for phase three  
13 and conducting phase three, and eventually the  
14 regulatory efforts associated with filing a product  
15 license application and licensure by the FDA,  
16 converging on completed facility and production  
17 capability so that the vaccine can be fielded.

18 Now another concept of the acquisition  
19 system, is that the entire life cycle needs to be  
20 managed, not just, you know, getting the clinical  
21 trial done or even building the facility, which is  
22 expensive, but maintaining this commodity over time.  
23 That is, someone has got to build into the budgets of  
24 the various people in the DoD that would take care of  
25 these things the money to do these various parts of

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1 this acquisition.

2 Now we are here today and this is where we  
3 hope to field this vaccine in 2009. So that's the  
4 schedule.

5 There are some uncertainties in this  
6 schedule related to what the FDA is going to ask for,  
7 and meetings with the FDA have not taken place yet but  
8 will soon. The boundaries are that they could accept  
9 this vaccine as one that's very similar to the old  
10 one, a little bit of immunogenicity comparability and  
11 they might say that's enough. Or they might ask for  
12 more safety studies, several thousand volunteers, or  
13 they might ask for those kinds of studies in addition  
14 to efficacy studies on training posts. Those will all  
15 extend the time line considerably and so the FDA is  
16 kind of a wildcard here.

17 Now in terms of performance, in terms of  
18 getting the job done, a manufacturer was selected,  
19 Barr. Much has been done to transfer everything that  
20 was known from Wyeth, but we're finding that  
21 everything that was known at Wyeth still may not quite  
22 have been enough. Lots of progress has been made by  
23 the manufacturer and lots of progress has been made at  
24 WRAIR.

25 The production facility -- this is just a

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1 simple picture but it's actually quite a nice -- and  
2 it's actually quite a nice facility -- has been  
3 completed. This facility was built from the ground up  
4 for this vaccine. It has all gone very well and  
5 actually the representative from the company is here  
6 if you have any specific questions about the -- Dr.  
7 Tole -- about the production facility itself.

8           The tableting equipment has been installed  
9 and Barr is actually very experienced at tableting.  
10 They make a billion pills a year I'm told and when I  
11 visited with the Wyeth people long ago, the tableting  
12 -- I was told that the tableting part of this vaccine  
13 was where the real art lay. So we're hopeful that  
14 we'll get this right the first time. This is the  
15 bottling line.

16           Now one of the things that has to happen  
17 in the contract is that the contractor needs to  
18 provide a quarterly report. I took the report and  
19 wanted to summarize it for you, the report that we  
20 received just a month and a half ago, and these issues  
21 here are mentioned in the report. There's some  
22 technical detail, but I wanted to provide some of that  
23 detail for you so that you can get a feeling for some  
24 of the irreducibility of the technical aspects of  
25 producing a vaccine.

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1 Bulk virus production. You know, you need  
2 to make enough virus to put in these pills and you  
3 need to grow it. They've demonstrated that it grows  
4 sufficiently well in the WI-38 cells that are the type  
5 of cells that were used by Wyeth. The production of  
6 the master virus banks was finished in September and  
7 the GMP lots for vaccine production were initiated in  
8 September. Both have been completed.

9 The initial lyophilization is being  
10 conducted at WRAIR, Walter Reed Army Institute of  
11 Research. Processes were developed last summer.  
12 Pilot runs without virus and then with non-GMP virus  
13 have been completed and with GMP virus lyophilization  
14 has now been completed as well. You can see that  
15 these things are happening practically right now. So  
16 we're really in a very active phase on this vaccine.

17 Assays have been developed at Barr for a  
18 number of important measures of the quality of the  
19 tablets. Sera that are needed to demonstrate lack of  
20 adventitious agents in the virus production have been  
21 produced. More are needed, however, and virus  
22 inactivation on equipment has been demonstrated.

23 The tableting facility I showed you a  
24 picture of has been completed and all the basic work  
25 there has been done. Five trial batches have been

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1 produced with pilot lyophilized material and material  
2 is being brought in from WRAIR for GMP production of  
3 tablets.

4 This is a picture of a mock tablet. You  
5 can see it's got an outer coating and an inner table  
6 that has to be suspended in this outer tablet. And  
7 this inner tablet is what contains the virus.

8 This is a schematic of the tablet. It's  
9 got a polymer outer coating, an inner virus core and  
10 an outer core of inert material so that the recruits  
11 will take this, it will be protected as it goes  
12 through the stomach and then it will infect the  
13 intestinal tract.

14 As I mentioned before, the regulatory  
15 strategy is to first strive in every possible way to  
16 make this vaccine the same as the Wyeth vaccine,  
17 except that it is being manufactured in a modern  
18 facility with modern equipment. And then to show in  
19 every possible way that the vaccine is similar or the  
20 same as the Wyeth vaccine was. So all the  
21 specifications are being designed with this approach  
22 in mind.

23 This table lists a number of important  
24 specifications -- type of cells, the seed virus, the  
25 growth media, the dye that's used in the tablet, that

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1 pink color, potency and route of administration. And  
2 you can see that across the board, except for the case  
3 of where antibiotics are not being used in the growth  
4 medium -- this is actually an improvement -- and the  
5 dye that is being used for the pink color is being  
6 changed. These are felt to be minimal changes but the  
7 major parameters of the virus, the type of cells, the  
8 seeds, the dose and the administration, they will all  
9 be identical to what was done before.

10 Now the first clinical trial has been  
11 planned and that will begin following meetings with  
12 the FDA, so in the next month or two I think. It'll  
13 be a very small trial, 30 volunteers will receive both  
14 adeno 4 and 7 or a placebo, mainly looking at safety,  
15 but also immunogenicity as well.

16 There are some specific issues having to  
17 do with the filing of the IND. Typically in the past,  
18 the DoD would file the IND with the Surgeon General of  
19 the Army as the sponsor. In this case, we felt that  
20 it would save time if Barr would file the IND itself,  
21 so that cross-referencing of a master file wouldn't be  
22 necessary. They would move smartly from IND through  
23 the clinical development plan to the product license  
24 application, all in their hands. So that's what we  
25 decided to ask them to do. Pre-IND letters have been

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1 written but the meeting has not been scheduled and the  
2 FDA will specifically be -- their opinions will be  
3 solicited on the manufacturing and on the proposed  
4 clinical trial plan.

5 DoD, for its part, did request Barr to  
6 file the IND and there are some contracting issues  
7 relating to the fact that there's a first phase of the  
8 contract and a second phase of the contract and that  
9 was I think advisable, so in case things hadn't been  
10 working out with the manufacturer, the DoD could  
11 pursue another option down the road.

12 Now there are a number of personnel that  
13 are involved with this and I won't recount their  
14 names. You all provide a very important role as  
15 advisor to ASD Health Affairs. We have requirements  
16 generators who really haven't weighed in on this yet,  
17 but milestone decision authority would be MAJ GEN  
18 Martinez-Lopez. That's in accord with AR 70-1. And I  
19 didn't mention that earlier but for those of you who  
20 are interested in whether or not, you know, vaccines  
21 should fall under the usual acquisition rules of the  
22 DoD, you might look at Army Regulation 70-1 -- you can  
23 get it on the internet -- and read through that and  
24 see if you don't think that applies to vaccines. The  
25 answer is it does. There's every intention for

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1 vaccines to fall under that regulation. And specific  
2 jobs are laid out for people.

3           Anyway, the Deputy for Acquisitions is Mr.  
4 Howell and it's Mr. Howell who asked me to come and  
5 give this presentation. The pharmaceutical systems  
6 project manager is Dr. Lightner. LTC Moser is  
7 actually the product manager for adenovirus vaccine  
8 and COL Wellington Sun at WRAIR has provided input on  
9 the clinical plan and test development. And Dr. Tole  
10 and Dr. Listz at Barr and Vacsgen have really in fact  
11 done all the work in terms of getting the facility  
12 ready and will continue to lead this effort from the  
13 company's side.

14           A lot more functions will have to be  
15 fulfilled as we move into the clinical development  
16 phase to make sure that the clinical trials are done  
17 right and up to snuff according to all the good  
18 clinical practices rules and all the other data  
19 management and all the other things that have to be  
20 done to actually do a clinical trial. The rules and  
21 regulations are changing almost by the day. And to  
22 really get to a top quality trial, you have to have a  
23 lot of people helping you get it right.

24           So I'd just like to conclude then. We  
25 talked, remember, about the initial -- all the initial

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1 history and the recommendations of the Board, the  
2 epidemiologic situation and all the work that has gone  
3 in so far to restoring this vaccine capability. It's  
4 on schedule I think to complete the first clinical  
5 trial by the fall of this year. I think there's some  
6 risks in the plan, it's not perfect. The FDA  
7 acceptance of the clinical development plan is  
8 unknown, whether they're going to give us the short  
9 option or the long option. I think the lack of formal  
10 requirements documents from the DoD may in times of  
11 budget crunches or needs for budget to go do something  
12 else may hurt us. DoD contracting always takes time  
13 and as acquisition staff and other staff turn over,  
14 that disrupts the continuity of this program.

15 On the plus side, the relationship with  
16 the company has been superb. Everyone that's been  
17 involved has been most enthusiastic, lots of good  
18 faith on both sides. Many problems have been dealt  
19 with successfully and we are hopeful that the  
20 replacement vaccine should be available by 2009.

21 So I wasn't keeping track of the time, but  
22 that's all I have to say.

23 DR. OSTROFF: Let me start out by thanking  
24 you for your willingness to give this update.

25 For those on the Board who haven't been on

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1 the Board for that long, the last time that we had a  
2 significant update on the adenovirus vaccine I believe  
3 was in San Diego possibly two years ago. I think it  
4 was done by Mr. Howell. And I guess I would start my  
5 comments, I recently heard a presentation on the SARS  
6 outbreak in Toronto by Alison McGeer, who was a  
7 participant in that outbreak, and she used a quote  
8 that always sticks with me, which is that if you think  
9 prevention is expensive, try diseases.

10 And it looks like that's a deficiency that  
11 the Department of Defense has made in this situation;  
12 when we had the update from Mr. Howell two years ago,  
13 he set out time lines as well and assured us at that  
14 time that there would be a product available in 2007  
15 and that by this time there would be phase two trials,  
16 et cetera. And now what we're hearing is that somehow  
17 the production table has slipped backwards to 2009.  
18 Even though I appreciate everything that was being  
19 said, I am missing the sense of urgency and Dr.  
20 Winkenwerder sat at that meeting and swore to us that  
21 he would do everything that was in his power to try to  
22 speed it up for 2007. And I'm trying to figure out  
23 where things aren't going right and what we on the  
24 Board can do to try to convey in our strongest  
25 possible terms that we are really, really concerned

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1 about what we are hearing. I don't know if other  
2 members of the Board share this concern, but you know,  
3 you're not hearing anybody that is suggesting that  
4 this isn't an urgently needed vaccine -- it is. And I  
5 guess I would like to be clear where are we now on  
6 this? Is it money?

7 COL HOKE: Well, I didn't hear Mr.  
8 Howell's presentation. My surmise would be that the  
9 actual -- to use some project management terminology -  
10 - the actual work breakdown structure and time lines,  
11 gantt charts had not been made at that time.

12 You know, the devil is in the details to  
13 some extent. When people really sit down and look at  
14 the things that need to be done and really look at the  
15 time lines, they do take sometimes longer than one  
16 thinks. There's some substantial risks that are being  
17 taken here to accelerate the process. For example,  
18 all the construction has been completed on the  
19 assumption that the vaccine is going to work, just the  
20 way it did before.

21 It appears to me that the manufacturer has  
22 worked very, very hard and very conscientiously to get  
23 that building up. I had a lot of slides that showed  
24 the construction going and so forth, but it's actually  
25 pretty remarkable to build the whole facility in this

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1 period of time.

2           Undoubtedly there are days and weeks that  
3 can be squeezed out of the schedule to shorten the  
4 time line and, to some extent, some of the trial plans  
5 do -- we were trying to shoot for the middle because  
6 we really don't know what FDA is going to ask for in  
7 terms of the amount of studies that are required. But  
8 you can see that the bulk of the time is used up in  
9 clinical trials.

10           So, you know, the Institute of Medicine  
11 recently completed the study on giving full measures  
12 to counter-measures, which was not at all  
13 complimentary to the DoD process, and I felt during  
14 some of those meetings that, you know, they might have  
15 looked -- focused a little more on the specific time  
16 lines to see where, in the judgment of the  
17 pharmaceutical people, development people, time could  
18 be squeezed out of those lines.

19           One presentation we heard suggested that  
20 going from, you know, from beginning work to  
21 completion of a vaccine took 14 years. So, you know,  
22 the fact that this is happening in -- well, nine years  
23 is better than 14.

24           I don't know how you can squeeze time out  
25 of a process when you've got to get up to about

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1 several thousand people safely receiving a vaccine and  
2 you've got to do it carefully. Protection of human  
3 subjects is the most important focus of the IRBs. But  
4 I do imagine that, you know, you could write the  
5 clinical protocol in a way that allowed you to go from  
6 10 to 100 to 1000 volunteers perhaps a little more  
7 efficiently rather than starting a new protocol at  
8 each phase.

9 DR. OSTROFF: With all due respect -- and  
10 I'll open it up to other Board members -- I mean if  
11 you're saying you don't know what FDA is going to  
12 require out of you, why doesn't somebody sit down with  
13 them later this week and ask them so that you know?  
14 You know, that's -- again, I'm just missing -- I'm  
15 trying to figure out like who's responsible for this  
16 and who is the single individual that we can sort of  
17 get to to say this is really, really essential and we  
18 need to be assured that everything possible is being  
19 done to truncate this process to the degree possible.

20 I appreciate that it takes 14 years to  
21 produce some other vaccines, but let's not lose track  
22 of the fact that this is a pre-existing vaccine. This  
23 isn't something being created from scratch. And so  
24 again, I'm missing some essential urgency here. And  
25 maybe others would like to comment on this. Greg.

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1 DR. GRAY: This is Greg Gray.

2 One way I'd measure the morbidity is some  
3 of the data that NHRC collected some time ago, where  
4 they saw in some months 1100 unnecessary clinical  
5 encounters, many of whom had been hospitalized. Maybe  
6 that's something that we could use as leverage in  
7 addition to these recent tragic deaths.

8 But it seems to me that there are several  
9 things that we could do as a Board. One, we could  
10 encourage the Army and the DoD to draft this  
11 requirement document that might give prolonged funding  
12 line to this such that this would never happen again.

13 That is, to lose a very effective vaccine. I don't  
14 know how we effect such a document, but it seems to me  
15 it's in the interest of the soldiers and sailors that  
16 come on in the future.

17 A second thing is we could write a letter  
18 to the FDA emphasizing our view on this and when  
19 Charlie and Mr. Howell or whomever meet with the FDA,  
20 they might have that as a document that would express  
21 our most strong urgency.

22 And finally, there's been a whole bunch of  
23 leaps forward in the solid organ and bone marrow  
24 transplant patient population who suffered rather  
25 egregiously from adenoviruses and then now there is

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1 real time PCR monitoring and somewhat pretty  
2 successful treatments with Sudafovir (ph.)

3 So that might be something to consider in  
4 some of the recruit camps. There's actually rapid  
5 testing now as well. Is there any role for aggressive  
6 anti-viral therapy when one of these kids comes down  
7 with multi-system failure due to adenovirus?

8 DR. GARDNER: Pierce Gardner.

9 Of course, the IOM has certainly come in  
10 very strongly on this as well, so we have a lot of  
11 people saying what to do. I agree with your thought,  
12 there doesn't seem to be any argument or lack of  
13 committee support, but there is a problem in staying  
14 on schedule.

15 I have a question and another comment.  
16 Would you refresh us briefly regarding the shelf life  
17 of this product and how it's stored. Why it's not as  
18 virus in a tablet, I'm wondering how -- is this  
19 something that's tricky?

20 COL HOKE: I really don't know the answer.

21 COL GRABENSTEIN: The shelf life was about  
22 two years and it was stored in the refrigerator in  
23 olden days.

24 DR. GARDNER: Normal refrigerator type.

25 COL GRABENSTEIN: Correct.

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1 DR. GARDNER: My comment actually follows  
2 a little bit what Greg said. One of the major  
3 bugaboos that the live virus vaccines have encountered  
4 in the last few years is what I think is an excessive  
5 reaction to the transmissibility of an attenuated  
6 virus to other populations. The early example is the  
7 varicella vaccine which was developed in Japan to give  
8 to kids with leukemia and lymphomas because they might  
9 get the real virus and by the time we licensed it in  
10 the United States, the people for whom it was  
11 originally indicated were on the contra-indicated list  
12 and they had to do further studies to show that it was  
13 safe.

14 We've just been through it this past year  
15 I think with the influenza, the live influenza virus  
16 where concerns about secondary transmission, which are  
17 minimal and have failed to show any real problems,  
18 have paralyzed the programs and had layoffs in  
19 hospitals and I think have very much inhibited its  
20 use.

21 So my advice is as you look at this new  
22 thing, I think you really have to look harder perhaps  
23 than in earlier studies to make sure you look at  
24 transmissibility and issues of possible consequence.  
25 I hope that this won't end up paralyzing this virus as

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1 it seems to have some others.

2 COL HOKE: It will be a problem. I didn't  
3 show you the data, but the team at WRAIR took some of  
4 the last tablets of the old vaccine and did a small  
5 clinical trial and looked at immunogenicity as well as  
6 shedding and, as had been shown many years ago, 100  
7 percent of volunteers shed the virus in their stool,  
8 the adenovirus from the vaccine, and none have it in  
9 their throat.

10 So that it is possible that issues of  
11 transmissibility will have to be addressed, especially  
12 when you realize that this is not an attenuated virus  
13 in the vaccine.

14 So you raise excellent points that may  
15 actually extend the studies that are needed.

16 DR. OSTROFF: Dennis and then I think  
17 there was a comment over here.

18 DR. SHANAHAN: I agree with the comments  
19 made by Greg. One thing that strikes me, having grown  
20 up in the military acquisition process is that I'm  
21 somewhat alarmed by the lack of formal requirements  
22 documents and I'd like to emphasize that. To me,  
23 that's just basically a procedural effort and one that  
24 we can distinctly influence, particularly through DoD.

25 In my experience, programs without

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1 requirements documents are hanging out and they can  
2 run into substantial problems down the road, given  
3 changes in administrations, changes in emphasis in  
4 terms of what the military is doing.

5           So I think that that's a relatively simple  
6 effort that we might be able to influence. Now  
7 there's going to be a lot of politics involved, but I  
8 think that that could be something that we could  
9 really come out strongly in favor of, because this  
10 program can get derailed on that basis alone.

11           But I just wanted to make a general  
12 comment about interacting with regulatory authorities  
13 such as the FDA. I think sometimes there's an  
14 assumption that they have the answer when you approach  
15 them with your dossier of evidence, that they knew all  
16 along what should be in it but didn't tell you. But  
17 really the issue is it's up to the applicant to  
18 persuade the FDA that they have provided the necessary  
19 evidence to license the product.

20           I would just suggest that that should be  
21 the way that if the AFEB was going to approach the  
22 FDA, they should be doing it in that spirit of  
23 assisting the applicant with providing the necessary  
24 evidence rather than suggesting to the FDA that they  
25 ought to speed things up or whatever.

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1                   Would you agree with that?

2                   COL HOKE: Absolutely. You know, we never  
3 want the FDA to lower its bar just because we're the  
4 DoD, because we must have products that are safe and  
5 effective, according to the highest standards. And so  
6 the onus is really on us to bring to the FDA a package  
7 that's convincing and we want them to be skeptical and  
8 ask questions and be concerned about safety, but we  
9 want them -- and we want them to be reasonable in that  
10 attitude as well.

11                   So the FDA is really, you know, looking  
12 out for the welfare of the ultimate recipients of the  
13 vaccine, so we don't want them to lower their bar in  
14 any way for us. But to help us make a -- I will say  
15 the FDA has been very good from the beginning when we  
16 first met with them about this with another contractor  
17 that we had. They were willing to bring in their  
18 facilities people and help with the blueprints from  
19 the very beginning so that we would get it right the  
20 first time.

21                   DR. OSTROFF: Let me just say that no one  
22 is at all suggesting that FDA does anything to lower  
23 their standards or requirements. I think that  
24 Department of Defense has a recent wonderful example  
25 of being able to get FDA to certainly work speedily to

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1 address an urgent concern, and there are ways that FDA  
2 can move in their traditional pace and there are ways  
3 I'm sure that they can move more expeditiously and  
4 make this among their higher priorities. And  
5 certainly I think all avenues should be explored to  
6 see how you can work collaboratively and cooperatively  
7 with them to make sure that there aren't any delays on  
8 either side.

9 I'm sure that they are quite willing to --  
10 you know, they sense the importance of this as well.

11 Greg.

12 DR. POLAND: I was on the IOM committee  
13 that first looked at phase one, and while there were  
14 lots of things that went wrong, it's interesting if  
15 you look at the very beginning of the genesis of this.

16 What we identified is that there was never a champion  
17 for this, there was never a very high level opinion  
18 maker who trumpeted this and said we need to do this  
19 and I will guide this through the process.

20 So I like Greg's suggestions, I like the  
21 idea of trying to re-engage Dr. Winkenwerder and maybe  
22 we need to identify a Congressman or a Senator who  
23 thinks this is a serious issue and can help drive it.

24 UNIDENTIFIED SPEAKER: What is known about  
25 the potential for recruit outbreaks to spill over into

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1 the community, and to what degree if that is a problem  
2 or potential problem could add some ammunition to the  
3 argument?

4 DR. PATRICK: I'm sure Greg has more  
5 database than mine. Having spent the better part of  
6 my career in college health, university health, there  
7 are other markets for this vaccine and other potential  
8 champions that could be brought to bear on this.

9 We certainly saw this in college health  
10 settings in San Diego where we would have episodes  
11 where we thought what else was this but adenovirus,  
12 but again, Greg probably has some more data.

13 DR. POLAND: I was going to mention the  
14 Great Lakes episode, but you probably know that better  
15 than I do.

16 DR. GRAY: Go ahead.

17 DR. POLAND: I'm aware of one report --  
18 and was it CDR Ryan reported it? There was an  
19 outbreak at Great Lakes Naval Training Center that did  
20 cross into the community. And I can't remember, the  
21 child was at least hospitalized, if not a fatal event,  
22 I'm not sure.

23 DR. GRAY: There's one well-documented  
24 study by the Army and I've forgotten, I apologize to  
25 the authors, but basically they showed from boot camp

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1 to a post training camp and I'll just tell you that in  
2 this country, contrary to some other countries,  
3 particularly Japan, surveillance for adenovirus is  
4 very poor. It often depends on whether the clinician  
5 orders a test or orders a culture, if that culture  
6 makes it to a laboratory that would then send it to  
7 the CDC. So it's a very low profile and so the data  
8 we have are very poor. But the data that we do have  
9 suggests that there are two new variants of 7, one of  
10 which has been associated with at least one of the  
11 deaths at Great Lakes and it probably is associated  
12 with about four out of the five last epidemics in  
13 confinement facilities.

14 So where there's a big threat to the  
15 civilian population I would say in addition to bone  
16 marrow transplant and solid organ populations would be  
17 these long term care, chronic care facilities,  
18 institutionalized children and adults. That's where  
19 we're seeing a lot of these outbreaks.

20 How you bring that to a Congressman's  
21 attention, I don't know.

22 DR. OSTROFF: One last comment and then  
23 we're going to have to move on.

24 VOICE: Should we be thinking about some  
25 systematic effort to monitor spillover from

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1 communities into selected sites where we know that the  
2 outbreaks recur predictably?

3 DR. OSTROFF: Greg.

4 DR. GRAY: Well, I just propose doing  
5 studies.

6 DR. OSTROFF: From my perspective, more  
7 data is always better than less data but I certainly  
8 don't want to give any impression that the impetus to  
9 have this vaccine is anybody else's responsibility but  
10 the Department of Defense, because it is, from my  
11 perspective. This is a niche vaccine, the niche is  
12 the recruit setting. We know there are problems  
13 there, we know the vaccine has to be used and the  
14 responsibility is the Department of Defense's to do  
15 everything they can to make sure that the vaccine is  
16 available.

17 Dr. Shamoo.

18 COL HOKE: Thank you very much.

19 DR. SHAMOO: Drugs and vaccine development  
20 is a continuing effort by DoD, I presume. All the  
21 time we have some kind of wanting some vaccine or drug  
22 development.

23 Is there in DoD or one of its contractors  
24 who continuously looks at expanding the drugs --  
25 expediting -- sorry, expediting -- drugs and vaccine

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1 development and should there be one? Because the  
2 process is the same, it's only the technology change.

3 The regulatory affair is the same, the FDA is the  
4 same. And you could have an expert group who could  
5 help any unit in expediting those issues on a  
6 continuing basis.

7 DR. OSTROFF: I think your point is a very  
8 well taken point. I mean, the Department of Defense  
9 has such an illustrious history in this particular  
10 arena, whether it's in the vaccine production arena or  
11 whether it's the drug arena. And you know, we hate to  
12 see any potential loss of that capability. And so --  
13 but I think as, you know, certainly Greg can point out  
14 or others can point out, there have been a number of  
15 recent studies that have looked at current  
16 circumstances under which DoD is operating and have  
17 come to the conclusion that basically it's just not  
18 working and that it needs to be fixed. And you know,  
19 that is a message that's coming out loud and clear  
20 from every direction.

21 So I think from at least my perspective,  
22 the Board needs to do whatever they can to help  
23 support efforts to correct the current situation.

24 You're the last comment.

25 DR. MORRIS: I'm the last comment. Glenn

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1 Morris.

2           Along those same lines, I guess this is  
3 actually a very interesting list that we were given  
4 this morning and there was one point I believe that  
5 the Board was receiving a regular sort of update on  
6 the status -- overall status of vaccines. And I would  
7 like to ask that perhaps we are able to see this on a  
8 regular basis with each meeting, with more than what's  
9 on here, sort of a pipeline analysis, particularly for  
10 the vaccines that are either in early stage  
11 development where there are no vaccines, or where  
12 there are significant concerns about reactogenicity,  
13 to get a feel for where things stand, what the funding  
14 levels are, how things are moving, so that at least we  
15 can get a look.

16           I mean, this is a disturbing chart --  
17 plague is in early development, we've got problems in  
18 terms of yellow fever, Japanese encephalitis -- and I  
19 think it would be worthwhile to see this on a regular  
20 basis at the meetings.

21           DR. OSTROFF: Usually we get that update  
22 at the May meeting, which is the meeting where we hear  
23 about the status of the biodefense vaccines. So I  
24 feel pretty certain that we'll get that at the next  
25 meeting.

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1 DR. MORRIS: I was wondering if we perhaps  
2 could do it not just at the May meeting.

3 COL HOKE: If I could just say a last  
4 word, that there are many people that would advocate  
5 one thing or another for the DoD to do, but it seems  
6 to me after 25 years of working in the DoD that all  
7 the best intentions and recommendations have to be  
8 translated into requirements that are approved by the  
9 appropriate authority. That was said earlier but  
10 without -- but that is a key aspect to establishing  
11 and sustaining an acquisition effort for any  
12 particular product that might be needed.

13 DR. OSTROFF: Thanks once again. We do  
14 appreciate your willingness to come and brief us and I  
15 would anticipate certainly hearing more from us.

16 Let's move on to the next presentation.  
17 We're a little bit behind schedule and we'll have a  
18 second round from COL Grabenstein concerning the  
19 question that's before the Board related to multiple  
20 vaccinations.

21 COL GRABENSTEIN: Thank you very much.  
22 It's always a pleasure to share the podium with Dr.  
23 Hoke and thanks for the chance to come back.

24 The question to the Board is at Tab 5 and  
25 I'll summarize it after discussing an Institute of

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1 Medicine Report about multiple vaccinations that I'll  
2 talk about in the course of my talk.

3 The core of the question is multiple  
4 simultaneous immunization has been a longstanding  
5 practice in military medicine, even though less  
6 published information is available regarding this  
7 practice in adults than in children. And then it goes  
8 on, to ensure current duty policy on vaccine  
9 administration meets our obligation to protect and  
10 preserve the health of the men and women who serve our  
11 nation, I request the Armed Forces Epidemiological  
12 Board to consider the scientific evidence regarding  
13 receipt of multiple simultaneous vaccinations,  
14 including combination vaccines, and whether there are  
15 potential combinations of vaccines that together might  
16 cause -- might be cause for safety concern when  
17 administered to adults. Signed by Ms. Embrey. So  
18 from that I take this presentation.

19 So in my words, the core question I  
20 believe for you is the one I have at the top of the  
21 slide. Is there a threshold above which giving  
22 simultaneous vaccinations to an adult in a short  
23 period of time -- whether that's a day or a few days -  
24 - is less safe than individual vaccinations, the same  
25 vaccinations given over a more prolonged period of

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1 time. In other words, if you get three vaccines on  
2 the same day, is that less safe than getting those  
3 vaccines a month apart or a week apart.

4           Although in common parlance we tend to  
5 talk more about multiple vaccinations, I would submit  
6 to you that the parameter here in question is  
7 simultaneity, the simultaneousness of the vaccination,  
8 not the quantity of them, but the quantity  
9 simultaneously. We are not talking about lifetime  
10 cumulative stimuli to the immune system. I think the  
11 Institute of Medicine has dealt with that  
12 substantially.

13           And so what is motivating this question?  
14 I would submit there -- I have four here, but I think  
15 two of them are really the major drivers. One is what  
16 is euphemistic, what we're referring to as the pin-  
17 cushion effect and that term comes from childhood  
18 vaccinations. But how much discomfort would  
19 simultaneous vaccinations cause? You know, is it  
20 better to have a sore arm on two different days or is  
21 it better to have a more sore arm just one day?

22           Every vaccination is a chance for  
23 anaphylaxis, so that may or may not be a matter of  
24 concern.

25           The third bullet is the second major

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1 domain, I would submit, and that is rare events. Is  
2 simultaneous vaccination prone to or established to  
3 trigger autoimmune conditions or other phenomena that  
4 are serious in nature? This has been referred to in  
5 the press as overloading the immune system; again, the  
6 IOM has dealt with that substantially in terms of  
7 human cumulative capacity and the like.

8 And then from an efficacy standpoint or  
9 immunogenicity standpoint, is there possibility of  
10 interference between antigens, and I'll discuss that  
11 as well.

12 So one of the most important things I  
13 think we need to reflect on is what we know about  
14 human life, life on this planet, and so I would take  
15 you to a normal summer picnic where you encounter  
16 bacteria in the potato salad. You skin your knees  
17 sliding into second base. You have skin-to-skin  
18 contact with your buddies on the team. People with a  
19 summer cold or ragweed pollen sneeze on you. You go  
20 swimming in the pond and ingest some of that stagnant  
21 water. You didn't wash your hands after using the  
22 outhouse. You got stung by a yellow jacket. There's  
23 ragweed in the air. You got poison ivy fielding a  
24 ground ball to left field. And alter that night, you  
25 had unprotected intercourse, or a different kind of

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1 skin-to-skin contact.

2 (Laughter.)

3 COL GRABENSTEIN: Anyway, the point is  
4 that the body is built to function normally in a  
5 landscape of multiple antigens, or if I can hazard a  
6 Naval analogy, we are awash in a sea of microbes. And  
7 it's happening right now in this room. We are being  
8 stimulated -- and those of you who flew in, traded  
9 viruses and bacteria in that recirculated air in the  
10 airplane that you flew in on. But we didn't write any  
11 of those things down in your shot records and they are  
12 just part of being a human being.

13 So what is the legacy or the history of  
14 combining various immunogens or antigens in one  
15 vaccine formula? It would seem to me -- well, among  
16 the modern vaccines, the first on this list is the  
17 trivalent influenza vaccine in 1945, the combinations  
18 of diphtheria and tetanus and pertussis vaccine came  
19 along in licensed form in the late '40s and mid '50s.

20 If you go back to obsolete vaccines, polyvalent  
21 vaccines were very common at the beginning of the 20th  
22 century, although of doubtful efficacy. But then you  
23 see a variety of combinations. There now is in the  
24 U.S. a five-fold or five disease combination for  
25 children and the others that you see listed on this

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1 slide.

2 Well, if we take the list of licensed  
3 vaccines for adults, this chart adapts some of Paul  
4 Offit's work that was repeated in the Institute of  
5 Medicine report on multiple vaccinations for children,  
6 and look at the number of what I'll call presumptive  
7 immunogens -- and I'll explain that in a minute -- it  
8 gives a number for each of the vaccines. This is  
9 probably an over-estimate in some of these cases, as  
10 I'll show you.

11 So anthrax vaccine presumably has --  
12 principally has two proteins in it, most especially  
13 protective antigen but a little bit of lethal factor.

14 Hepatitis A is essentially a single protein;  
15 Hepatitis B, a single protein; the combination product  
16 then has two. The influenza vaccine, traditional  
17 injection has one protein for each of three viral  
18 types, so three antigens. But FluMist has nine  
19 proteins for each of the three types of 27.

20 For some of these viruses, the number  
21 shown is the number of genes or the number of proteins  
22 expressed by the virus and so the numbers start rising  
23 -- MMR, a total of 24; pneumococcal polysaccharide  
24 vaccine, 13; poliovirus, 15; smallpox vaccine, 198 --  
25 wow, that seems like a really big number until you

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1 start to think about the oral typhoid vaccine. I  
2 don't know the precise number of proteins for the  
3 strain in the oral typhoid vaccine capsules, but  
4 presumably it's something akin to 4600 or so proteins;  
5 69 in varicella; 10 in yellow fever. BCG vaccine is  
6 also in the 4000 range.

7 So let's get a common nomenclature and the  
8 subtitle here is "More can be Less." What people  
9 think about, what our customers think about is the  
10 number of sticks or jabs or shots -- I put jabs up  
11 there for our Canadian friends, the vaccination in the  
12 sense of the giving of the vaccine, vaccine  
13 administration. So one stick with influenza vaccine  
14 or poliovirus vaccine protects against one disease  
15 with three stimuli, three immunogens. But the 23  
16 valent pneumococcal polysaccharide is one stick, one  
17 disease, 23 stimuli, 23 immunogens or molecules; MMR,  
18 one stick, three diseases. You can think of it as  
19 three stimuli or 24 stimuli, at the protein level and  
20 then there's the issue of its liveness as opposed to  
21 these other vaccines. So maybe we count that as 24.

22 If on the same day you got a tetanus-  
23 diphtheria booster and a dose of typhoid injection  
24 vaccine, the VI polysaccharide vaccine, and an anthrax  
25 shot, you'd get three sticks, four diseases, four or

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1 five stimuli and roughly five protein molecules to  
2 stimulate you, but it was three sticks, and that's  
3 less than the ones over here.

4 And then I put in a really late child who  
5 was getting caught up on all the vaccines they were  
6 overdue for the same day; diphtheria-tetanus-  
7 pertussis-Hep B, polio, Hemophilus influenza and  
8 measles, mumps, rubella, varicella and pneumococcal --  
9 four to six jabs, nine to 11 diseases, 11 to 14  
10 stimuli, but 126 proteins. So is that a lot? I don't  
11 know.

12 What do we encounter in human nature?  
13 Wild type infections involve, especially bacteria, on  
14 the order of thousands and more complex immune  
15 stimuli, it is generally agreed, than vaccination per  
16 se. And the vaccine selected tends to be attenuated,  
17 milder or a narrower array of proteins than the  
18 circulating microbes, especially for subunit vaccines.

19 Now that previous simplification suffers  
20 from several limitations. It looks at the humoral  
21 immune system, not the cellular immune system and that  
22 tends to get at what I was trying to capture with the  
23 liveness parameter. It doesn't consider, you know,  
24 which of those proteins are a meaningful immune  
25 epitope, recognizing that the immune system doesn't

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1 look at major histocompatibility complex responses to  
2 specific antigens; again, the liveness issue,  
3 conversion of naive T-cells to memory T-cells. The  
4 immune system is not static, as I described it. You  
5 don't step in the same river twice I guess. And then  
6 there is immunogenetic variants among individuals.

7 Humans are humans, humans are not  
8 livestock, but there is an animal model. There are  
9 hundreds of thousands or millions of animal models in  
10 respect to what happens with veterinary vaccination of  
11 livestock and it is very common to give, with one  
12 stick, vaccines against 10 or so diseases for  
13 principally cattle, swine and other livestock.

14 So I don't want to discuss only safety, I  
15 want to make sure we talk about efficacy. There's  
16 substantial literature supporting simultaneous  
17 administration of influenza and pneumococcal vaccines,  
18 simultaneous administration of Hep A and Hep B  
19 vaccines and a great variety of childhood immunization  
20 regimes. At Tab 5, you have what I've billed as an  
21 incomplete bibliography of simultaneous vaccinations  
22 that establish a lack of interaction or confirmation  
23 of joint efficacy.

24 There are a few places where there are  
25 idiosyncracies to the combining of antigens. Some

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1 combinations of diphtheria-tetanus-pertussis,  
2 Hemophilus influenza B and inactivated poliovirus  
3 vaccines don't have quite as good immunity as other  
4 combinations and so there's a little bit of tiptoeing  
5 with combinations and permutations of those products.

6 There is a little bit -- not quite the same amount of  
7 immunogenicity giving MMR -- measles, mumps, rubella -  
8 - and varicella vaccines simultaneously, so my naive  
9 understanding is that a combined quadrivalent product  
10 would resolve this by giving -- by having a higher  
11 dose of varicella virus in the vial.

12 And with oral rotavirus and oral  
13 poliovirus vaccines, there was reduced efficacy of the  
14 rotavirus vaccine with some strains but not others.  
15 So those are live vaccines in a case where -- I use  
16 the word idiosyncrasy because sometimes it's okay and  
17 sometimes it's not, it seems.

18 Well, how big of a problem is this  
19 simultaneous vaccination thing? This is immunization  
20 counters in the Army's immunization database from  
21 September of '02 to October of '03. One vaccination,  
22 one stick a day, two sticks a day, three sticks a day,  
23 four sticks a day, active component, National Guard,  
24 Army Reserve, Army civilians and then the percentage  
25 for each row. Seventy-four percent of the encounters

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1 got one vaccination, that's probably skewed by flu  
2 shots, and then 13 percent for two a day and so at --  
3 let's see, children sometimes can get five a day, so  
4 that's -- at the threshold for what is common practice  
5 for pediatric vaccinations, 98 percent of immunization  
6 counters in the Army were below that. We do have on  
7 the order of magnitude of a few tens of thousands  
8 getting six, seven, eight, nine, ten or eleven a day.

9 And Dr. Ostroff asked me to find out what the tens  
10 and the elevens were, and they principally are travel  
11 vaccines or various combinations of them. Somebody  
12 probably not previously vaccinated, not well screened  
13 or kept up to date getting Hep A and Hep B and  
14 tetanus-diphtheria and yellow fever and typhoid and  
15 flu in the fall and et cetera, et cetera and it runs  
16 that gamut.

17 Now it's also worth noting that there is a  
18 disproportion in terms of the rising numbers of --  
19 well, let me phrase it this way -- in the Reserve  
20 component, the numbers don't fall off, descending the  
21 chart, as fast in Guard as they do on the active duty.

22 My inference from that is we're not doing a good  
23 enough job at keeping Reserve folks up to date, which  
24 means that when they do get ready to deploy, they need  
25 more. And so that's an issue that we're beginning to

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1 address.

2 Corresponding data for the Air Force from  
3 their software system, same date range, comparable  
4 numbers, comparable percentages, 99.9 percent at the  
5 five or fewer sticks per day level and the proportion  
6 stayed proportionate in the Guard and the active duty  
7 so my inference is the Air Force is doing better at  
8 keeping their Guard and Reserve up to date than the  
9 Army is.

10 So what do we know from the literature?  
11 There was a study out of Fort Detrick of 99 lab  
12 workers, all men, who received on average 97  
13 milliliters, three ounces of vaccines during their  
14 careers, against an incredible variety of antigens or  
15 diseases. There was a small control group. The  
16 principal conclusion, no unusual diseases or  
17 unexplained symptoms among this group. Some of them  
18 did die over the course of that 30 some years, but not  
19 any greater than expected and so the conclusions of  
20 the authors are reassurance that the schedules for  
21 routine immunization with a diversity of vaccines  
22 should not produce untoward effects merely because of  
23 the frequency of inoculation.

24 That IOM study I talked about looked at --  
25 was pediatric focused, reported out in February of

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1 2002, and Rick brought a few copies of it with him,  
2 and I have mine. Their conclusions were that multiple  
3 vaccinations -- that the evidence favors rejection of  
4 a cause and effect relationship heterologous  
5 infection; rejection of a causal relationship with  
6 type-1 diabetes; inadequate evidence with regard to  
7 allergic diseases of childhood, particularly asthma;  
8 and they did not consider the question of sufficient  
9 merit to recommend any kind of policy review with  
10 regard to childhood immunization.

11 Well, what about adults? Are adults just  
12 big kids or is there less risk, is there more risk or  
13 are they just different populations?

14 What we know from -- this summarizes two  
15 reviews of travel clinic data, noting that people  
16 preparing for overseas travel have time constraints,  
17 oftentimes get multiple vaccinations in a compressed  
18 period of time. This is 1100 healthy travelers and  
19 people getting two sticks had 36 percent adverse event  
20 rates -- this is a combination of a variety of  
21 symptoms, 40 percent for triples and 50 percent for  
22 three or more. For greater than two -- two or more  
23 vaccinations, side effects less frequent than  
24 published literature but excellent tolerability of  
25 multiple vaccination. And although the numbers rose,

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1 the authors concluded that multiple vaccines can be  
2 given at the same time with limited subjective side  
3 effects.

4 This article is quite similar, 984  
5 patients, local reactions 45 percent with one stick,  
6 78 percent with three or more, systemic reactions 25  
7 percent with one stick, 70 percent with three or more,  
8 but number of vaccines did not influence duration or  
9 severity of reaction. Age and gender did not  
10 influence frequency of reactions. The reactions were  
11 generally mild and not reason to withhold multiple  
12 vaccinations, when indicated.

13 What are the Advisory Committee of  
14 Immunization Practices recommendations in this regard?

15 They note that experimental evidence and  
16 extensive clinical experience strengthen the  
17 scientific basis for simultaneous vaccination. It's  
18 critical when preparing for foreign travel -- that  
19 happens to us a lot. And so the recommendations from  
20 ACIP are -- hyper-summarized -- two inactivated  
21 vaccines, give them at the same time or at any  
22 interval before or after and inactivated and live  
23 vaccine, give them at the same time or any interval  
24 before or after, with one exception which no longer  
25 applies, because parenteral cholera vaccine is no

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1 longer licensed in the U.S. -- or anywhere else that I  
2 know of.

3 Two live vaccines simultaneously or give  
4 them 28 days apart. There's an exception for that  
5 one, but it's more permissive and that's that yellow  
6 fever vaccine can be given any time after single  
7 antigen measles vaccine and then the oral route is  
8 different from the parenteral route so that oral  
9 typhoid vaccine is not subject to the other  
10 precautions.

11 This is a summary of the bibliography that  
12 I've provided -- 13 articles on live and live  
13 vaccines; 33 articles on live and inactivated  
14 vaccines; 33 articles on inactivated and activated  
15 vaccines; four general reviews and 11 other, including  
16 some animal models. As you peruse it, I've sequenced  
17 them so that the live virus vaccines go first and  
18 apropos the combination of adenovirus type 4 and  
19 adenovirus type 7 is first on the list and then it's  
20 sorted alphabetically by disease.

21 So, there is a pin-cushion effect, that's  
22 what you saw in that travel clinic data, so how can we  
23 minimize that? Well, if we have the luxury of time,  
24 let's spread them out. We can do more screening to  
25 see -- if you're already immune, we don't need to give

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1 you that vaccine. And as states more frequently turn  
2 over to us recruits who have been vaccinated as  
3 children, maybe we -- especially with Hep B vaccine  
4 and other vaccines being given in childhood, maybe we  
5 can give fewer shots, spend less money on vaccine, by  
6 importing or accepting their childhood records.

7           One of the dilemmas that we have  
8 encountered -- and I've not really identified a good  
9 clear way to resolve it is we give a bunch of vaccines  
10 in basic training that sometimes people lose their  
11 records over -- poliovirus vaccine, for example. And  
12 so I've got field units repeating polio vaccine  
13 because they've lost their record. But how do I issue  
14 instructions to the field to give constructive credit  
15 for basic training if the records aren't available?  
16 Do I just assume that they're immune? What if they  
17 slipped through the cracks? We go places where there  
18 is polio. Do we disregard the lack of records except  
19 in an outbreak setting, do we tell the computers to  
20 keep track of it but don't flash any red lights? What  
21 do we do?

22           There is need in the Army, I believe, to  
23 increase the frequency of medical readiness reviews in  
24 the reserve component and maybe we work up some kind  
25 of order of merit list that we tell medics to pay more

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1 attention to, for example, Hepatitis A and anthrax  
2 vaccine, pay less attention or, you know, work it down  
3 to the bottom of the list for polio and MMR because  
4 they likely have gotten it somewhere before, even  
5 though the records may be deficient.

6 Well, what are the vaccines given in basic  
7 training, initial entry training? Meningococcal  
8 vaccine, MR or MMR, polio, tetanus-diphtheria, Hep A,  
9 Hep B, some -- in the Navy and Marine Corps, yellow  
10 fever commonly; influenza everywhere but seasonally;  
11 pneumococcal at Pendleton; varicella after screening,  
12 if they're susceptible; and we hope some day soon -- I  
13 don't know what year to put on here -- to put  
14 adenovirus.

15 Well, how could we spread that out? I  
16 think we could do it by recognizing -- organizing  
17 these into two categories -- imminent risk of  
18 contagion, the diseases of basic training camps --  
19 meningococcal disease, MMR, adenovirus, flu, varicella  
20 and pneumococcal disease. And then diseases that are  
21 generic travel risks. We're preparing them for their  
22 life in the service and that would be tetanus-  
23 diphtheria, Hep A, Hep B, polio, flu, yellow fever. I  
24 am told that it is common in the Navy to go straight  
25 from initial entry training to a duty station rather

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1 than to -- or to a ship rather than advanced  
2 individual training, so this might need to be  
3 customized, but -- so maybe this is the list when you  
4 graduate from basic rather than when you arrive at the  
5 next place, but that could be worked out.

6 And there are more vaccines we are  
7 probably going to want to give our folks --  
8 meningococcal conjugate vaccine, acellular pertussis  
9 vaccine, papilloma virus vaccine, not just for the  
10 women probably but for the men as well, subunit  
11 vaccines.

12 Well, what are we doing about all of this  
13 stuff? We have -- we are in the process of developing  
14 -- we have established and are in the process of  
15 developing a group called the vaccine analytic unit  
16 evaluating the Defense Medical Surveillance System at  
17 the Army Medical Surveillance Activity, AMSA, part of  
18 CHPM, which is a joint effort with CDC as well as the  
19 Food and Drug Administration.

20 And so what they are in the process of  
21 doing is using the computer databases to take an  
22 inventory of what are the most common simultaneous  
23 combinations? Are there some combinations more  
24 problematic than others? How are they going to define  
25 problematic?

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1           Looking at total healthcare utilization,  
2 there's internal debate about whether that's too non-  
3 specific and that will be worked out over time.

4           From the discomfort, pin-cushion,  
5 perspective, what are the minor problems or  
6 discomfort, the most common sick call kinds of ICD9  
7 codes?

8           And then the other piece is looking at the  
9 rare events, the autoimmune diseases. And highest on  
10 the list to pursue are probably going to be multiple  
11 sclerosis, Guillain-Barre, diabetes and lupus. Also  
12 to see if we can answer the question about allergic  
13 diseases or asthma and then anything else that seems  
14 logical that comes to mind.

15           And then looking at co-variants in terms  
16 of demographics, live versus inactivated vaccines, the  
17 amount of aluminum to get at Th1, Th2 stimulation,  
18 whether they've had Guillain-Barre in the past and  
19 then other risk factors, to the extent that we can.

20           Other possible efforts, we're engaging  
21 AFIP to see if it's possible for us to look into  
22 deaths to address the question of cause of death and  
23 recency of vaccination and also we have the DoD serum  
24 repository as a resource to look at immunogenicity  
25 studies as well as serologic risk factors such as was

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1 shown with rheumatologic serum markers.

2 So this slide concludes my portion and it  
3 crystallizes what I believe to be true and I would  
4 offer it to you as a starting off point for the  
5 discussion.

6 And that is that there is no known ceiling  
7 of simultaneous immunizations that is "too many".

8 Simultaneous immunization bears  
9 considerable advantage in efficiently increasing the  
10 immunity of military personnel, returning them to duty  
11 with the fewest medical visits.

12 Published evidence and accumulated  
13 experience of tens of millions of simultaneous  
14 vaccinations over decades suggests that harm from  
15 simultaneous vaccinations per se -- the combining as  
16 opposed to the individual vaccinations on different  
17 days -- is either rare or non-existent.

18 Additional work is needed to help identify  
19 risk factors that might predispose to rare problems.  
20 And we believe we have an obligation, because we have  
21 the databases, to go look.

22 Because objective evidence is finite and  
23 because databases offer a unique opportunity, these  
24 databases should be evaluated further.

25 I'll stop there.

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1 DR. OSTROFF: Thanks very much.

2 We have one additional presentation from  
3 COL Engler and then we'll open it up for discussion,  
4 unless there are any questions that are very specific  
5 to COL Grabenstein's presentation.

6 Go ahead, Dave.

7 MAJ GENERAL KELLEY: John, I just had a  
8 quick question, on the studies that looked at the  
9 multiple immunizations and the side effects increasing  
10 with numbers of vaccinations, did they make any  
11 attempt to look at whether that was really just  
12 additive for the known side effects for those vaccines  
13 or synergistic, meaning it was more than would have  
14 been expected, just by numbers of vaccines?

15 COL GRABENSTEIN: I don't remember the  
16 fine points. I've got the studies in my room -- I  
17 don't think they went very sophisticated in terms of  
18 statistics, I think they just pretty much reported it  
19 out.

20 MAJ GENERAL KELLEY: The thought being  
21 just that with different, you know, side effects for  
22 different vaccines.

23 COL GRABENSTEIN: Yeah, a certain number  
24 of people are going to have a headache on any given  
25 day whether you vaccinate them or not, and then you

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1 add on, you know, one overlay or two overlays. I  
2 don't think they addressed it that specifically.

3 DR. OSTROFF: Thanks very much.

4 COL ENGLER: Thank you. I also want to  
5 thank COL Riddle for all of his work and for giving me  
6 this opportunity to come to you today to give you an  
7 overview of the Vaccine Healthcare Center Network and  
8 its potential dovetailing as an infrastructure that  
9 supports a robust capability within the Department of  
10 Defense to address some of the complex rare adverse  
11 events issues and certain quality improvements from a  
12 clinical perspective in immunization healthcare.

13 For those of you who are new to the Board  
14 or may not be familiar with the Vaccine Healthcare  
15 Center Network, it grew out of Congressional and  
16 Government Accounting Office concerns related to  
17 deficiencies in support for clinical problems arising  
18 out of the Anthrax Vaccine Immunization Program and  
19 generic new vaccine safety issues, new rare vaccine  
20 adverse events reports that may not be amenable  
21 particularly to epidemiologic study because they are a  
22 rare event, and because they are complex; therefore,  
23 coding with an existing database is not particularly  
24 reliable.

25 It also grew out really prior to the

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1 anthrax vaccine program in 1999, this Board on  
2 sponsorship from Health Affairs conducted a review of  
3 vaccines in the military and within there was a  
4 chapter that addressed the issues of deficiencies in  
5 immunization healthcare throughout the enterprises  
6 related to the many new demands of an increasingly  
7 complex world of vaccines, vaccine safeties and the  
8 growing national concern regarding standards for  
9 vaccine administration, particularly in non-  
10 traditional sites.

11 The DoD leadership liaisons to Congress  
12 responded to those concerns in regards to addressing,  
13 first of all, what were the issues, and how may they  
14 be solved. And you have -- there's not time this  
15 morning, but in your handouts, you have the vision,  
16 mission and goals, all of which grew out of specific  
17 hearings and issues that were asked to be addressed.

18 The initial funding for this initiative  
19 actually came through the Centers for Disease Control,  
20 the National Immunization Program Office, which had  
21 been directed by Congress to work with the Department  
22 of Defense on clinical vaccine safety programs, and  
23 among those being the funding of the dose reduction  
24 route change study for the anthrax vaccine.

25 The DoD requirement from the AFEB report

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1 addressed really prior to the anthrax vaccine program  
2 initiative that there were increasingly more vaccines  
3 with safety concerns, there was increasing complexity  
4 and that the standards in general were not well known  
5 among front line providers or nursing personnel, and  
6 the literature is replete, both within and outside of  
7 DoD with the fact that nursing personnel and providers  
8 of varied specialties get minimal to no training on  
9 vaccines and vaccines were sort of an orphan drug set  
10 which were administered rotely but not necessarily  
11 with awareness of the standards for adverse drug  
12 reaction management that have been developed over the  
13 last 10 years.

14           There is also a growing community of  
15 decreased trust in vaccines and this new field of risk  
16 communication, which really no one was prepared for in  
17 the front lines facing some of the complex challenges  
18 that arose, that of access to information, both good  
19 and bad, on the internet.

20           If we take the anthrax and now the  
21 smallpox program as models for the challenges that  
22 will face us with any new vaccine insertion or  
23 certainly with any mass immunization that might be  
24 done in a bioterrorism response, there is an  
25 increasing need for clinical and educational support

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1 and that expertise in this kind of consultation for  
2 the outliers, if you will, that are complex.

3 But in the world of adverse drug reactions  
4 -- and the FDA has recognized this fact in the  
5 increasing focus on phase 4 post-marketing  
6 surveillance -- it is not until you give it to  
7 millions of people with any new drug do you begin to  
8 learn about the rare adverse event. And then about  
9 one or two percent of the population, which is not  
10 minor if you consider the 2.4 million active and  
11 reserve service members, given a drug will experience  
12 a side effect or an adverse event where either the  
13 patient or the provider caring for the patient will  
14 have concerns about safety of continuing the drug, and  
15 the decision matrix and the guidelines for how to  
16 assess these problems and either move ahead with  
17 continued challenge, modified administration of the  
18 drug such as penicillin to an anaerobic brain abscess  
19 in the setting of penicillin anaphylaxis where you  
20 still have to give the drug. Those kinds of clinical  
21 guidelines really had not been developed or addressed  
22 and were lacking.

23 The identification and management of  
24 adverse reactions over time, new case definitions for  
25 rare events and a face that cares, for mandatory

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1 vaccine programs, particularly in relation to  
2 understanding that rare adverse events do occur, even  
3 if they're not listed in the package insert.

4 It was these kinds of clinical support  
5 resources that in the Congressional hearings were  
6 identified as being needed and being perhaps  
7 insufficient.

8 In that context, because many of the  
9 problem cases came to Walter Reed and the Immunology  
10 Department there, which has a long history of  
11 supporting tri-service education and immunizations  
12 through its school, the cases became rapidly  
13 overwhelming in their complexity and work demands and  
14 the question arose what is DoD doing about multiplying  
15 this kind of resource or center of excellence for  
16 vaccine safety to other sites to support the broader  
17 mission.

18 Since that time, the first regional site  
19 opened at Walter Reed on September 6 in 2001, and we  
20 are now at four sites in various staging of  
21 maturation, as you see here with Wilford Hall being  
22 our most recent. Opening ceremonies pending for  
23 Portsmouth Naval Medical Center, Fort Bragg and  
24 Wilford Hall hopefully this year.

25 Initial work has been done to consider the

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1 European theatre and this extended support and  
2 requirement there with starting functions but pending  
3 a business case analysis that's being reviewed this  
4 month and next month in regards to budgeting.

5 Each of the sites shown here were  
6 identified as proposed sites based on larger regional  
7 support requirements and hundreds of immunization  
8 sites, active and reserve, that were asking for help,  
9 support and outreach education.

10 In that context, over the last couple of  
11 years, working closely with the Center for Disease  
12 Control -- and I just want to point out, although my  
13 printer is not working, that while this was being  
14 developed, the CDC in parallel began to mature a  
15 comparable concept known as the CISA network or  
16 Clinical Immunization Safety Assessment Centers,  
17 recognizing that there is a need for clinicians with  
18 expertise in vaccine safety to be involved in the  
19 evaluation, follow-up and documentation of rare  
20 cases, and that frequently the various documents on  
21 these cases were very inadequate, incomplete and  
22 requests for follow-up did not provide the kind of in-  
23 depth analysis of the case and review that made it a  
24 document that a reviewing group would have adequate  
25 information to review.

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1                   So in that context, there are now seven  
2 sites that are under contract with CDC, clinical  
3 immunization safety centers, including the northern  
4 California Kaiser and Boston, et cetera. And if  
5 anyone needs that, I can make that available for a  
6 listing.

7                   In that context, the vision that Dr. Bob  
8 Chin had, as the champion at CDC, is that these sites,  
9 if everybody sees one very rare case and they are  
10 networked in a hub and spoke kind of fashion with an  
11 ongoing clinical conference review process, that  
12 eventually there would be three or four cases where  
13 you could begin to build a case definition, begin to  
14 define ways in which to investigate and develop a  
15 research program, or in ways to address the database  
16 searches that might be do-able subsequently. So a  
17 living and breathing, if you will, civilian. And with  
18 the VHC DoD comparable network for this kind of  
19 surveillance and clinical case management, it is the  
20 hope of the CDC that the functions that the VHC is  
21 providing now will be provided as a byproduct at the  
22 civilian sites, although they are not able to fund  
23 them for clinical services. This would be in addition  
24 to the public health surveillance, if you will, for  
25 rare adverse events to vaccines.

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1           Several years ago, I had talked with  
2 members of the Board about a chartered clinical  
3 advisory board that was really clinically focused for  
4 case reviews and presenting some of the work that we  
5 are struggling with, and that that is still in a  
6 pending status and we hope will be finalized this  
7 year.

8           For the DoD, vaccine adverse events,  
9 particularly if they are considered possible contra-  
10 indications or reasons for medical exemption, have  
11 some issues that are not as prevalent in the civilian  
12 community. Career implications in regard to retention  
13 and recruitment and duty and flight status were high  
14 visibility during the initial phases of the anthrax  
15 program.

16           With all due respect to COL Grabenstein's  
17 briefing, I would say that since the initial phase,  
18 the clinical advocacy to move towards a better  
19 understanding of medical exemptions so that people  
20 didn't have to get out because they had an adverse  
21 event and felt they were pressured to be vaccinated,  
22 that we built in a safety valve in regards to the  
23 adverse vaccine reaction algorithm that encouraged  
24 people to understand the medical exemption process and  
25 a referral process for evaluation by people who could

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1 potentially continue to immunize in a safe environment  
2 with special precautions and special treatments.

3 All of that, I think has contributed  
4 greatly to the reduction in problems, because during  
5 the phase one, it was the clinician's perspective that  
6 many of the controversies actually arose out of people  
7 who had medical issues and a lack of understanding of  
8 the exemption process.

9 In addition, we now have, particularly in  
10 the Army, there is not an absolute prohibition to  
11 deployment. If you have a medical issue requiring a  
12 valid exemption and you've had a couple of doses, you  
13 are still deployable. And I think we are moving to  
14 some flexibility in the system to recognize that  
15 vaccines are just like every other prescription drug.

16 They're not 100 percent and there are issues that  
17 arise clinically that prevent continuation.

18 But clearly, in a setting where the  
19 disease is only preventable by a single drug or a  
20 single vaccine, we need to develop ways to give that  
21 vaccine, just like we give penicillin to a penicillin  
22 allergic patient who is dying from an infection where  
23 there is no other antibiotic. And this is really a  
24 challenge that is of greatest need within the  
25 Department of Defense.

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1           So really, there is a clinical need for  
2 developing solutions in the setting of a VAERS or a  
3 vaccine adverse event report. And if the unusual,  
4 unexplained and complex arise, we need to improve our  
5 understanding of long-term disability and quality of  
6 life impact that ultimately may roll into disability  
7 definitions, and to struggle with the IOM's criteria  
8 for what represents biologic plausibility of  
9 causality, and have a credible process of review, with  
10 multi-disciplinary input on a clinical side to show in  
11 an open process efforts that are being made to fairly  
12 address those concerns, and all of that rolling into a  
13 public perception and that there is not a disregard  
14 for those rare adverse events and that there is  
15 competency in addressing them and thereby improving  
16 the trust in the delivery of care.

17           We give penicillin, we kill people with  
18 penicillin every year, but no one is presuming that  
19 that is a drug that should be recalled or withdrawn.  
20 It's understood in the medical side and I think the  
21 same standards that apply to all drugs need to be  
22 applied to vaccines, including our understanding of  
23 how to manage the problems.

24           In regards to rare adverse events  
25 challenges, there are many. And certainly the VAERS

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1 process, the epidemiologic review that is so superbly  
2 addressed in these forums as well as others such as  
3 the IOM, the ACIP, et cetera. But they leave --  
4 there's that but for the clinical side, and that is  
5 these rare events that have a very strong temporal  
6 association where the differential diagnosis comes up  
7 with nothing else, and the awareness of possible  
8 associations by reporting clinicians.

9 One of the anecdotes told in relation to  
10 hair loss in Hepatitis B on the pediatric side is that  
11 the mother brings the child in, the hair falls out  
12 after Hepatitis B, the pediatrician says it can't be  
13 Hepatitis B. The second dose, the hair falls out and  
14 the pediatrician says it can't be Hepatitis B. The  
15 third dose and the hair falls out and the pediatrician  
16 still says it's not Hepatitis B. But there is now a  
17 growing body of evidence, both for the biologic  
18 causability of alopecia with Hepatitis B and it needs  
19 to be recognized. But if there is a bias on the  
20 clinical front lines, it will never appear in the  
21 VAERS system and it will not be recognized. Very,  
22 very rare events again, but because of  
23 reproducibility, it would suggest that there's  
24 biologic plausibility, causality in those rare events.

25 So there is a tremendously steep learning

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1 curve to educate healthcare workers regarding the  
2 potential for unexpected and ill-defined adverse  
3 events. People get very angry when they are told this  
4 can't be the vaccine because it's not in the package  
5 insert. We don't tell people with other adverse drug  
6 reactions that kind of a response. So how to  
7 communicate and relay to our service members and our  
8 patients who receive vaccines.

9 Understanding that reporting and proof of  
10 causality are not linked is still something that we in  
11 our work are finding is not a given and is complex for  
12 many people. Epidemiologic safety assessments do not  
13 preclude rare adverse events requiring additional  
14 clarification and study beyond epidemiologic review.

15 We've heard often in the safety reviews  
16 that local reactions are no big deal. This make some  
17 patients very, very angry, particularly if their  
18 nodules last for more than three months, are very  
19 painful or to the point where they have requested that  
20 they be surgically removed. These are real cases that  
21 we have dealt with.

22 We also have cases of large local  
23 reactions complicated by neuropathy. The AVEC review  
24 committee actually recommended that the usual location  
25 for subcutaneous administration of the anthrax vaccine

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1 be shifted to the deltoid because of the large local  
2 inflammatory reactions that can secondarily inflame  
3 the nerve. We are still struggling with getting that  
4 message out. Websites alone don't do it. Person-to-  
5 person contact and this tool that you all have on your  
6 desk -- and I'm sorry, if anyone wants them, they can  
7 request them, is a four-year project that grew out of  
8 the need to get information out into the hands of  
9 people, have it in their pockets to bring some of  
10 these points across.

11 The individual that is followed by the  
12 VHC, who has bilateral ulnar neuropathy from anthrax  
13 vaccine and has disfunction from that was very angry  
14 when the IOM report came out and said that there are  
15 no safety issues and no serious adverse events. To  
16 that person, his adverse events are serious.

17 We have been very successful through our  
18 efforts of clinical outreach and being a presence at  
19 presenting hospitalizations where severe inflammatory  
20 local reactions were mistaken as cellulitis and would  
21 have been admitted for IV antibiotics. Certainly one  
22 of the returns on investment in building a network of  
23 competency that reaches out and touches to the front  
24 lines in the immunization and healthcare arena.

25 Perceptions here are a reality, but I

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1 would venture as a clinician coming to this body now  
2 for several years and having witnessed much of the  
3 wars around vaccines both on the civilian side and  
4 within the military, that we have a challenge in the  
5 21st century to balance the clinician's perception,  
6 the patient's and the epidemiologist's, and that each  
7 component is important as part of the whole.

8           It's one elephant but different views, and  
9 how to combine them in a whole that is balanced,  
10 evidence-based and credible, I think is extremely  
11 challenging in the times ahead and with all the new  
12 vaccines to come.

13           In regards to humility and lessons that I  
14 have learned, the Vaccine Healthcare Center in its  
15 operations, among the hundreds of patients' cases that  
16 have come to us, collected three cases of pemphigus  
17 vulgaris temporally linked with the anthrax vaccine.  
18 The first case, we dismissed; the second case, we  
19 dismissed; the third case, the staff in the clinical  
20 conferences said okay, let's look at these together  
21 and think about this some more.

22           We then partnered with an expert in  
23 pemphigus vulgaris, a Dr. Stanley at the University of  
24 Pennsylvania, who is an immuno-dermatologist, who has  
25 characterized the auto-antibodies that are pathogenic

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1 in this disease -- anti-desmoglein skin antigen  
2 antibodies.

3 We are able, using the DoD serum  
4 repository under informed consent by the patients, to  
5 access their sera prior to their illness and showed  
6 that they did not have these auto-antibodies prior to  
7 the anthrax vaccination. These anti-desmoglein skin  
8 antigen antibodies can, if you infuse them into a mal  
9 smali (ph.), you can produce the disease, so this is a  
10 well-characterized and very, very, very rare auto-  
11 immune blistering skin disease.

12 It can present with oral ulcers and we've  
13 had cases, but we've not been able to track them down  
14 after the identification of this, that had transient  
15 oral ulcers after anthrax vaccination.

16 But the question was raised by the  
17 dermatologist at the University of Pennsylvania, is  
18 this a form of subclinical disease. And there are in  
19 the VAERS system complaints of transient oral ulcers  
20 and rashes.

21 In this partnership, Dr. Stanley became  
22 very interested in our dilemma and all of the sera  
23 available on these patients were sequentially  
24 analyzed. And he then subsequently -- and I'm going  
25 to digress because time is of the essence here from

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1 some of what I was going to tell you -- but identified  
2 that there is actually an antigenic sequence within  
3 the anthrax bacterial cell wall that has sequence  
4 homology to desmoglein skin antigens. That is, if you  
5 search the massive Cray computer for everything that's  
6 ever been sequenced on the earth and ask what has the  
7 greatest homology with desmoglein skin antigen, we  
8 were extremely surprised to find out up popped this  
9 particular sequence.

10 So suddenly the question that this is a  
11 proof of concept, if you will, of molecular mimicry,  
12 became a very important research question. And as  
13 such, Dr. Stanley, who has NIH grants that pay for the  
14 assays, has partnered with us and we just received  
15 approval finally after many, many months to access the  
16 DoD serum repository and pull out 300 paired samples  
17 of individuals who had received anthrax vice 300 who  
18 didn't. Because presumably from a molecular  
19 rheumatology, immunology perspective, there's a  
20 hypothesis that perhaps a couple of percent of people  
21 will develop these auto-antibodies transiently without  
22 evidence of disease.

23 And then the question becomes how do we  
24 identify people who have oral ulcers that are  
25 transient and what is the implication for a clinical

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1 guideline to alert people in the community that if  
2 they see someone with a transient oral ulcer, to  
3 consider referral and evaluation to the network, so  
4 that we can send their sera to Dr. Stanley and further  
5 characterize this.

6 In talking to some of those communities,  
7 particularly the oral surgeon community, the dental  
8 community, we are developing a plan to try to get the  
9 information out so that patients will have access to  
10 the Vaccine Healthcare Center for further support for  
11 exemption and evaluation.

12 This is not one of our patients, but this  
13 is a -- pemphigus is a very serious blistering disease  
14 that, prior to the era of steroids, had a 90 percent  
15 fatality but has been very, very well characterized.  
16 So clearly if someone develops this, they should have  
17 a contra-indication exemption for further anthrax,  
18 although the recombinant PA antigen vaccine should be  
19 fine because there would be no bacterial cell wall.

20 So these are the kinds of clinical  
21 guidelines we're trying to develop and evolve from  
22 real clinical experience.

23 Erythema multiforme is -- there's a lot of  
24 rashes after vaccines, and it's really -- the VAERS  
25 system is non-granular, very poor and our

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1 understanding of these is also poor.

2           When is a rash an absolute contra-  
3 indication, when is it like an ampicillin rash where  
4 we still give ampicillin because we have some safety  
5 data? It is the hope as the network matures, that it  
6 will be able to collect the outcomes data and this  
7 kind of individual case management data to help build  
8 the information that clinicians need at the front  
9 lines to manage immunization healthcare questions.

10           I hope with the existence of the network  
11 now, we won't have people getting immunized five  
12 times, biopsy proven erythema multiforme and somebody  
13 thinking they should be given prednisone to give them  
14 their sixth anthrax shot so they are compliant. These  
15 are real cases -- not making them up -- and we have a  
16 lot of them.

17           So in that regard, the complexity of the  
18 risk communication, everything -- one of my  
19 rheumatology colleagues made the statement on one of  
20 my days of feeling totally overwhelmed and frustrated  
21 with all there is to do, said you're kind of where  
22 rheumatology was 30 years ago, trying to figure it  
23 out, define it, like the Brighton Collaboration  
24 Internationally which we are participating in, just to  
25 get the case definitions of what's being seen and then

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1 develop programs for management.

2 That raises this issue of beyond side  
3 effects, and I appreciated one of the members of the  
4 Board asking the question, because side effects in  
5 clinical medicine, in the new JACO world requirements,  
6 are important. And the entire medical establishment  
7 has been accused of being relatively indifferent and  
8 blind to the fact that if you treat somebody and you  
9 think their disease should be treated because the lab  
10 test is okay, but the side effects make their life  
11 miserable, you have not been a success. How we give  
12 drugs, how we treat people in the clinical setting is  
13 important, how much pain we cause is important. And  
14 that is a standard of care.

15 But when does a side effect become  
16 something more than a side effect? When does it  
17 impact on quality of life and again, what is the  
18 safety of repeating the dose, when to exempt and when  
19 not to exempt and how do you manage those assessments  
20 and what is the ethics of the risk counseling we give  
21 to people.

22 In that regard, I wanted to pull the  
23 Tripler study of 601 healthcare workers who received  
24 anthrax and I thought the study was very nice and one  
25 of the few studies that actually tried to grade

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1 severity of adverse events. And you see here, one to  
2 two percent of people whose side effects were so bad  
3 that even with medication for symptoms, it interfered  
4 with their function. We don't understand the  
5 mechanism of this, there is a lot of work to be done  
6 and when these kinds of symptoms persist for weeks or  
7 months, what does that mean and how do we best manage  
8 it?

9 In that regard, we've had dozens of cases  
10 that were kind of hard to get our arms around in  
11 regard to persistent systemic symptoms, but we've  
12 pulled out five cases that were very, very clean  
13 cases. These five cases had 19 doses of anthrax and  
14 with each dose they got reproducible worsening of  
15 their symptomatology. These cases have been  
16 extensively reviewed with rheumatologists,  
17 immunologists and in some cases, their symptoms  
18 persisted for more than a year. An abstract has been  
19 submitted to the National Immunization Conference to  
20 attempt to draft a preliminary case definition.

21 One case requested that he be re-  
22 challenged and in that context, I don't have time to  
23 go into the details, we modified the way we  
24 administered, we pretreated, but he still had  
25 reproducible symptoms with a marked elevation of his

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1 anti-protective antigen antibodies spiking very high  
2 and he's currently, after four months of still being  
3 symptomatic, with a rheumatology consultation, we are  
4 treating him with low dose steroids to try to  
5 interfere with the process.

6 So early recognition I think is important  
7 in someone struggling over the issue of how to manage  
8 them. They are rare, thank God, or the healthcare  
9 system could handle them, but we have to make sure  
10 that there is a visible process that supports an  
11 attitude of openness as to cause, specific diagnosis  
12 when possible and to treat symptoms and follow-up.

13 In that regard, we've got -- I just wanted  
14 to mention in regards to the smallpox program, it was  
15 the BHC at Walter Reed with the allergy-immunology  
16 program that tested, beat up and refined the screening  
17 tool so that it was user friendly, and that this kind  
18 of clinical work in making a vaccine program a success  
19 is crucial to the success of the program. And then the  
20 backup support.

21 John already showed you the data a week  
22 ahead, but again, what I want to focus on is that the  
23 eczema vaccinatum was zero, the progressive vaccinia  
24 was zero, those were preventable causes. We fought  
25 very hard to make sure that this was done properly but

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1 we have handled thousands and thousands and thousands  
2 of e-mail consultations saying here's the history I  
3 got, here's what I think, do I vaccinate, don't I  
4 vaccinate. A massive workload that was the backend of  
5 this effort, that tried to help the front lines and  
6 again, for me, the clinician, and nursing and service  
7 member gratitude for our intervention and support in a  
8 rapid way, in a rapid response way was very much  
9 appreciated.

10 And the myopericarditis support is another  
11 function of the VHC. I've got to rush through.

12 I just want to mention that providing a  
13 root cause analysis, one of those myopericarditis  
14 cases was the death case, in that there was autopsy  
15 evidence, but we spent many hours interviewing people,  
16 providing the materials that fed into the review  
17 process, and what frequently happens is without the  
18 interviews, what's written down in the records may not  
19 reflect totally the story and so for review and root  
20 cause analysis, I think we have a very important role.

21 This is the workload just for fiscal year  
22 '03 that the VHC network, while it was growing,  
23 supported over 100,000 clinical consultations by e-  
24 mail, by telephone, by direct contact, et cetera, both  
25 to providers, civilian providers in the Tricare

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1 network frequently who are confused, don't know what  
2 the adverse event is or how to manage it.

3 This is a case just to show you an example  
4 of intervention, they were going to take him to the OR  
5 and debride him in a civilian emergency room, through  
6 the DoD call center referred to us, we were able to  
7 convince them not to do that and leave it alone.

8 In the myopericarditis case, we don't have  
9 time to go through the details but we have been tasked  
10 with coordinating the two year follow-up. There's an  
11 average of over 300 pages of paper on each of these  
12 case that the VHC staff reviews, summarizes and the  
13 VAERS folks have already told us how appreciative they  
14 are of the quality of the VAERS they get. There is a  
15 lot of work that goes into classifying those cases,  
16 whether they are possible, probable or confirmed, and  
17 digging and hunting, a huge amount of work that  
18 ultimately feeds into the data that is so nicely  
19 summarized on one slide.

20 We've saved two people getting a Medical  
21 Board for coronary artery disease who actually had  
22 myopericarditis and were recovering and didn't need a  
23 lifelong label of disability.

24 DR. OSTROFF: COL Engler, you need to wrap  
25 up.

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1 COL ENGLER: Yeah. You can tell, I've got  
2 more to tell you than I've got time to, but this  
3 algorithm grew up in less than six months, again  
4 hosted and pulling in -- it's just some of the  
5 examples of the kind of workload that the VHC as a  
6 network with multiple sites has been supporting and  
7 brings to the table in regards to the challenges we  
8 face.

9 Just to let you know about the study that  
10 has now been approved, I just last week got the  
11 letter. Walter Reed and Brooke Army Medical Center  
12 will be hosting, looking prospectively at 600 primary  
13 vaccinees for smallpox and 200 influenza vaccinees  
14 with a hypothesis based historically on the  
15 Scandinavian experience of a two to three percent  
16 incidence of subclinical myopericarditis. The initial  
17 funding comes through the CDC CISA group and  
18 partnering with the University of Washington molecular  
19 immunology and northern California Kaiser.

20 We have a lot of challenges ahead and I  
21 just feel that we've begun to scratch the surface of  
22 quality improvement for immunization healthcare for  
23 partnering with the epidemiologic surveillance process  
24 for vaccine safety and developing the tools to help  
25 people do a better job. This being one of the tools

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1 and then you have in your binder also a description of  
2 our distance learning tool with 19 modules to try to  
3 objectify competency and knowledge among providers who  
4 are involved in immunizations.

5 Thank you.

6 DR. OSTROFF: Thanks very much.

7 Let me open it up for a few minutes of  
8 discussion before we break for lunch. There will be  
9 some additional presentations after the lunch hour  
10 from our invited guests.

11 Are there comments or questions from the  
12 Board members for either COL Engler's presentation or  
13 COL Grabenstein's?

14 DR. GRAY: I'd just like to comment --  
15 this is Greg Gray -- I think COL Engler's Center is  
16 something that the DoD really needs. If you look at  
17 the progression of questions regarding immunizations  
18 and the success of Chuck Ingle's employment health  
19 clinical center, it certainly seems to augment that  
20 center pretty well, so congratulations, I think that's  
21 great.

22 COL Engler: I appreciate the Board's  
23 support because I am in the battle of a business case  
24 analysis for something for which there is no  
25 comparable business and any endorsement the Board

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1 could give this effort would be very much appreciated,  
2 particularly the question has arisen of why does it  
3 need to be a network. If it's only one site, all  
4 we'll do is document problems, we won't work  
5 solutions. I think we need a network of multiple  
6 sites because it isn't until you have people out there  
7 connecting and talking to people and working with the  
8 front lines that you learn all the things that need to  
9 come back. I think we are putting principles in  
10 action and ombudsmen to the front lines that has long  
11 been needed for the system.

12 UNIDENTIFIED SPEAKER: This is a question  
13 actually to both of you. You're sort of the backend  
14 and Dr. Grabenstein is the front end. I'm wondering  
15 is there any potential for conflict in information  
16 given to the providers that may confuse them in this  
17 process?

18 COL ENGLER: I think that is a very good  
19 question, thank you. The Military Vaccine Agency and  
20 the Vaccine Healthcare Center network, we see it --  
21 John and I see it as two bookends. People have asked  
22 why do they need to be separate -- because we are a  
23 clinical entity and I take very great pride in the  
24 fact that the vaccine NO (ph.) groups refer patients  
25 to us and trust us. We are not policy, that's John's

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1 shop. And what John does and his group does is not  
2 what we want to do. We truly complement each other  
3 and all of the things that come out -- and you have  
4 actually a draft information sheet, brochure that grew  
5 out of the death case as a potential quality  
6 improvement initiative which we would very much  
7 appreciate your comments on, but you know, the  
8 credibility -- we work everything together and we  
9 provide hundreds and thousands of hours of support  
10 work for the MILVACs and other agencies frankly -- the  
11 CDC used us a lot and a lot of the civilian providers  
12 as well, because we have a clinical competency that  
13 isn't really replicated in the civilian world.

14 I am just amazed at how poor the  
15 understanding of adverse events is in the clinical  
16 community. So I'll let John speak, but I feel we're  
17 complementary.

18 COL GRABENSTEIN: I perfectly agree. We  
19 could not -- DoD could not have implemented the  
20 smallpox vaccination program without the VHC network.

21 The way you phrased your question was about  
22 communication. When we don't have much time, we tend  
23 to over-simplify and so in just the statement "the  
24 vaccine is safe" -- does that mean perfectly safe?  
25 Certainly not, no vaccine is perfectly safe. But if

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1 you give me two sentences, I can tell you more, you  
2 know. So it depends on how much we're forced to  
3 simplify.

4 DR. OSTROFF: Other comments?

5 Dr. Berg.

6 DR. BERG: Bill Berg. COL Engler, do you  
7 have any sort of overall summary of the conclusions  
8 you've drawn, the sort of reactions you've seen and  
9 sort of stratification of the evidence that are due to  
10 vaccines? You presented some very dramatic, you know,  
11 short case series, but can you give us any sort of big  
12 picture issue?

13 COL ENGLER: One of the things in the  
14 context -- my resources are maxed out and beyond,  
15 supporting the myocarditis registry and still trying  
16 to train people in the network. So we've actually --  
17 we're starting -- with CDC, we're developing a VAERS  
18 disease management web-based tool so the data can be  
19 synchronized. And one of our to-do's if we could get  
20 a chance to breathe is to go back and now relook and  
21 further analyze. We've got partnerships going with  
22 the CISA group, so that's certainly on our to-do list.

23 Right now, we're busy providing the  
24 services that support the program, plus targeting the  
25 highest areas of concern that pop on the top. Which

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1 means some of the things that are issues have fallen  
2 off the table, just because we didn't have the  
3 resources to address. But clearly it is our hope that  
4 as we get the tools in place, that we'll be able to do  
5 an annual, you know, kind of review for this Board and  
6 others who are interested. We just haven't had the  
7 manpower to do it right now.

8 DR. BERG: Thank you.

9 DR. OSTROFF: We have time for one last  
10 question before we break for lunch, or last thought.

11 (No response.)

12 DR. OSTROFF: If not, thank you very much.  
13 We'll finish one minute early.

14 Since we have a fairly lengthy program for  
15 the afternoon and we're scheduled to finish somewhat  
16 on the late side, I think what I would propose, if  
17 it's okay with the Board, is that we try to get back  
18 instead of an hour and 15 minutes for lunch, that we  
19 restrict it to an hour, and that we start back up at  
20 1:00 and hopefully we'll be able to finish a little  
21 bit earlier than what we have listed on the schedule.

22 Is that okay with the Board members?

23 VOICE: Absolutely.

24 DR. OSTROFF: Great. Okay, that's what  
25 we'll do. 1:00.

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1                   (Whereupon, a luncheon recess was taken at  
2 11:59 a.m., the meeting to reconvene at 1:00 p.m., the  
3 same day.)  
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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 DR. OSTROFF: Why don't we go ahead and  
3 get seated.

4 COL Riddle, according to my schedule, you  
5 open with a few administrative issues before we launch  
6 into the first presentation.

7 COL RIDDLE: That's right.

8 DR. OSTROFF: Why don't we go ahead and  
9 get started with the afternoon presentations. We're  
10 fortunate enough to have several presenters of  
11 international stature helping to inform us on this  
12 difficult issue of multiple immunizations.

13 The first of our presenters is Dr. Charles  
14 Hackett from the NIH, from NIAID and he's going to  
15 give us an update and a presentation on this subject.

16 Thanks very much.

17 DR. HACKETT: Thank you very much. I'd  
18 like to thank COL Riddle and the rest of the Board for  
19 inviting me here and what I would like to do today is  
20 focus on the immunology of multiple simultaneous  
21 immunizations.

22 What I would like to do, in particular, is  
23 to focus on the capacity, first of all, of the  
24 adaptive immune system. This is the immune system  
25 that actually tailors the response specifically to the

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1 organism that the vaccine is designed to prevent.

2 DR. OSTROFF: Let me just interrupt by  
3 saying Tab 7 in the briefing book -- your slides are  
4 in Tab 7.

5 DR. HACKETT: All right, thank you.

6 The second thing I'd like to talk about is  
7 an area that in the last seven years has really  
8 exploded in terms of our knowledge, and that is the  
9 innate immune responses to vaccines, adjuvants that  
10 are added or inherent adjuvant activity of vaccines.  
11 The question of immediate and long-term immunological  
12 effects, based on both the innate and adaptive immune  
13 system. And then I wanted to update you briefly on  
14 some of the basic immunology research that we have  
15 recently funded at NIH that might be relevant to the  
16 question of the safety and efficacy of multiple  
17 simultaneous vaccinations.

18 This is a picture of the immune response  
19 that occurs in all successful vaccines. That is that  
20 each immune response starts out with the tweaking of  
21 the innate immune system and this is not responsible  
22 for the immune memory that you get, but it is  
23 absolutely necessary to kick off the immune response  
24 and it's been the realization -- immunologists have  
25 known this for 60 or 70 years, that you need to add to

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1 the substance if it's not already in your immunogens  
2 in order to get a strong and satisfactory immune  
3 response. And we sometimes forget about this because  
4 intrinsic in many of the vaccines, there is something  
5 that stimulates the innate immune system, and that's  
6 what I really want to talk about today, is how do you  
7 kick off the immune responses and what does that mean  
8 for adaptive immunity.

9 So this sort of summarizes the situation  
10 about innate and adaptive immunity in vaccination.  
11 All vaccine immune responses require both innate and  
12 adaptive immunity. Innate responses trigger and  
13 direct the adaptive immune system and it is the  
14 adjuvants which are either added or intrinsic in the  
15 vaccine that trigger the innate immune system. And  
16 very importantly -- and I will go into this in more  
17 detail -- there are distinct receptors, receptor  
18 molecules, used by the innate versus the adaptive  
19 immune systems.

20 So I want to take a few slides and just  
21 compare them in the basic elements. See, the adaptive  
22 immune system is more familiar probably when you think  
23 about vaccines. The adaptive immune system is  
24 composed of the T-cells and B-cells. The innate  
25 immune system is actually a network of other cells

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1 that sound the first alarm to any invasion, and actual  
2 pathogen infection or a vaccine. And these are, for  
3 example, the macrophages, dendritic cells that can be  
4 in various tissues, skin, circulating. Natural killer  
5 cells are probably somewhere on the boundary between  
6 really innate and adaptive but then there are  
7 neutrophils, eosinophils and many other cells that  
8 fulfill the function of the cellular component of  
9 innate immunity.

10 The antigen receptors are quite different.

11 The innate receptors are inborn, we have them all  
12 that we're going to have from birth. However, with  
13 the adaptive immune system, these have to develop,  
14 that's why you have to give vaccines, you have to have  
15 experience with foreign antigens in order to develop  
16 the adaptive immune system. The specificities of the  
17 innate system are fixed. They don't change depending  
18 on what you've experienced in life. They're what  
19 you're born with, contrary to what you see with the  
20 adaptive immune system, where you can have an infinite  
21 repertoire and the more antigens you see, the more the  
22 immune system is competent to handle.

23 But with the innate, it starts at the  
24 beginning with these receptors that are already  
25 dedicated. And the group that's probably the best

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1 known right now is -- are the toll-like receptors  
2 which is a family of 10 molecules that have emerged in  
3 the last seven years as being some of the key  
4 receptors that sound the alarm. They are dedicated to  
5 recognize various components that are found on  
6 pathogens and found in adjuvants and I'm going to go  
7 into that a little bit in a little bit more detail in  
8 the next slide.

9 But the toll-like molecules are only some  
10 of the receptors. There's also some receptors known  
11 as the NODs, which have to do with muramyl dipeptide,  
12 and NOD stands for nucleotide oligomerization domain  
13 binding proteins, which has nothing to do with their  
14 function, but they happen to be known as NODs. CD14  
15 which is a molecule you perhaps have heard of with  
16 recognition of endotoxin. RP105 is something like a  
17 toll molecule that's found on B-cells. Mannose  
18 binding protein -- there are many others.

19 Whereas with the adaptive immune system,  
20 you only have two kinds of receptors, immunoglobulin  
21 and the T-cell receptors. But they can take on, of  
22 course, a huge number of forms.

23 So the molecules that are recognized are  
24 also quite different. The innate immune system  
25 recognizes structures that are unique to microbes.

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1 For example, lipopolysaccharide. There's -- no  
2 mammalian enzymes can make lipopolysaccharides. So  
3 these are, by definition, foreign and we have evolved  
4 the toll-like receptor 4 molecule that recognizes the  
5 lipopolysaccharide.

6 Viral double strand RNA, also something  
7 mammals don't make, double stranded RNA. So if it's  
8 there, it's foreign and it's recognized by toll-like  
9 receptor 3. Bacterial flagellin by toll-like receptor  
10 5; muramyl dipeptide by NOD2. There's also  
11 peptidoglycan recognition molecule and there's going  
12 to be a lot more molecules discovered that are  
13 dedicated to components of the microbes.

14 Whereas, in the T-cells and B-cells, they  
15 see a much more limited set of compounds. T-cells, by  
16 and large, see peptides that are protein fragments and  
17 only in the context of major histocompatibility  
18 complex molecules. However, there's a large number of  
19 peptides that can exist, estimated that this  
20 combination is around 10 to the 12th could maybe  
21 possibly exist in the whole universe, but it's a lot.

22 And the B-cells, of course, can see  
23 accessible regions of essentially any molecule.

24 So I just want to point out here that they  
25 see different things and they actually -- the two

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1 systems work jointly.

2           So I want to, at this point, talk about  
3 some issues about capacity. Now for the adaptive  
4 immune system, because we understand something about  
5 how diversity is generated and the T-cells and B-cells  
6 are a much more defined population, we can do some  
7 calculations relevant to multiple simultaneous  
8 vaccinations.

9           And let me show you this first. This is  
10 an example of a kind of calculation that you can do.  
11 There are many different ways of doing a calculation  
12 about the capacity of the adaptive immune system and  
13 this particular one is based on the concept that if  
14 you want to talk about a simultaneous administration  
15 of multiple vaccines, you want to say what's there now  
16 and what could they respond to. I'm not talking about  
17 waiting for a response to come up very slowly from  
18 cells that have to be generated still in the thymus,  
19 and kind of say what's there.

20           And for antibodies, you can make some  
21 assumptions based on the fact that if you just assume  
22 there's about 100 antibody epitopes per vaccine.  
23 That's really just an arm-waving calculation, but it  
24 probably is real. There may be more, there may be  
25 less.

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1                   We know that there's about 10 to the 7th  
2 B-cells per (sic) blood; so therefore an individual,  
3 theoretically, could respond to 10 to the 5th vaccines  
4 at once and each one of those B-cells --

5                   (Laughter.)

6                   DR. HACKETT: -- within seven days give  
7 you a protective amount of antibodies. But in fact,  
8 we believe that the actual response capacity is much  
9 less. We don't think really you could probably get  
10 100,000 vaccines simultaneously one time and make a  
11 full response to them for several reasons. And one of  
12 them is that some of these B-cells that we're seeing  
13 in the blood are already plasma cells or dedicated  
14 cells to responses you've already had. So they're not  
15 ready to go really. So that knocks the number down  
16 and we don't know to what extent it really knocks it  
17 down. It would be variable per person, but let's say  
18 it would knock it down by a couple orders of magnitude  
19 at least.

20                   Also, many of these responses require T-  
21 cell help in order to be initiated and that may be  
22 limiting, so you may not be able to get a T-cell for  
23 every one of these B-cells.

24                   However, I would say that looking at the  
25 kind of scales that we're talking about, we're far --

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1 UNIDENTIFIED SPEAKER: Eleven?

2 DR. HACKETT: Eleven should be okay.

3 Now I'll show you in the next slide that  
4 maybe 11,000 is okay -- I'm sorry, I'm going to go  
5 first into T-cells, yes. T-cells we know less about  
6 because their product, the antibodies, are not as  
7 easily -- their products are not as easily followed as  
8 antibody products.

9 We know from HIV patients who were  
10 suddenly able to increase their CD4 counts when they  
11 were getting anti-viral drugs, that it looks like the  
12 human immune system can make about two times ten to  
13 the ninth T-cells per day. It can do it. We don't  
14 know if this is normal, we don't know if this is only  
15 when there's stress on the system and it's pumping out  
16 cells, but we do -- again, assuming that there's a lot  
17 of play here on how many cells you actually need in an  
18 immune response, it looks like we're several orders of  
19 magnitude ahead of where the minimum we would expect  
20 to be. In other words, it's not going to be limiting  
21 that we don't have enough T or B cells.

22 And the next slide, that's when I can show  
23 you it may be possible that you can do 10,000 vaccines  
24 at once. This comes from animal model data where  
25 researchers who are trying to find protective antigens

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1 in large groups. This is the first study that I was  
2 aware of that was Stefan Johnson's group where they  
3 used a microplasma gene library and they made that  
4 into thousands of -- at least in this case, they start  
5 out with maybe about a thousand expression vectors and  
6 put them all into one mouse and the mouse made a  
7 protective immune response.

8 This type of research has been used by  
9 other investigators with much larger than a thousand  
10 members. They've gone up to over 10,000 that I'm  
11 aware of, maybe 30,000 but I don't know how  
12 reproducible all that is. But the point is that it is  
13 possible to give a mouse or a rat a very huge number  
14 of -- you might call them vaccines, it's plasma  
15 expressing an antigen that you want to know if it's  
16 protective or not. You look at the animal that gets  
17 these thousands of plasmas, challenge them with the  
18 pathogen, they're protected and then it's possible to  
19 whittle down that library successively. And it says  
20 basically that in the midst of all this, you can --  
21 the animal's immune system can pick out the protective  
22 antigen and you can actually whittle down and find out  
23 what it is.

24 So the next slide just sort of summarizes  
25 some of that. It shows that protective immune

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1 responses can be obtained to antigens in complex  
2 immunogens, and I mean very much more complex than  
3 what you would be delivering with the multiple vaccine  
4 programs.

5 And it shows that in the presence of many  
6 others, the immune system can still find the  
7 appropriate antigens and make responses.

8 Now I can conclude then that, you know,  
9 the antigen load that you use in the military,  
10 multiple immunizations will not challenge the adaptive  
11 immune system from a theoretical point of view.

12 I want to go now a little bit into the  
13 function of the innate immune system because I think  
14 that's the one that we probably have to think about a  
15 little bit now because we haven't thought about it in  
16 this way probably, because we haven't had the  
17 information. But that is that the innate immune  
18 system response to vaccine adjuvants. And the  
19 adjuvants can either be an added adjuvant such as the  
20 aluminum hydroxide, aluminum phosphate and other  
21 compounds, or it can be an intrinsic adjuvant that's  
22 in the actual vaccine as part of it. And some  
23 examples of these would be double stranded RNA that's  
24 seen by toll-like receptor 3 of the human innate  
25 immune system. This is very commonly seen in

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1 attenuated viruses. Bacterial DNA, especially those  
2 that are rich in the motif of CPG, the cytosine  
3 phosphate guanine (ph.) and that's recognized by human  
4 toll-like receptor 9. And other bacterial cell wall  
5 components, for example -- toll-like receptor 2, 4,  
6 NOD1 and 2, mannose receptors and so on.

7 Now the point here is that in any vaccine,  
8 you're going to have adjuvant activity if the vaccine  
9 works. And if the vaccine is devoid of these  
10 intrinsic compounds, then you're going to have to add  
11 the adjuvant. Actually with alumide, I don't think  
12 it's clear what the receptor is and in fact, it might  
13 end up being -- it might be antigen focusing  
14 activities, depo activities, but certainly there has  
15 to be some assistance to the innate immune system  
16 provided by the treatment with alum.

17 So the next slide says what do these  
18 things do. Well, the first thing that the adjuvants  
19 do is they ignite the immune responses, and they do  
20 that by at least a couple of ways that I am aware of.

21 One is that the stimulation of the toll-like  
22 receptors, for example, with double stranded RNA,  
23 cause costimulatory molecule induction, which is  
24 needed to trigger T-cells. I'll have a little  
25 illustration of that in the next slide.

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1           It also appears to cause temporary  
2 inactivation of suppressive activity. And this is a  
3 function that has just kind of emerged basically in  
4 animal studies, but the fact is that the immune system  
5 is generally in a state of control and it's necessary  
6 so you don't have wildly auto-immune reactions and so  
7 on, so that there's a state of control of the immune  
8 system carried out in part, at least, by some T-cells.

9           And some evidence exists that stimulation of the  
10 innate immune system can cause release -- I think it's  
11 generally thought of now as being interleuken-12 that  
12 can cause a very local repression of the suppression  
13 and then that allows an immune response to come up.  
14 Then the repressors can assert their activity again.  
15 So it's a temporary inactivation.

16           The innate immune system also sets the  
17 appropriate Th1 or Th2 type of response. And another  
18 topic that I think we don't talk too much about, but  
19 it also initiates control of attenuated viruses in  
20 certain vaccines.

21           This is kind of an illustration. The  
22 adjuvant molecule interacting with an innate immune  
23 receptor leads to a pathway that, among other things,  
24 there's one definite part of it leads to expression of  
25 costimulatory molecules, which, along with the process

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1 vaccine antigen get presented to T-cells and the T-  
2 cells are pivotal in driving the responses both for  
3 cell mediated immunity and also for antibody  
4 responses.

5           The Th1, Th2 direction may also be related  
6 to the type of stimulation that occurs on the surface,  
7 for example, of a dendritic cell that's part of the  
8 innate immune system, and certain molecules from  
9 certain antigens appear to drive a Th1 response  
10 through an inflammatory type reaction and other ones  
11 can drive a Th2 type reaction. So this is again on  
12 the level of the innate immune system, driving  
13 adaptive immunity.

14           I want to just talk about this a little  
15 bit, because I think it's something you have to kind  
16 of reflect on a little bit, which is that most  
17 virulent pathogens have sophisticated innate immune  
18 evasion mechanisms. In other words, they can get  
19 through your first line of defense because they have  
20 evolved mechanisms to do that. Not too many of these  
21 are known, but when -- I think when more function of  
22 viral genes are well understood, you'll see that a lot  
23 of them will be related to their ability to evade  
24 innate immunity.

25           Attenuated viruses that have been looked

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1 at, they frequently have less ability to evade innate  
2 immunity and so this may be -- this role may be  
3 central in allowing the function of certain attenuated  
4 viruses.

5 I just want to give an example from a  
6 virus that we're not actually using in vaccines right  
7 now but maybe they will soon, which is the modified  
8 vaccinia ankara. This is derived by passages in  
9 fibroblasts and among many genes that are altered, the  
10 genes that -- several genes at least that function in  
11 immune evasion have been disrupted so that what this  
12 would suggest to a lot of people looking at these  
13 situations, that some of the component of attenuation  
14 in viruses such as this that have been not  
15 particularly -- no one has done the actual genetic  
16 engineering, but it ends up that the immune evasion  
17 genes can be modified in these and that makes them  
18 very susceptible to control by the innate immune  
19 system. And so this is another function of innate  
20 immunity I think we sometimes forget about, but it  
21 allows us to give these vaccines -- or may contribute  
22 at least to giving these vaccines safely. A lot more  
23 work has to be done on this particular topic.

24 I think the idea that you can pass a virus  
25 in a situation where let's say you don't have an

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1 innate immune system in a fibroblast or a situation  
2 that is devoid of innate immune system, would allow  
3 that virus to lose the genes that would -- that are  
4 part of the evasion mechanism, because there's a lot  
5 of baggage to carry around if there's no selective  
6 advantage and the ones that have lost those genes can  
7 grow out. And what we've done for ourselves then is  
8 create a virus that's very controllable by the innate  
9 immune system, which is inborn in all of us. So  
10 that's something else to keep in mind.

11 Okay, so what are some of the risks from  
12 innate immune activation and how can we start to look  
13 at these? Well, we know that shock, septic shock, is  
14 the best example. This results from a high systemic  
15 dose of innate immune stimulants and this comes from  
16 infection. This is not the level that you would get  
17 in a vaccine. This comes from the bacterial  
18 infections that go systemic. And we know from animal  
19 model studies that septic shock comes from the innate  
20 immune over-reaction to the bacterial -- it's a  
21 danger, but it's not a danger of a vaccine adjuvant.

22 Another side effect of innate immune  
23 stimulation has been activation of retroviruses as has  
24 been seen in animal studies. It's not known if that  
25 occurs in humans, it's seen in animals so far.

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1           Auto-immune activation, there has been --  
2           and I want to go into a couple of slides about this --  
3           evidence in some auto-immune prone animal models and  
4           this example that I want to take is one of a systemic  
5           lupus erythematosus model in mice.

6           In this particular animal model, the cells  
7           were from an animal that had a proclivity to make  
8           auto-antibodies very much like you see in lupus. And  
9           in this study that was done, the initial study I'm  
10          looking at here was in vitro. The auto-reactive B-  
11          cell had the ability to recognize immune complexes  
12          because the B-cell itself had an antibody against its  
13          own immunoglobulin. But because of that, it could  
14          pull in immune complexes that contained DNA from a  
15          bacteria that could react with toll-like receptor 9,  
16          by the ability of doing two things. One thing is to  
17          first cross link the antibody molecules on the surface  
18          of the B-sell; and secondly, within that same B-cell,  
19          receive a signal from toll-like receptor 9, that B-  
20          cell became activated and produced auto-antibodies.

21          So if we can look at the next slide  
22          please. This then says that there at least is, in  
23          principle, a way of stimulating the innate immune  
24          system in a way that you could, because B-cells have  
25          innate immune receptors. You could directly stimulate

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1 B-cells that could directly release auto-antibodies.  
2 Now the point is that these are done so far in auto-  
3 immune prone mice, we don't know if that is valid in  
4 humans. The research that was done in whole animals  
5 employed systemic injections of the bacterial DNA in a  
6 different way than we would envision vaccines being  
7 given in terms of interperineal injections. So  
8 there's a lot of differences between that kind of  
9 study and the kind of study that you'd do to see what  
10 would happen in a real vaccine.

11 The current vaccines do not have major  
12 bacterial DNA components. I should say, the major  
13 injected vaccines. I guess it's worth asking about  
14 vaccinia because vaccinia may have bacterial  
15 contamination in some of these -- I'm not saying lots,  
16 but I'm saying in the intrinsic process of it. I  
17 don't know.

18 COL GRABENSTEIN: So you can modify the  
19 vaccine to include it, but it's not guaranteed to be  
20 sterile except for the vaccinia.

21 DR. HACKETT: That's right. So again, we  
22 don't know. I think there's a lot of unknown.

23 So the relationship to the number of  
24 injections delivered at one time also is not  
25 established. So while there appears to be a mechanism

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1 by which you can stimulate the toll-like receptor 9 on  
2 B-cells, and if the B-cells are auto-reactive B-cells,  
3 they may become activated to release auto-antibodies.

4 We're far from knowing if that can actually occur in  
5 a vaccination situation and if it is related at all to  
6 the number of vaccines given at one time.

7 I want to point out that -- and this is a  
8 very important detail to keep in mind, which is that  
9 the innate immune system, if anything, is extremely  
10 highly regulated so that it does not run out of  
11 control. In septic shock, it does go out of control  
12 and that is very hard to save people's lives who --  
13 there are many thousands of people who die of  
14 bacterial septic shock each year and it's very  
15 difficult to stop this response of a runaway innate  
16 immune system. But for the day-to-day life, and our  
17 experience with microbes and our experience with  
18 vaccines, there are many ways in which the innate  
19 immune system down-regulates itself.

20 So I just took a drawing of an example of  
21 a signaling pathway of one of the -- of sort of a  
22 generic toll-like receptor molecule, and it shows some  
23 of the steps that it can take to activate the cell and  
24 showed you that there are now known a number of  
25 molecules that have to do with controlling the innate

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1 immune system.

2           And I just actually sort of wrote some of  
3 those out. There's a molecule called IRAK-M, which is  
4 inducible when the innate immune system is stimulated  
5 and it then undertakes an anti-inflammatory part of  
6 the response. So as the TLRs get tweaked, the  
7 inhibitory part also comes up.

8           There's a variety of other molecules that  
9 I have listed here, including -- I just want to say  
10 the last one -- B-cells that see a lot of self-  
11 antigen, they're often called anergic because they  
12 don't seem to respond even though they see a lot of  
13 self-antigen. And it turns out that there's very much  
14 a tolerogenic signaling pathway in them which prevents  
15 them from becoming activated by self-antigens.

16           So I think the question comes down to  
17 something that we have to think about; that is, that  
18 in general the innate immune system is very highly  
19 self-regulating, it does not go out of control and as  
20 a general rule, everything is completely handleable  
21 because it's used to getting infections constantly,  
22 daily.

23           Now there may, however, be individuals who  
24 have mutations in innate immune receptors that we know  
25 right now can contribute to greater risk of certain

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1 diseases. And there are some examples of this.  
2 There's some examples of mannose receptors in  
3 childhood respiratory disease, toll-like receptors,  
4 there are reports of toll-like receptor 2 mutations  
5 that lead to increased staphylococcal infection, some  
6 evidence that toll-like receptor 4 can lead to  
7 increased risk for people who come down with, to have  
8 a more serious form of sepsis. Toll-like receptor 5  
9 has been shown to increase the risk for serious  
10 Legionnaire's disease.

11 So these mutations exist in the human  
12 population, they appear to be -- to influence the  
13 degree of severity that can accompany certain  
14 infections, but we have no information about whether  
15 they may be related to adverse response to adjuvants.

16 So, I think what we need to do is to be  
17 aware that there can be variability in the human  
18 population in molecules that are receptors for  
19 components that might be included in vaccines and  
20 those individuals, although they may not be numerous,  
21 may respond differently to a vaccine component than  
22 the majority of people.

23 And what is the percentage of people that  
24 would have these? For some of the mutations they are  
25 actually above one or two percent, up to several

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1 percent. For others, I think they are much more rare.

2 So we're talking about rare events, but existent in  
3 the human population.

4 So what NIH has done to try to address  
5 some of these issues related to immune responses is,  
6 one thing they have done is we recently have put out  
7 and received -- I think they're under review right now  
8 -- some contracts to study the human population  
9 genetics of immune responses, to try to link immune  
10 responses, infections and so on, to the variability of  
11 certain genes, especially genes for the innate immune  
12 system, but adaptive immune system responding genes as  
13 well.

14 We also have some contracts to try to  
15 improve our pipeline of vaccine adjuvants. So now  
16 it's alum, there are some other in the potential  
17 pipeline, but most of them are rather limited -- it's  
18 a rather limited number of agents that are being  
19 looking at. And so we recently funded three contracts  
20 to look at discovery where people do high throughput  
21 and try to find new molecules that would stimulate the  
22 innate immune system and try to de-link toxicity from  
23 stimulation. So those have been funded. The first  
24 one has not been even reviewed yet, these have just  
25 been funded, and then we have a concept to look at

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1 rational attenuation of viruses based on innate immune  
2 interactions and that one is not -- I don't know if it  
3 will be funded, but the council thought that this was  
4 another approach that could be used to help make  
5 vaccines safer.

6 So this just kind of summarizes some of  
7 the NIH research that we're doing to try to move along  
8 the idea that some events might be rather rare, but  
9 you have to know what the capacity of the human  
10 population is to have different types of reactions to  
11 molecules that stimulate our innate immune system, to  
12 try to make better adjuvants and try to see if we can  
13 make better attenuated vaccines, based on our  
14 knowledge of innate immunity.

15 This is just an indispensable component of  
16 vaccines. You'll never eliminate it. The systemic  
17 side effects of vaccines, these are rare. I don't  
18 know how relevant some of the animal studies are to  
19 humans, we would have to study that more. And  
20 research on human diversity and better adjuvants is an  
21 approach I think that is very valuable. So, thank  
22 you.

23 DR. OSTROFF: Thank you, very much.

24 (Applause.)

25 DR. OSTROFF: Thanks very much for a

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1 wonderful presentation. Let me ask if there are one  
2 or two specific questions for Dr. Hackett before we  
3 move on to the next presenter. There will be more  
4 time for general discussion after the second  
5 presentation.

6 DR. GARDNER: That was a wonderful  
7 presentation.

8 DR. OSTROFF: Please identify yourself.

9 DR. GARDNER: Pierce Gardner. Do we know  
10 -- thinking of things that we know influence a  
11 response to our immunogens. For instance, in most  
12 studies smoking has been a detriment in terms of  
13 antibody responses. We know that age certainly is a  
14 problem. We know that in young children they don't  
15 respond very well to polysaccharide antigens. Can you  
16 fit some of those into this wonderful equation you've  
17 set up here?

18 DR. HACKETT: Yeah. You know, the smoking  
19 I think is definitely -- with the Legionnaire's study  
20 it showed toll-like receptor 5 was one of the -- a  
21 mutation in that gave you a proclivity to have a more  
22 serious disease. I think smoking actually was even  
23 worse. So these -- I don't know what the effect is.

24 I think that my belief is that whatever  
25 kinds of factors we're looking at, if it's age or if

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1 it's an environmental factor, you have to start  
2 looking at the innate immune system. You can't just  
3 say it's bad for your tissues, it's bad for what in  
4 the tissues? And I think it merits looking at the  
5 dendritic cells, the macrophages and seeing -- you  
6 know, it is possible -- the innate immune system is so  
7 highly regulated that the responses have to be  
8 controlled. We have to come to terms with our own  
9 normal flora and I think also to environmental  
10 hazards. So I think it is possible to down-regulate  
11 your innate immune system. We know it's possible from  
12 experimental studies. You give enough -- it's the  
13 same thing, your body says we're not going to put out  
14 that receptor anymore for that innate immune stimulus.

15 So I think that's one way of looking at some  
16 environmental hazards like smoking. Say does it down-  
17 regulate some of these toll-like molecules and then  
18 make you less capable of making a response to a  
19 vaccine adjuvant or a vaccine adjuvant like activity.

20 So I think that's really the direction  
21 that I would say -- it's the only light I can shed on  
22 it right now. You have to start looking specifically  
23 at receptors.

24 DR. OSTROFF: Dr. Brown, one last  
25 question.

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1 DR. BROWN: Yeah, a quick question.

2 You hinted at this, but I'm not quite sure  
3 if I understood it. Is there some data that shows  
4 that there are negative side effects from standard  
5 aluminum-based adjuvants?

6 DR. HACKETT: No, none that I'm aware of.  
7 We don't know the receptor -- if there is a single  
8 receptor for the aluminum-based adjuvants. I know of  
9 no data that says that there are hazardous side  
10 effects to the innate immune system or to the  
11 functioning at all of them. It's just that I think  
12 that -- my feeling is that since we don't know exactly  
13 at what level they're functioning, I think we should  
14 either -- you know, there should be some studies to  
15 find out really what receptors are being tweaked by  
16 alum.

17 DR. BROWN: What was the call for greater  
18 research on adjuvants? Was it just basic research --

19 DR. HACKETT: New adjuvants -- yeah, new  
20 adjuvants. My thought would be, if we -- alum is  
21 actually a very good adjuvant for the T helper 2 type  
22 responses, but we don't know exactly how it works. We  
23 don't know how to optimize it. I would say if we  
24 could get new adjuvants in the pipeline that could  
25 also do Th2, but we knew how they work. There is some

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1 hope of unlinking toxicity from the co-stimulatory of  
2 adjuvants based upon biochemical data. You can  
3 actually show that there's a bifurcation of pathways.

4 So one goes to co-stimulatory molecule expression and  
5 not to inflammatory media. So it may be possible --  
6 at least you can entertain discussing how to bring  
7 that up. So I'm just saying if we can become more  
8 specific we would be able to replace what we had that  
9 works but we don't know how it works with things that  
10 work in ways that we can rationalize.

11 DR. OSTROFF: Thanks very much.

12 DR. HACKETT: Okay.

13 DR. OSTROFF: COL Grabenstein, I would ask  
14 you to hold your question until we finish the next  
15 presentation.

16 We have two speakers that very graciously  
17 agreed to travel across the pond from Great Britain.  
18 The first of those presenters is Dr. Mark Peakman.  
19 Dr. Peakman is -- his current position is the British  
20 Diabetic Association Senior Clinical Research Fellow,  
21 Reader in Immunology and Honorary Consultant  
22 Immunologist. He is from the Department of  
23 Immunology, Guy's Kings and St. Thomas School of  
24 Medicine in London. We really appreciate you taking  
25 the time out of your schedule to better inform us.

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1 DR. PEAKMAN: Thank you for the  
2 introduction. Thank you, COL Riddle for inviting me,  
3 it's a pleasure to be here.

4 I have to say that although we never met  
5 until last evening, Dr. Hackett's last talk was a  
6 beautiful introduction to what I'm going to say, and I  
7 hope that what I will say will address some of the  
8 issues that have come up.

9 I'm really going to present what I'll call  
10 primary data. So rather than some of the talks that  
11 we've heard, looking at what's in the literature, I'm  
12 going to present data that comes from our laboratory.

13 It's related to some of the studies that I've been  
14 doing in collaboration with others at King's. So I  
15 called it the King's experience. The first part of  
16 the talk will be looking at some outcome -- some  
17 consequences of deployment in the first Persian Gulf  
18 War. So this is looking at UK Gulf War veterans. The  
19 reason for doing those studies were the  
20 epidemiological studies by Simon Wesley and colleagues  
21 that linked multiple vaccines given in the theater of  
22 war to an outcome of multi-symptom illness. Those  
23 studies are in the public domain and they are  
24 published. I won't discuss those specifically, but  
25 they were the things that prompted our own work. That

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1 work is really addressed -- a hypothesis that's out  
2 there in the literature. That's the Rook and Zumla  
3 Th1/Th2 hypothesis of Gulf War multi-symptom illness.

4 For the latter half of the talk I will be  
5 then discussing in-vitro model that we have tried to  
6 develop to look at vaccine interactions with the  
7 innate immune system very much along the lines of what  
8 Dr. Hackett has described, and using that to then try  
9 and decipher whether there are multiple vaccine  
10 effects and whether we can study them in that way.

11 Then toward the very end, I'll present  
12 some very preliminary data that looks at T-cell  
13 immunities, some of the vaccines that were given  
14 during the first Persian Gulf War conflict.

15 So stated very simply, the Rook and Zumla  
16 hypothesis that we analyzed in the cohort of veterans  
17 from the first Gulf War was that a combination of  
18 factors could have contributed to a preponderance of  
19 Th2 over Th1 immunity and that that could lead to what  
20 they described as a Th2 mediated disease. So the  
21 factors that they highlighted were things like  
22 multiple vaccines, although I have to say the  
23 literature they used on that was fairly weak. They  
24 cited the example of pertussis being in some cases --  
25 in some reports of Th2 biasing, actual effect, and, of

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1 course, stress we know through glucocorticoid steroid  
2 pathways can induce a certain Th2 type of  
3 responsiveness.

4 I always felt the weakness in this  
5 proposal really was the link between all of this,  
6 which as an immunologist I could understand and could  
7 perhaps analyze and what they described as a Th2  
8 mediated disease. Really there, they were trying to  
9 highlight some of the features of the multi-symptom  
10 illness such as the musculoskeletal effects, the  
11 hypersensitivity. But really it's a constellation of  
12 40 or 50 different symptoms that go up to make this  
13 multi-symptom illness. It was always hard for me as a  
14 hard core immunologist to make the link between Th2  
15 effects and what was being seen in those individuals.

16 Nonetheless, we set out to try and lay to rest once  
17 and for all this hypothesis. Next slide please. So  
18 just to remind you very briefly of the epidemiological  
19 study that Simon Wesley and colleagues  
20 initiated after that first conflict, this was a stage  
21 one and stage two study. Stage one was a postal  
22 questionnaire sent out to this number of UK Gulf War  
23 Veterans and it was a control group of soldiers either  
24 deployed in Bosnia or era controls. They were  
25 individuals who were prepared for conflict but were

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1 not deployed. And from the postal questionnaire they  
2 were able to do the studies that I described, and I  
3 think probably a lot of you are familiar with, and  
4 make the assessment that there was an increase in  
5 multi-symptom mental health in this group.

6 Stage two was then really to get a  
7 percentage of those individuals up to King's and carry  
8 out a certain number of different clinical  
9 examinations, and at that point we had access to blood  
10 for our own studies. And the stage two recruiting was  
11 based on an illness definition which was based on the  
12 physical functioning scale, on the FS36, and illness  
13 was defined as those individuals in the lowest 10th  
14 percentile of functioning on that scale.

15 So what we ended up with in our cohorts  
16 for our immunological studies were around 57  
17 symptomatic Gulf War veterans defined in this way;  
18 around 63 well Gulf War veterans and 58 from the era  
19 and Bosnia controls. Of course, the definition of  
20 illness at this stage for recruitment to stage two was  
21 based on their symptoms at stage one, which does  
22 become a slightly interesting point for one of the  
23 result slides that I'll show you.

24 So not to go too heavy on the immunology  
25 and the analyses that we did, but we decided to take a

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1 very direct approach to this hypothesis, not to  
2 measure cytokines in soups or in serum which can be  
3 produced by any number of different cells and can vary  
4 under any number of different conditions. We decided  
5 to directly enumerate the Th2 cell population. They  
6 were identified by staining ... looking forward which  
7 is the prototypic Th2 cytokine and CD4 which is the  
8 marker of T helper cells.

9 So we were essentially just counting these  
10 cells after polyclonal activation. The cells that you  
11 count there are memory cells that have been biased in  
12 a previous period for however immunological memory  
13 lasts, many number of years as far as we're aware. So  
14 it's really looking at the cytokine potential of that  
15 individual over many years. Next slide please.

16 So I'm just going to show you two or three  
17 graphs of the results and really what I think are the  
18 salient findings. Actually from here -- from this  
19 angle these results look more impressive than they do  
20 from straight ahead.

21 (Laughter.)

22 DR. PEAKMAN: Because you can probably see  
23 those lines look pretty similar, and in fact they do.

24 So this is the counting of Th2 cells in the three  
25 clinical groups that I've described. And in

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1 statistical terms there's no difference between those  
2 three groups. I should say that there is an  
3 interesting phenomenon here that relates to the stage  
4 one/stage two recruitment, because the clinical  
5 classification here is based on stage two. So that's  
6 how they were when they answered the questionnaire at  
7 stage two and, of course, we have recruited them on  
8 the basis of how they were at stage one. And so there  
9 were some sick veterans that crossed over into the  
10 well group.

11 And if you could just press the button  
12 again you'll see that there were individuals who  
13 crossed into the well group who had very high levels  
14 of Th2 cytokines. And if you do the analysis on the  
15 basis of how they were at stage one, this difference  
16 is significant. So we struggled with this manuscript  
17 for about 18 months trying to get it published and  
18 trying to get it right. I think you would agree that  
19 this is a very difficult study to do 10 years after  
20 the conflict, and we've come out with a rather  
21 equivocal answer for which I can only apologize, but  
22 say that the way that we've reported it -- and it is  
23 coming out fairly soon -- is that there is no  
24 difference in the number of Th2 cells in these three  
25 groups at the time the blood was drawn according to

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1 their clinical stages.

2           There was an interesting finding that was  
3 unexpected. This was the hypothesis we had set out to  
4 look at and had found really negative. There was an  
5 unexpected finding which was an increase in IL-10  
6 producing cells, which I'll talk about a little bit  
7 more. This just shows the results of that. So IL-10  
8 producing cells appear to be elevated in disease  
9 because they were higher in the symptomatic Bosnia and  
10 era veterans, and also there was an effect of Gulf  
11 deployment because they were higher in the sick Gulf  
12 veterans compared to the sick Bosnian and era  
13 veterans.

14           There was one other way of trying to look  
15 at the Th1/Th2 hypothesis and that was to look at  
16 exposures. Simon Wesley and Matthew Hausoffer had  
17 been the group that had shown the relationship to  
18 multiple vaccines. And so we've looked at the  
19 individuals that we've studied divided according to  
20 the number of vaccines they had and they were divided  
21 into different quintiles for that purpose. And if you  
22 do a statistical test, the trend on this data there is  
23 a significant trend for decline of Th1 cells with  
24 increasing number of vaccines which would in some ways  
25 indirectly support the Th2 hypothesis of Rook and

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1 Zumla. There was no evidence of an increase in Th2  
2 cells. So again, it's a slightly equivocal result  
3 here. And again, you can see that the individuals  
4 that had perhaps the lowest number of vaccines here  
5 under zero really don't have levels that dissimilar  
6 from the ones who had the most vaccines. It's just  
7 this decline from 1 to 4 that appears to give you this  
8 significant P value. Next slide please.

9 So there is abnormal CD4 T-cell cytokine  
10 balance in Gulf War related illness. It doesn't  
11 appear to be a strong and robust identifiable increase  
12 in Th2 activity. A caveat for that is we're looking  
13 10 years after the events and, of course, that will  
14 dilute out any strong effect.

15 We were intrigued by the expansion of  
16 memory cells producing interleuken-10. It is a major,  
17 if not the major, immuno-regulatory cytokine. It is  
18 very potent in inhibiting a number of facets of the  
19 adaptive immune system, including activation of  
20 function of TE cells, particularly T helper cells -- T  
21 helper 1 cells, and also angstrom (ph) presenting  
22 cells.

23 So a number of questions cropped up for us  
24 to address. One of which was the mechanism of this  
25 IL-10 effect. Could we pinpoint perhaps what had

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1 caused this increase in IL-10 producing cells? And  
2 really also the question of its consequences for  
3 vaccination in that if you produce a lot of IL-10  
4 during a brief period, you might predict that they  
5 would not be a good thing to be doing when you're  
6 trying to generate Th1 and Th2 mixed immunity because  
7 this would counter-regulate that. So I can't tell you  
8 that we have answers to these questions necessarily,  
9 but we have some pointers to these answers.

10 So for the next part of the talk I'll move  
11 on to describing this in-vitro model of vaccine  
12 interactions with the innate immune system and how  
13 we've used that to try and address the question of  
14 multiple vaccine effects. It's still our hypothesis  
15 for a number of the observations that we've made.

16 So I think as we heard very elegantly from  
17 Dr. Hackett, the critical first interaction between a  
18 pathogen and the immune system is the mucosal and  
19 skin level. It involves an interaction with a  
20 particular cell, that is the dendritic cell, the  
21 immature dendritic cell in the tissues. We often use  
22 the word -- term when we're teaching this to describe  
23 the cell as the sentinel, which means it's a guard.  
24 It's the front-line defense of the immune system.  
25 It's the first cell -- the first immune cell to

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1 interact with any invading pathogen and it needs to  
2 acquire three sets of information.

3 The first is some information from the  
4 antigen, because it will need to go on to promote an  
5 antigen-specific response. The second are the  
6 activating signals that Dr. Hackett described as co-  
7 stimulatory signals, and the third, just missing off  
8 the bottom there, are polarizing signals. So the  
9 signals that dictate whether the immune system takes a  
10 Th1 type of route, a Th2 type of route or a regulatory  
11 type of route.

12 The immature dendritic cell has to get all  
13 of that information, gather it quite quickly and then  
14 sets off on a journey to the local lymph node where it  
15 interacts with the naive T helper cells and there the  
16 information is imparted to the naive T helper cell and  
17 the differentiation takes place into effector, whether  
18 it's Th1, Th2 or Tr1 type of cells.

19 So the vaccine that we're trying to  
20 develop and use needs to use the same pathway, as  
21 we've heard already, and needs to mimic these three  
22 sets of signals in order to produce a balanced  
23 physiological response to the pathogen when it's next  
24 encountered.

25 And essentially therefore the dendritic

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1 cell is integrating a number of different sets of  
2 information which are to do with the particular  
3 antigens that it will present, the co-stimulatory  
4 molecules that it will generate in order to activate T  
5 helper cells, and missing again off the bottom here,  
6 the polarizing signals that will determine what kind  
7 of outcome we have. Next slide please.

8           You've already had some examples of this,  
9 but just to reiterate those. These activating and  
10 polarizing signals, if, for example, they are coming  
11 from intracellular bacteria or viruses will most  
12 typically drive a Th1 response because that's the most  
13 powerful way of generating effect is to deal with  
14 intracellular bacteria and viruses. Like the  
15 polysaccharide tends to give us a mixed response,  
16 helminths extracellular parasites, it's good to make a  
17 Th2 response and then there are some elements from  
18 pathogens that will drive a regulatory response,  
19 presumably as part of an immunization strategy.

20           So our in-vitro model tries to address all  
21 of these issues. We've been using it now to ask  
22 specific questions about multiple vaccine effects. So  
23 we take human monocytes and incubate them for about  
24 six days in the presence of a cytokine cocktail that  
25 is known to induce a dendritic cell from a monocyte.

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1 At that point the cell is immature so it's like the  
2 cell I showed you in the beginning sitting in the skin  
3 or sitting in the mucosa, it's an immature dendritic  
4 cell, really there as the sentinel.

5 What we've done with the immature  
6 dendritic cells is to culture them under different  
7 conditions to try and represent what it's like to  
8 encounter a pathogen, or in our case we've been using  
9 vaccines. Next slide please.

10 After 48 hours, we assess the degree of  
11 maturational expression of co-stimulatory molecules.  
12 It's a critical event in the maturation process where  
13 the dendritic generates these co-stimulatory  
14 molecules; otherwise, there's no T cell activation.

15 We look at the cytokine potential. This  
16 is the polarizing signal I talked about, signal 3 that  
17 dictates what kind of immune response you're going to  
18 have. We then were also able to look at the  
19 integration of these signals by taking cells -- mature  
20 dendritic cells for quite a long time with naive T  
21 helper cells in the presence of the vaccines. We can  
22 see whether our prediction about the integration of  
23 these signals is actually evidenced by the outcome in  
24 terms of what sort of T helper cell you produce.

25 For the multiple vaccine studies we've

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1       been -- I think really for the pure hell of it decided  
2       to work with these more difficult vaccines than the  
3       ones that are more standard.    So we've been using the  
4       anthrax vaccine that's available in the U.K. which is  
5       a precipitate from the bacillus culture that's alum  
6       absorbed.    Contained within that vaccine we know  
7       there's a fair amount of protective antigen, but also  
8       lethal and edema factors.

9                Plague vaccine is again the one that was  
10       used in the original Gulf War conflict.    One of the  
11       features of the U.K. soldiers was that wholesale  
12       pertussis was used at that time as an adjuvant to try  
13       and promote immunity in the context of these two  
14       vaccines which are known to give a slightly limited  
15       response and known to need -- they need to keep being  
16       boosted.    And so pertussis was used and we decided  
17       that we would look at pertussis as well to see whether  
18       -- trying to represent what actually happened in those  
19       -- in those soldiers in our test tubes, could turn out  
20       to give us some clues as to whether this was a  
21       reasonable, safe and effective thing to do.

22                So I'm going to show you some raw data  
23       slides now.    This is the maturation.    So it's 24 hours  
24       -- 48 hours after incubation of immature dendritic  
25       cells with a particular fact or vaccine.    These are

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1 the three co-stimulatory molecules that we have chosen  
2 to look at. And the line to focus on here is the  
3 white one. That's the immature dendritic cell. You  
4 can see it doesn't have very much of any of those  
5 three. MF is maturation factor. It's a positive  
6 control that we use just to show that everything is  
7 working fine. You can see that when you use that, the  
8 signal goes up. That's represented by a shift to the  
9 right. If you do this with anthrax vaccine you can  
10 see there's no shift to the right. If you do it with  
11 plague vaccine you can see there's no shift to the  
12 right. So these vaccine agents are just not able to  
13 mature dendritic cells in our in-vitro culture system.

14 If you use pertussis here -- I haven't  
15 bothered to put the line in -- but it gives you  
16 fantastic and enormous shift to the right for all of  
17 these co-stimulatory molecules. It's a very potent  
18 activator of dendritic cells. Our next question  
19 really was -- having shown those single vaccine  
20 effects, really a very poor maturation signal from  
21 anthrax and plague vaccines. Our next question was  
22 well what would happened if these were exposed to  
23 dendritic cells together? So we tried to mimic the  
24 multiple-vaccine effect that we wanted to dissect out.

25 And if you do that with anthrax and plague, you can

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1 see that essentially nothing and nothing still gives  
2 you nothing, but if you add in pertussis as your  
3 strong essentially adjuvant effect, which you know  
4 causes maturation, it's able to overcome the effects,  
5 the negative effects or the non-effects of the other  
6 two vaccines. So I think as a message in terms of  
7 multiple vaccination it's clear that there isn't some  
8 idiosyncratic effect here. This is a predictable and  
9 summative effect of one very powerful agent overcoming  
10 a negative effect of two other agents.

11 So that's the part of the study that  
12 addresses this question here of co-stimulation. Does  
13 the picture look similar when we look at the cytokine  
14 potential? So the beginning of the polarization  
15 signals now. So here again are the controls -- and  
16 I'm presenting here just some representative data on,  
17 for example, Interleuken-12 here which is the  
18 prototypic Th1 promoting cytokine produced by  
19 dendritic cells. I've got tuminocosis (ph.) back to  
20 alpha as a prototypic pro-inflammatory cytokine,  
21 Interleuken-8 is a useful attractor of other cells to  
22 the site and Interleuken-10, as I've already said, is  
23 I guess sort of an anti-inflammatory cell.

24 So if we use our control preparations,  
25 again just to validate the system, we see nice

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1 production, Interleuken-12 particularly, with Th1  
2 promoting cocktail which is gallen (ph) plus  
3 maturation factors, plus the gallen (ph) in E2 is  
4 known to promote a Th2 effect. So it's good that we  
5 don't see very much IL-12 there. The control factors  
6 induce production of TNF of IL-8 and small amounts of  
7 IL-10.

8 So what happens with our vaccines? Okay,  
9 so -- again, as one might expect from the lack of  
10 simulation of dendritic cells that I showed you on the  
11 previous slide you really don't see any good  
12 production of polarizing signals -- polarizing  
13 cytokines by these dendritic cells exposed to plague  
14 and anthrax vaccines. There is very little IL-12,  
15 very little or no TNF IL were detectable. There is  
16 IL-10 production and it accords with the idea that in  
17 some way these vaccines are inhibiting dendritic cell  
18 maturation, holding them in an immature state, and  
19 that is typically associated with an IL-10 production.

20 But there could be other reasons which I'll talk  
21 about in a second.

22 As you can see, pertussis is a fantastic  
23 Th-1 polarizer and pro-inflammatory set of antigens,  
24 if you like. This is a whole cell pertussis vaccine.

25 And again, looking at a mixture of pertussis, does

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1 mixing these things in together give us anything  
2 idiosyncratic or is it all entirely predictable? Next  
3 slide.

4           It's reasonably predictable in that  
5 anthrax and plague, while they're still not doing very  
6 much together, but with pertussis, the top left there,  
7 there is now a suggestion that there is some IL-12  
8 production, a little bit of pro-inflammatory cytokine,  
9 a little bit of Interleuken-8 and the same amount of  
10 Interleuken-10. So this is not quite as clear cut as  
11 the maturation data, but it does suggest again that  
12 you have predictable summative effects and nothing  
13 totally idiosyncratic is happening.

14           Okay, the final set of analyses is what  
15 sort of outcome is there for the T-cell -- once the  
16 dendritic cell has integrated these signals what kind  
17 of T-cell immunity do we end up with? Again, here are  
18 our controls. So now we're looking at intercellular  
19 production of interferon gamma which would be a Th1  
20 cell. These are naive T cells that were growing out  
21 in culture. Here is Interleuken-4, the Th2 cell. So  
22 if we take our standard control that we know drives  
23 it, a mixed patent, you can see that we get some Th2  
24 and some Th1 cells. Here in the middle panel, what's  
25 our typical Th1 polarizer gives us a very strong set

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1 of Th1 cells and nothing really for Th2, and Th2  
2 driving stimulus with prostaglandin E-2. Now we're  
3 getting some Th2 cells and we've reduced the amount of  
4 Th1-ness that we induce.

5 So what about our two vaccines? It's  
6 reasonably, I think, predictable that they would not  
7 give you strong Th1 polarization for the fact that  
8 they didn't induce good co-stimulation, they didn't  
9 induce good amounts of IL-12. We expected them  
10 probably to not really polarize T-cells that much.  
11 They have in fact skewed towards the Th2 kind of  
12 response, which on balance at least means that they're  
13 doing something and may be a useful response. But I  
14 would still have liked -- if I wanted a vaccine, I  
15 think I would have still liked to have seen some Th1  
16 response as well. Next slide please.

17 So what happens when we do the multiples?  
18 Here is the data I've just shown you with Th2  
19 polarization of anthrax and plague. Pertussis, as we  
20 might predict, very strong Th1 polarizer. When you  
21 add in the anthrax and plague together you really get  
22 what you already had. When you add in pertussis you  
23 now get a reduction in the Th2 polarization and fairly  
24 strong Th1 polarization. So again, a summative effect  
25 of these three agents.

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1           So the conclusions from that part of our  
2 work really are that we can mirror what we would  
3 expect to find using this in-vitro system of the  
4 interaction between dendritic cells and vaccines. As  
5 one might expect from the fact you need to give things  
6 like anthrax multiple times, they are poor immunogens  
7 and it's presumably as a consequence of this poor  
8 interaction with the innate immune system. In fact,  
9 while we were doing this work two really fantastic key  
10 papers came out. One in July in Nature showing that  
11 the lethal factors from anthrax severely impairs  
12 dendritic cell function. It blocks matcarnase (ph)  
13 which is on one of the pathways that Chuck Hackett  
14 showed us and just stops the cells' maturing. And  
15 everything that I've shown you is in that paper, but  
16 done in mouse -- in mice in terms of blocking  
17 dendritic cell maturation and cytokine production.

18           And then there was a very nice study in the  
19 Journal of Experimental Medicine in October 2002  
20 showing the usenia-V (ph.) antigen inducing R-10  
21 production from dendritic cells. Again, which was  
22 something which would explain why that's -- you get  
23 poor antigen presenting cell function from that  
24 vaccine.

25           So our third conclusion which really comes

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1 on the back of adding pertussis into those cultures is  
2 that we do -- we can get summative effects from using  
3 multiple agents. Next slide please.

4 I think this is just about my final data  
5 slide. But we're just beginning to start to look at  
6 the veterans one more time. So this is now 11 or 12  
7 years after their deployment. We're looking at recall  
8 responses in T-cells to different vaccine agents. So  
9 now here we're using early-spot technique, which means  
10 you can measure the number of cells that respond with  
11 a particular cytokine profile to a particular  
12 stimulus. This is typically what you would expect. I  
13 think if we went around this room and did this  
14 analysis for tetanus, you would see a very nice  
15 mixture. So each dot here represents an individual  
16 blood sample for the different cytokine profiles. You  
17 would see a mixture with tetanus of Th1-ness,  
18 interferon gamma ... on the lefthand side; Th2-ness,  
19 particularly with IL-13, Interleuken-4 tends to be  
20 secreted at very low levels anyway. Usually you see a  
21 few Tr1 type of cells induced as well in the middle  
22 there. We've done this with two vaccine agents,  
23 anthrax and plague as well.

24 I think focusing first of all on the  
25 right-hand side, I think what is very clear is that

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1 there is in a number of individuals quite a long time  
2 after their exposure some evident T-cell immunity to  
3 these agents. So despite all of the things that I've  
4 said were very bad about these vaccines in terms of  
5 inducing good balanced immune responses actually to  
6 anthrax, we really do get quite a good overall  
7 response which is mixed. And plague really just isn't  
8 quite as good. There are some individuals giving a  
9 nice Th1 response but really not as many. We haven't  
10 got enough numbers here to relate this to what their  
11 vaccine exposures were, and that's something we  
12 obviously will go on to do when we've done slightly  
13 more numbers. We haven't dissected these out. These  
14 are again the same cohort of individuals who were ill  
15 and who were well. So again, we'll need to look at  
16 that dichotomy.

17 So the conclusions from that were, which  
18 is very much ongoing, is that we are able to detect  
19 recall responses to the vaccines that were given 10 or  
20 12 years ago. Preliminary data suggests a mixed Th1  
21 and Th2 and Tr1 immunity to anthrax with a poorer  
22 immunity to plague.

23 And my last slide -- last but one slide, I  
24 think is just to summarize all of that presentation.  
25 We have got some unaccounted for evidence of cellular

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1 immune activation in Gulf War veterans, U.K. Gulf War  
2 veterans. It's not clear yet whether that relates to  
3 multiple vaccination. There could be at least three  
4 other factors which could have influenced that.

5 I'm talking really particularly about the  
6 IL-10 response. We know that pertussis is a very  
7 strong IL-10 promoter. We've seen evidence that  
8 plague can induce IL-10 and we've seen evidence that  
9 both of these agents give you immature dendritic cells  
10 which tends to promote an IL-10 response. So there  
11 are multiple possible explanations for that data.

12 The in-vitro model of dendritic cell  
13 activation using vaccines I think provides quite a  
14 nice technology. We're looking at single vaccine  
15 effects and now I think we're also looking at multiple  
16 agents. It essentially shows that multiple agents  
17 have predictable and summative effects which is  
18 reassuring.

19 I would like to acknowledge that this work  
20 was done with Simon's great help and support at King's  
21 College, London and also with support from Gareth  
22 Griffith and Leah at DSTL.

23 Thank you.

24 (Applause.)

25 DR. OSTROFF: Thank you very much. Let me

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1 open it up. If there are any questions or comments.  
2 Dr. Poland.

3 DR. POLAND: If I understood, whole cell  
4 pertussis vaccine is given simultaneously to provide  
5 some sort of --

6 DR. PEAKMAN: I think was. Not is but was  
7 in that particular...

8 DR. POLAND: Okay. And when you used it  
9 in your in-vitro model is it at some sort of  
10 physiologic concentration, which is one question. The  
11 second question is, did you do any sort of dose  
12 response relationships there with the idea that you  
13 should see a shift one way or another if it really is  
14 pertussis and having this effect, that as you decrease  
15 the dose maybe you'd see less of it and increase it,  
16 you would see more of it?

17 DR. PEAKMAN: Yes, I've got all that. I  
18 haven't shown all that data but I've got all that  
19 data. I mean that's something we can discuss. But  
20 yes, you see dose effect. Clearly you get into the  
21 realms of toxicity with these so you've got to be  
22 careful, if you're seeing only an inhibitory effect,  
23 but that really -- you know, that's why we use the  
24 dose response to check out that that's not happening.

25 DR. POLAND: What kind of concentration of

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1 the pertussis did you use for these studies?

2 DR. PEAKMAN: Do you want me -- I can't  
3 give you off the top of my head the concentration in  
4 terms of numbers of bacteria. I can give you the kind  
5 of dilutional effect -- the dilution we've been using  
6 from the whole vaccine. It's around one part per  
7 thousand in those cultures.

8 DR. POLAND: I wonder, is that -- that  
9 sounds high compared to what one would expect, you  
10 know, in-vivo physiologically.

11 DR. PEAKMAN: Well, I can -- I've got the  
12 manuscript in my bag. I mean I can translate that  
13 into numbers of organisms for you. I can't do it off  
14 the top of my head.

15 DR. OSTROFF: Other questions or comments?

16 ((No response.))

17 DR. OSTROFF: I have one. In terms of the  
18 abnormal cell mediated immunity that you're seeing in  
19 the ill Gulf War veterans, it gets to the same  
20 question that our group that deals with chronic  
21 fatigue syndrome deals with so often which is cause  
22 and effect. Is the abnormal cell mediated immunity a  
23 result of their illness or is it potentially causing  
24 their illness, and do you have any way to try to tease  
25 that out?

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1 DR. PEAKMAN: I mean there are two things  
2 you can do I guess. One is look at them prospectively  
3 and see whether you can relate changes to changes in  
4 their clinical status. I think overall there is an  
5 improvement in clinical status. One could repeat the  
6 studies and do it that way. The other thing is to do  
7 comparisons with chronic fatigue syndrome, which we've  
8 done. We don't see -- we see abnormalities but  
9 they're not always the same kind of abnormalities. So  
10 they don't look immunologically identical. They look  
11 similar but not identical.

12 DR. POLAND: I guess one other question  
13 is, so they are sort of screened and categorized at a  
14 retrospective distant point in time and then moved  
15 forward in time and at some time point you drew blood  
16 on them? Did you know whether they had -- you know,  
17 immediately prior to that blood draw whether they had  
18 had, I don't know, influenza vaccine or an upper  
19 respiratory infection or, you know, any of the things  
20 that might be expected to potentially skew it one way  
21 or another, particularly if there were seasonal  
22 differences in when cohorts were brought forward to  
23 have blood drawn?

24 DR. PEAKMAN: Well, things were done in a  
25 fairly random way. I don't mean by that we didn't

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1 know what we were doing. Every sample is coded and  
2 there's no patent to bringing up all of the ill ones  
3 and then all of the other ones. Everything was done  
4 really in concert. It's been a three or four-year  
5 program of doing this work. So I don't think that  
6 would account for those differences. You would have  
7 to argue that it only applied to one group or the  
8 other, which I think is unlikely.

9 DR. POLAND: So it may be that people who  
10 endorse items on the SF36 form, which they may think  
11 are due to service in the Gulf War receiving vaccines  
12 are less likely to get influenza or other vaccines and  
13 the other group would be less reticent to get those  
14 vaccines. So unless you know in the weeks before you  
15 drew blood whether they had gotten vaccines or had any  
16 illnesses it's at least a confounder.

17 DR. PEAKMAN: It's a potential confounder.  
18 I would grant you that.

19 DR. OSTROFF: Thank you very much. I  
20 think what we'll do is to go ahead with our third  
21 presentation before we take a break. Our final  
22 presenter, who has also graciously come across the  
23 Atlantic from the U.K., is Dr. Leah Scott. She is the  
24 Group Leader Biology at the U.K. Defense Science and  
25 Technology Laboratory in Porton Down. She is going to

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1 discuss with us the results of a study using the  
2 marmoset model.

3 I'll ask her to go ahead and give her  
4 presentation. Thank you very much for agreeing to be  
5 here. We're sorry we couldn't make it a little bit  
6 warmer for you.

7 DR. SCOTT: That's no problem, perhaps the sun  
8 will happen tomorrow.

9 As you've heard, I'm Group Leader Biology  
10 at the Defense Science and Technology Laboratory at  
11 Porton Down and I'm going to talk about something just  
12 a little different. I'm going to talk about some of  
13 the animal studies that we've been doing, and what I  
14 hope do to in the next 25 minutes or so. This is the  
15 overview. I would like to concentrate on the  
16 investigation of the effects of multiple vaccinations  
17 in the context of Gulf health, with a little bit of  
18 background to start off with, and say a little bit  
19 about the approaches that we've employed and the  
20 methodologies that we've developed and refined.

21 I would like to finish off with a few  
22 words about what I see as the implications of the  
23 model for other studies and other areas of interest  
24 that we've been talking about around the table this  
25 morning.

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1           So I need not dwell on the first bullet  
2 point in this slide where we've been looking at  
3 aspects -- just two aspects of the complex environment  
4 associated with deployment during the Gulf conflict,  
5 multiple vaccinations and the nerve agent  
6 pretreatment, pyridostigmine bromide. Next. Thank  
7 you.

8           We were asked to address this very  
9 difficult exam question. Did the administration of  
10 multiple vaccines with and without pyridostigmine give  
11 rise to long-term adverse effects? It's difficult  
12 from a number of perspectives. The caveat in the box  
13 is a very important one. We didn't set out to  
14 establish a model for Gulf conflict related illnesses.

15       What we did was we looked at the most frequently  
16 reported signs and symptoms reported by ill Gulf  
17 veterans and we set our study out to determine whether  
18 multiple vaccinations and/or pyridostigmine gave rise  
19 to those signs and symptoms.

20           The next slide shows you a little bit  
21 about the approach that we adopted. It centered on  
22 multifaceted non-human primate studies which optimize  
23 extrapolation of animal-derived data to man -- a  
24 terribly important concept for us. And you'll see  
25 what we've highlighted in the second bullet point

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1 there, emphasizing functionally significant indices  
2 which would reflect those signs and symptoms that I  
3 was talking about earlier on. Functionally  
4 significant. We didn't want just to be able to show  
5 whether there were changes in various indices. We  
6 wanted to understand what the biological significance  
7 of any changes that we saw were.

8 The experimental design and the conduct of the  
9 study was overseen by a cross-disciplinary panel of  
10 experts who advised U.K. MOD on the conduct of the  
11 study. The studies were conducted and analyzed blind.

12 The analysis was undertaken by an independent body,  
13 the University of Reading in the U.K.

14 There were three phases. First of all, a  
15 dose ranging study in guinea pigs, then a dose ranging  
16 confirmation -- a dose confirmation study in marmosets  
17 and finally, the worst case study, as we call it, in  
18 marmosets. I'll concentrate on that aspect of the  
19 study for the rest of the talk. Thank you.

20 We couldn't have undertaken such an  
21 ambitious study without substantial earlier work.  
22 We've just been touching upon a very important issue,  
23 identification of appropriate dose levels and regimens  
24 for the health and hygiene vaccines and the anti BW  
25 vaccines that we were going to be looking at. We

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1 consulted very, very widely for advice and information  
2 about how we should pitch those doses in our animal  
3 studies to optimize rate across to man. The advice  
4 that we got ranged from one-two hundredth or one-three  
5 hundredth of a human vaccine to multiple human  
6 vaccines with all points in between. A very difficult  
7 issue and perhaps there'll be an opportunity to  
8 discuss the sort of thought processes and preliminary  
9 studies that we undertook. Suffice it to say at the  
10 moment that the rest of the studies that I'll be  
11 talking about today were conducted with one-fifth of  
12 the human vaccination.

13 The schedules were discussed with MOD  
14 colleagues and agreed with the independent panel.

15 The approaches substantially de-risked  
16 from a technical risk point of view on the basis of  
17 two previous studies that we conducted in marmosets.  
18 We looked at the long-term effects of the nerve agent  
19 sarin, which is funded by the MOD in a program that  
20 reported a few years ago, and also the U.K.  
21 Department of Agriculture sponsored us to do some work  
22 in the marmoset model to look at the effects of a  
23 range of doses of diazinon. I'll say more about that  
24 in a moment.

25 The final bullet is up there to remind me

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1 to say one thing. Of course, these studies were  
2 conducted to address these important duty of care  
3 considerations. And I always think that our duty of  
4 care considerations have two arms -- first of all, we  
5 need, of course, to make sure that the medical kinds  
6 of measures that we put in place are safe for our  
7 military personnel. The other arm of that is to make  
8 absolutely sure that we have confidence in terms of  
9 the medical countermeasures that we issue, and if  
10 there are aspirant medical countermeasures on side, we  
11 need to do everything that we can to bring those  
12 forward. And that's where I see some of the model  
13 issues that we'll talk about later coming into being.

14 The next slide shows you the marmoset. I  
15 don't know how many of you are familiar with the  
16 marmoset as a model, but they are becoming very widely  
17 used in neuroscience research and have now become much  
18 more widely recognized and accepted in regulatory  
19 models these days.

20 Just to give you an idea of scale, this  
21 marmoset, Josh is sitting on the top of my hand --  
22 small new world primates weighing about 400-450 grams.

23 These were the characteristics and the indices that  
24 we measured in the diazinon and sarin studies that I  
25 just alluded to. We used cognitive tests, we

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1 monitored the brain electrical activities of these  
2 animals and we looked at sleep. This was all because  
3 about 30 years ago, Birchfield and Duffy did a very  
4 important study in which they looked at the effect of  
5 the nerve agent sarin and they showed that one year  
6 following administration of a low dose of sarin, they  
7 got small, but statistically significant changes in  
8 brain electrical activity.

9 What we attempted to do in this study was  
10 to do the so-what. To understand the functional  
11 significance of any changes in brain electrical  
12 activity that we might have seen; hence, the addition  
13 of cognitive performance and sleep patterns.

14 And then you've had a preview of this  
15 already, many years of work rolled up into three short  
16 bullet points. We monitored cognitive behavior, EEG  
17 and sleep for up to 12 months following exposure. We  
18 saw some short term effects but at the dose levels and  
19 regimens tested, we saw no long term effects.

20 The next slide tells us a little bit about  
21 the worse case study design. Now I quake in my boots  
22 in front of so many epidemiologists to talk about  
23 sample sizes of N equal to 12.

24 (Laughter.)

25 DR. SCOTT: But of course you will also

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1 know, and you'll be terribly aware, that for non-human  
2 primate studies of this type, N equal to 12 is quite a  
3 substantial number and of course we've done the prior  
4 calculations to make sure that we can draw the  
5 inferences that we can from the study at the end of  
6 the day.

7 The first group, of course the control  
8 group; the second group just received pyridostigmine;  
9 the third group just the vaccines; and the fourth  
10 group, what we really described as the worse case  
11 group, the vaccines and pyridostigmine.

12 The left hand side of this schedule, there  
13 you'll see the preparatory stage of the study where  
14 the animals were trained to perform the cognitive  
15 tests and trained to perform the muscle function test.

16 It's not just me -- what a relief.

17 (Laughter.)

18 DR. SCOTT: So the animals are trained to  
19 perform the behavioral tests and the muscle function  
20 tests that I'll tell you about in a moment, and the  
21 telemetry transmitter, which allows us to monitor the  
22 brain electrical activity was implanted.

23 Then we move into minus 3 to zero, that  
24 three month baseline phase where we collect baseline  
25 information on the parameters that I'll tell you about

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1 in a moment. And then during period 1, you can see a  
2 complex schedule, over 51 days of vaccine  
3 administration.

4 Mark has told you about some of the  
5 vaccines already and on day 0 for example, the animals  
6 had anthrax and pertussis for the reasons described,  
7 polio and yellow fever and the three typhoid tetanus  
8 and Hep B; day six, meningitis and cholera; day 23,  
9 plague 1, anthrax 2, pertussis 2; and day 51, plague 2  
10 and anthrax 3. On the advice of colleagues at MOD, we  
11 didn't put in a third pertussis dose here because this  
12 schedule was designed to reflect what it says, a worse  
13 case situation. And generally speaking, I think there  
14 were only one or two very small instances of a third  
15 pertussis being given.

16 In the middle of the vaccine  
17 administration, the animals were implanted with an  
18 osmotic mini-pump and for 28 days received either  
19 pyridostigmine or saline.

20 And we monitored parameters in three month  
21 periods. In the period six here, the animals were  
22 challenged with an antigen that they hadn't seen  
23 before, to test their immune responsiveness, and then  
24 at 18 months, the animals were killed and some  
25 electrophysiology conducted on their tissues and full

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1 post-mortems.

2           The next slide just tells you a little bit  
3 about the parameters that we measured during that 18  
4 months following administration of vaccines. We've  
5 heard a little bit about cognitive behavior before,  
6 but you will see that these boxes reflect the most  
7 frequently reported things that people complain about.

8       People complain about inability to concentrate, the  
9 behavioral test measures ability to concentrate.  
10 People talk about compromised poor sleep quality, the  
11 model allows us to look at that. Compromised muscle  
12 function, the model allows us to look at that.  
13 Compromised stress responses and compromised  
14 immunological responses.

15           The next slide has a little bit about some  
16 of the underpinning approaches, and of course, I've  
17 mentioned already implantable telemetry so that the  
18 animals can continue to live in social groups and have  
19 their brain electrical activity monitored. Home cage  
20 behavioral testing using a test which is analogous to  
21 the Wisconsin card sorting test from the Cambridge  
22 Bureau of Psychological Test Automated Battery called  
23 CANTAB. Sleep, I've alluded to, muscle function.  
24 These are presented in the animal's home cage. And  
25 the animals, wherever possible, were trained to

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1 cooperate with procedures. We did not attempt during  
2 the study to address the stress issues. We wanted  
3 this to be a very clear study so that we could draw  
4 conclusions.

5 The next slide shows you CANTAB in  
6 operation. Here you can see marmoset in its home  
7 cage. Normally the animals live in big interlinked  
8 cages. During behavioral testing, in this case a  
9 touch sensitive screen is wheeled up to this little  
10 bolt on that's in front of animal's cage and you can  
11 see that it's really up to the animal whether they  
12 want to engage in the behavioral test or not. And  
13 that's very important because it has opportunities for  
14 looking at motivational state as well. And you can  
15 see that because we were very enthusiastic about home  
16 cage testing, that all the other animals in the room -  
17 - you can see one just poking its head up just here --  
18 are all interested in the task.

19 And this is what the animal sees. You can  
20 see that it's just putting its hand through the screen  
21 just there. The screen has icons and the animals is  
22 trained to perform sequences of discriminations and  
23 one or two people in the room have visited the  
24 laboratory and have pitted their wits against common  
25 marmosets -- I shall say no more.

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1 (Laughter.)

2 DR. SCOTT: The marmosets of course are  
3 motivated to perform the task, not through sheer fear  
4 of shame and despondency, but because they're rewarded  
5 with access to banana milkshake -- it's a fantastic  
6 motivator -- disgusting taste but it's a fantastic  
7 motivator.

8 When you consider these animals have been  
9 working for two and a half, nearly three years in some  
10 cases, that's quite a commitment because these tests  
11 are performed every day Monday through Friday.

12 The next slide shows you how we go about  
13 sleep monitoring. You see the animals live in pairs  
14 and they sleep in this bucket which hangs from the top  
15 of the cage. This is a radiotelemetry receiver which  
16 is strapped to the bottom of the sleeping bucket,  
17 there's a camera up here and this is what the camera  
18 sees. For reasons that we haven't got time to go into  
19 now, there's a shortcoming in the technical solution  
20 here and so one of our young colleagues, or a number  
21 of our young colleagues have had to sit and look at  
22 video of animals sleeping in the bucket, and they can  
23 differentiate between the two, so that we can be  
24 absolutely sure when we're talking about when the  
25 animals go into rapid eye movement sleep, because we

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1 have just a single channel of EEG. But fantastically  
2 stable patterns of sleep.

3 Muscle function, very simple little test,  
4 rather Heath-Robinson in approach, but it works  
5 awfully well, again presented in the home cage.  
6 Simple little pulley system. One adds weights just  
7 here and the animal is trained to pull a bar in order  
8 to access little bits of chopped nut this time, which  
9 fall into the retrieval chamber and the animal  
10 stretches out to retrieve it. Again, this test was  
11 presented twice weekly and very stable levels of  
12 performance again. Motivational element as well as  
13 looking at muscle function per se.

14 Suffice it to say the animals were trained  
15 to present morning urine in a controlled manner. And  
16 that's terribly important because again, minimizing  
17 stress was a key feature of the sort of approach that  
18 we had. Next slide.

19 This was a really big problem for us,  
20 because many of you in the room will know perhaps that  
21 marmosets have not been well characterized and have  
22 traditionally not been very widely used in  
23 immunological studies. We had three specific  
24 immunological questions to ask of these animals.  
25 First of all, within the limits of the animals's small

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1 size, remember, and the opportunities for drawing  
2 blood, relatively small, we had to make sure that the  
3 animals saw the vaccines in immunological terms. We  
4 wanted to be able to monitor the sequelae of  
5 vaccination over time to see whether there were  
6 differences across groups. And then with the KLH  
7 challenge, we wanted to test the immunological  
8 responsiveness of the system, again to see whether  
9 there were differences across groups.

10 The data after three months following  
11 vaccination have been reported already at a number of  
12 meetings last spring. The in-vivo elements of the  
13 study were completed in autumn of last year. The  
14 electrophysiological studies and pathological  
15 investigations completed just last month. The data  
16 analysis nearing completion and we're expecting to  
17 report the key findings in the spring of 2004. I am  
18 very sorry to say, and it would be clearly  
19 inappropriate of me to discuss what I think the  
20 outcome is going to be just at the present time. But  
21 by the time you have your next meeting, hopefully at  
22 least some sort of report should be able to be tabled  
23 at that stage so that you can get a feel for the  
24 outcome of the study from that point of view.

25 The bottom line is still very compelling

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1 as far as I'm concerned. I am confident that if there  
2 are changes that would be clinically significant,  
3 resulting from multiple vaccinations and/or  
4 pyridostigmine, we will see them in the study -- I am  
5 quite confident of that.

6 Lessons learned so far, because I can't  
7 think of another study of this kind that's happened  
8 anywhere, so there were some important lessons. Quite  
9 frankly, you know, if one had really appreciated just  
10 how complex and difficult it was, I'm not actually  
11 sure that we would have undertaken it -- well, we  
12 would, because it was a very important question to ask  
13 and address.

14 But we have now finalized and sorted the  
15 strategies for the experimental design. Data  
16 reduction strategies are absolutely pivotal to this  
17 study in terms of drawing conclusions in a short time,  
18 because you'll see there's a relatively short time  
19 between completion of the study and the availability  
20 of results, which should be coming along shortly.

21 This is really such an important issue --  
22 scaling vaccine dose in preclinical models. I've said  
23 addressed, I wouldn't pretend that we'd sorted it, but  
24 at least we have some criteria that we're fairly  
25 confident are meaningful, happy to discuss offline.

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1 We've had to do a bit more method development, as you  
2 see, to look at muscle function, to look at urinary  
3 cortisol and to look at the immunological aspects.

4 The next slide just tells you that we were  
5 really starting off from a very low baseline. We  
6 really didn't know when we started off, how we were  
7 going to approach these issues, but we now have the  
8 wherewithal to look at the sort of cytokines that Mark  
9 has just been talking about and the next slide makes a  
10 rather dramatic claim -- we are now in a position to  
11 monitor all phases of the immune response in the  
12 marmosets.

13 As with all of our animal model studies,  
14 I'm not beginning to pretend that the marmoset is a  
15 perfect read across to man, but what I am saying to  
16 you is that I think we are now in a position to  
17 understand the relative merits and shortcomings of the  
18 marmoset as a model in this context.

19 So we've developed this model which  
20 enables key questions on the effects of vaccines to be  
21 investigated and interpreted. And of course, the  
22 approach, we've already used it for organo-phosphorous  
23 compounds, has implications and opportunities for  
24 looking at other xenobiotics.

25 There is one thing I'd just like to

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1 highlight though. Because we're talking about long  
2 term studies, one needs to think about whether one  
3 waits until there's no option but instigating such  
4 studies or whether one instigates studies early so  
5 that the answers will be coming on line when arguably  
6 you need them. But that also has to be qualified with  
7 an important remark that we are looking about -- we're  
8 not talking about regulatory acceptability here, we're  
9 looking at issues at a far greater level of complexity  
10 than that. The bottom line, optimizes opportunities  
11 for extrapolation to man.

12 Rats can't do the sort of behavioral tests  
13 that these animals do. Marmosets sleep like non-human  
14 primates sleep in general, the same sleep architecture  
15 as human sleep and is affected by drugs in the same  
16 way. I believe that it optimizes extrapolation to  
17 man.

18 And the final slide just shows all the  
19 people who've been involved in this exercise. The  
20 project manager Dstl Andy Bowditch. My colleagues  
21 Peter Pearce, Gareth Griffiths, John Tattersall, Neil  
22 Hughes and Jeremy Smith, their various teams who  
23 pulled the whole thing together and made it happen.  
24 Our collaborators at Bristol Psychopharmacology Unit,  
25 David Nutt; at Newcastle, John Harris, who looked at

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1 the electrophysiology and the pathology with us; David  
2 Pritchard at Nottingham and Bert t'Hart at the BPRC in  
3 the Netherlands has helped us characterize the  
4 marmoset as a model in immunology. And of course, the  
5 independent panel, enormous contribution on the study  
6 and would really not have been the same without them.

7 So I'll stop there.

8 DR. OSTROFF: Thank you very, very much.

9 (Applause.)

10 DR. OSTROFF: All I can say before I open  
11 it up for questions is I thought I had an interesting  
12 job.

13 (Laughter.)

14 DR. OSTROFF: This must be a fascinating  
15 study to conduct.

16 DR. SCOTT: It is.

17 DR. OSTROFF: Dr. Poland.

18 DR. POLAND: You mentioned that you have  
19 the three month data that you've reported at a  
20 scientific meeting. Could you briefly summarize those  
21 findings for us?

22 DR. SCOTT: Nothing major to report.

23 (Laughter.)

24 DR. SCOTT: Is that brief enough?

25 DR. POLAND: That's brief enough.

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1 DR. SCOTT: You must understand that  
2 because the question was about -- the experimental  
3 design was loaded towards looking at long term effects  
4 and so we've had a very cursory examination, which has  
5 been reported in that three month stage. We are now  
6 in the throes of re-analyzing some of those three  
7 month data, because it puts a different perspective.  
8 But some acute changes, as you would expect, because  
9 that's an enormous vaccine load for a little animal  
10 like that. And cholinesterase inhibition of about 30  
11 percent as well.

12 DR. POLAND: I don't know anything about  
13 marmosets, but are these -- would these be considered  
14 immunologically mature animals?

15 DR. SCOTT: In terms of age?

16 DR. POLAND: Yes.

17 DR. SCOTT: The animals were 18 months at  
18 the start of training and they are absolutely --  
19 they're sexually mature by 11 months.

20 DR. POLAND: What kind of life span do  
21 they have?

22 DR. SCOTT: Well, that's a very important  
23 issue. In captivity, marmosets will live and survive  
24 and continue to breed until they're 14 or 15 years  
25 old. So if one believes the issue about scaling years

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1 per animal, we've been looking at 18 months following  
2 vaccinations and if it's appropriate to scale that,  
3 that's the sort of time frame that would have  
4 accounted for veterans complaining of ill health.

5 DR. OSTROFF: Yes.

6 DR. BROWN: Couple of questions. Could  
7 you get those marmosets to type memos?

8 (Laughter.)

9 DR. SCOTT: Sadly, no.

10 DR. BROWN: But more seriously, you  
11 mentioned a study by Birchfield and Duffy that got a  
12 lot of people's attention, of course, because they  
13 showed long term effects on the EEG after poisoning  
14 with sarin and some other organo-phosphorous agents,  
15 but my recollection is that when they were looking at  
16 those, that humans that were involved in those studies  
17 weren't low dose in the sense that Gulf War veterans  
18 were low dose, but these were people who survived  
19 fairly severe poisoning accidents, the equivalent of  
20 industrial accidents -- well, they were industrial  
21 accidents.

22 So I'm wondering if you could comment  
23 specifically about the kinds of doses of  
24 pyridostigmine bromide. You mentioned that some of  
25 these animals were showing a 30 percent cholinesterase

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1 inhibition, for example.

2 DR. SCOTT: Oh, yes.

3 DR. POLAND: That seems kind of a high  
4 dose.

5 DR. SCOTT: No, no.

6 DR. POLAND: No.

7 DR. SCOTT: Three things. Let me just  
8 clarify the Birchfield and Duffy issue. The reason  
9 that we did the marmoset study with sarin was to  
10 clarify their non-human primate study, the Birchfield  
11 and Duffy non-human primate study, which looked at EEG  
12 one day and one year after about a tenth of an LV-50  
13 of sarin, and that's just the sort of dose regimen  
14 that we used as well. Because as you know, there's a  
15 great paucity of information about low dose OP  
16 effects.

17 So this EEG change perpetually came up as  
18 almost the only citation for many years about what  
19 happened at really low doses, and so that was our  
20 attempt, to address that. I wasn't talking about the  
21 human study at all, I was talking about study in  
22 rhesus monkeys.

23 The question about pyridostigmine dose is  
24 that the schedule for pretreatment for nerve agent  
25 poisoning in the U.K. and in the U.S. as well, is that

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1 one inhibits cholinesterase -- the dose regimen of  
2 pyridostigmine is designed to inhibit red blood cell  
3 cholinesterase by 30 percent.

4 DR. POLAND: That would be taking the  
5 recommended dose --

6 DR. SCOTT: That's correct. That's one  
7 tablet every eight hours.

8 DR. POLAND: So that's what you achieved  
9 with --

10 DR. SCOTT: We did, but of course, that is  
11 physiologically -- I've got a real thing about -- I  
12 have to confess that I'm a pharmacologist so I have a  
13 real thing about pharmacologically equivalence and  
14 that's one of the reasons that I started asking all  
15 these difficult questions about vaccine doses and  
16 scaling it. So that's my pharmacology showing there.

17 So yes, I mean one couldn't have  
18 undertaken -- one would have been very ill-advised to  
19 undertake these studies with doses of either vaccines  
20 that were not physiologically relevant.

21 DR. POLAND: Thank you.

22 DR. OSTROFF: Other comments?

23 Dr. Grabenstein.

24 COL GRABENSTEIN: A question for Dr.  
25 Hackett, when we've concluded with Dr. Scott. You

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1 alluded before that theoretically the human body could  
2 accept 100,000 vaccinations simultaneously, but then  
3 perhaps scaled it back to 10,000. I just wanted to  
4 map your use of the word vaccine to my several uses of  
5 the word vaccine. Did you mean the contents of a  
6 syringe, did you mean one microbe being protected  
7 against -- I think it probably pivots on your hundred  
8 epitopes (ph) per--

9 DR. HACKETT: Something that contains  
10 about 100 epitopes (ph), so if you call that entity a  
11 hundred and --

12 COL GRABENSTEIN: Roughly speaking, a  
13 microbe perhaps.

14 DR. HACKETT: Yes, because I think there's  
15 a lot of immunodominance, so that even though  
16 potentially there may be, you know, infinite numbers,  
17 there's discrete areas and so I think you're talking  
18 about a vaccine that would have a certain amount of  
19 complexity, maybe up to 100. Sort of gives you the  
20 idea of a human pin cushion.

21 DR. OSTROFF: Other comments?

22 I have one quick question for you, Dr.  
23 Scott.

24 Was this a one time study or are you  
25 planning to do follow up studies now that you've gone

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1 through all the rigor of developing this particular  
2 model? Are there other questions that you're seeking  
3 to try to answer?

4 DR. SCOTT: I think there are many  
5 questions that we would like to answer, but of course,  
6 as you said, it's a very complex study, it's expensive  
7 in terms of resource and years. I think that one  
8 could bolt in a number of exam questions to that  
9 study. For example, one could look at that sort of  
10 approach for any of the other aspects of the  
11 environment that one would be exposed to in a Gulf  
12 situation. I think one could easily address some of  
13 the stress issues in a quantitative way, one could  
14 look at all of the other toxicological complexities  
15 and I really believe that these sort of multi-system  
16 test beds are what we really need to be looking for.

17 Furthermore, we talked a little bit this  
18 morning about how one would accelerate vaccine  
19 acquisition programs and there may be some options for  
20 speeding the play in terms of if one had well  
21 characterized animal exposure models -- for example,  
22 if one had the sort of information that -- of course  
23 you wouldn't need information on all of the parameters  
24 that I was talking about there, but you know, I  
25 believe this is the approach for the future, frankly.

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1           And you will also know that we've looked  
2 at a worse case situation here. If we'd looked at a  
3 matrix and compared all the possible combinations, we  
4 still wouldn't have an answer in 30 years time. So  
5 that's why we've gone for the worse case. So I'd just  
6 like to put a little bit of my response on hold until  
7 the output of this current study is in the public  
8 domain.

9           DR. OSTROFF: Thank you once again. We'll  
10 very much look forward to hearing more about the  
11 results of this particular study.

12           Let me ask COL Engler.

13           COL ENGLER: I just have a question. My  
14 understanding as a human immunologist is that the  
15 complement system in primates is really quite  
16 comparable. Are you in your immunological studies  
17 actually looking at complement split products and in  
18 follow up to the comment in the innate immune system,  
19 one of the things clinically that I think is very hot  
20 right now in the context of chronic fatigue syndrome  
21 and chronic fatigue syndrome like STs where there's a  
22 myriad of immunologic studies that are inconsistent,  
23 but a recent study that was published in the Journal  
24 of Allergy and Clinical Immunology used the history of  
25 the fact that all of these patients complained that

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1 when they attempted to do conditioning exercise, their  
2 symptoms exacerbated and worsened, unlike other  
3 chronic disease states. And in that nine year study,  
4 they actually did an exercise challenge on the  
5 patients versus a control group with a myriad of other  
6 issues and showed that the only consistent  
7 discriminator was the pattern of complement split  
8 product formation post-exercise that was correlated  
9 very nicely with the symptoms that the patients  
10 complained of.

11 This whole struggle in follow up to the  
12 innate immune -- in that area also, I would take one  
13 exception with that presentation which is that side  
14 effects are not rare, we're talking about one or two  
15 percent, which isn't rare, where they're severe. And  
16 the question is whether it's in that compartment and  
17 all the usual standard compartments have been  
18 confusing and unhelpful, but when you really like what  
19 is happening with the patient and that as a marker,  
20 that that may be a very important compartment to pay  
21 attention to.

22 DR. SCOTT: One of the things I'd just  
23 like to say Mark might want to make a remark -- no?

24 (Laughter.)

25 DR. SCOTT: I'm just about volunteering him

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1 to answer questions. One of the things that I would  
2 say is that we now know more about our marmoset model  
3 than we do about human subjects, because we don't know  
4 about sleep patterns over two and a half years, we  
5 don't know about stress responses over two and a half  
6 years, we don't know about willingness to engage in  
7 conditioned tests and so on. So I don't want to  
8 bounce the question back at you in that way, but you  
9 know, I think that's something that we should  
10 remember.

11 One also should remember, I think, that in  
12 immunological terms, new world primates are not as  
13 good as old world primates, but there are a number of  
14 advantages from using small animals that breed very  
15 readily and prolifically in captivity. And again, for  
16 better understanding the relative strengths and  
17 weaknesses of the model.

18 DR. OSTROFF: Thanks very much.

19 I think what we'll do now -- what we plan  
20 to do is during the executive session later on this  
21 afternoon, we'll have some extended discussions,  
22 trying to address the question that's before the  
23 Board.

24 So since, believe it or not, we're a  
25 little bit ahead of schedule amazingly, I think what

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1 we'll do is we'll take our 15 minute break now and  
2 then when we come back, we will shift the topic to a  
3 discussion of mortality associated with Operation  
4 Iraqi Freedom, a subject I'm sure all of us will be  
5 very interested in hearing about.

6 Thank you again for all of our presenters  
7 and a great appreciation for your willingness to take  
8 time out of your schedules to be here.

9 (A short recess was taken.)

10 DR. OSTROFF: Okay, as I mentioned before  
11 the break, we're going to shift gears a little bit and  
12 I would ask you to turn to Tab Number 10 and point out  
13 that there is another question that's before the Board  
14 that was posed by Health Affairs dated October 7  
15 concerning review of medically-related fatalities in  
16 Operation Iraqi Freedom. And as I was pointing out  
17 before the break, if you look at this dated October 7  
18 the number of fatalities were approximately 300 at  
19 that time and now as I'm sure all of you know, it's up  
20 over 500, which, you know, is very sobering to all of  
21 us and sort of brings home to all of us the reason  
22 that we're here, to support the troops and make sure  
23 that we can do whatever is feasibly possible from our  
24 perspective to try to reduce the burden of morbidity  
25 and mortality in theater and most of you will remember

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1 that at the last meeting we had an update from Craig  
2 Mallak from the Medical Examiner's Office and it was a  
3 very sobering presentation and I know the Board at  
4 that time was very concerned to try to do what we  
5 could to make sure that there were sufficient  
6 resources available to that office to do the very  
7 difficult work that they have to do in terms of  
8 following up on all of these cases.

9 Today, we have Lisa Pearse is here. I see  
10 you standing up in front. And she's the Chief of the  
11 Mortality Surveillance Division in the Armed Forces  
12 Medical Examiner's Office in AFIP. And she's going to  
13 give us an update on the situation and we look forward  
14 to your presentation and some discussion afterwards.

15 Thank you very much.

16 MAJ PEARSE: Thank you.

17 Well, this is a huge shift in gears for  
18 something completely different. I'm Lisa Pearse, as  
19 you've already heard, I'm from the Medical Examiner's  
20 Office. I am not a medical examiner, I'm a preventive  
21 medicine physician. So we do have a forensic  
22 pathologist in the group here in CPT Kilbane and I may  
23 end up deferring some of those types of questions to  
24 him, with his permission.

25 As you all know, the Office of the Armed

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1 Forces Medical Examiner is led by Dr. Mallak and we  
2 have the role of autopsying all of the casualties that  
3 are coming out of OIF, OEF and just about any other F  
4 you can think of right now.

5 (Laughter.)

6 MAJ PEARSE: For Operation OIF, we have  
7 autopsied all but one. That one happened very early  
8 in the conflict and it was an in-hospital death that  
9 occurred out of theater and that was before we had  
10 established the lines of jurisdiction that stated that  
11 all the F's would come to us. He's going to come back  
12 and bite us, you'll hear about him later.

13 Through the Mortality Surveillance  
14 Division, which is my shop, we try to identify all of  
15 the active duty casualties throughout DOD, not just  
16 within the office. And we try to get the autopsies on  
17 to folks that have come home after serving in OIF,  
18 which is more challenging. Frequently they're no  
19 longer in the military and they die in civilian  
20 facilities without announcing to their provider before  
21 they die that they were in Iraq three months before.

22 Our goal is to get a full evaluation and  
23 reckoning of our OIF casualties. Next slide please.

24 We find out about casualties from the  
25 field from Mortuary Affairs who says a body is on its

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1 way; Fox News, the same way as you all, CNN. We get  
2 casualty reports, there's a lag of 24 to 48 hours in  
3 the casualty reports, but they contain the necessary  
4 demographic data for us to produce death certificates  
5 and get the process rolling with identification.

6 We get more detail information from the  
7 Criminal Investigative Services of all three services,  
8 primarily CID because Army is the biggest player and  
9 they provide detailed reports -- slowly but detailed.

10 And then finally, we've hooked in with  
11 Army Safety to get a different slant on the accidental  
12 deaths.

13 We have the authority to do autopsies  
14 under Title 10. Most of the autopsies are done at  
15 Dover Port Mortuary in Delaware -- that's the vast  
16 majority of the autopsies out of OIF. There are a few  
17 that are done at Landstuhl, those are primarily  
18 fatalities who were stationed in Europe before they  
19 went into theater. So there's a sense of  
20 possessiveness, they're our soldiers and they do the  
21 autopsies there. The forensic pathologist there is  
22 affiliated with our office and we communicate and we  
23 support that office.

24 We also have done a few autopsies at  
25 medical treatment facilities -- Walter Reed, San

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1 Antonio -- when we've had died of wounds fatalities  
2 down the road. Next slide please.

3 A little bit of the process. One of the  
4 most important things that we do is identify the  
5 decedent and in the old days we had the dog tags.  
6 That's not good enough. Guys can swap dog tags, they  
7 can have somebody else's ID card. So we rely on  
8 fingerprints, we rely on dental identifications and we  
9 rely on DNA.

10 One of the questions that we're frequently  
11 asked is, "Why do you bother with the fingerprints or  
12 the dental x-rays, you can just do DNA?". And the  
13 reason for that is it's slow, it's two to three days  
14 before we'll have a DNA back on an intact individual.

15 If we have an intact decedent and we can get a  
16 fingerprint ID, typically that's half an hour to an  
17 hour from the time we start processing those remains.

18 That allows us to release the decedent back to the  
19 family for burial and that's our first priority, is  
20 getting them home as soon as we are completed with  
21 what we need to do for analysis.

22 Another thing we try to do is figure out  
23 why they died. We are doing complete, full autopsies  
24 on every fatality. I have heard it said that we only  
25 did that with 20 percent of the goal 4 fatalities.

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1 I've not seen that in print and I can't verify that,  
2 but I do know that visual inspection was common  
3 practice. They would just look at the body, say yeah,  
4 that's a gunshot wound through the head and bless it  
5 and off it would go. We're not doing that any more,  
6 for a lot of reasons -- documentation being the  
7 biggest one.

8 We do full toxicology on every death and  
9 on our natural deaths, we're aggressively looking at  
10 them. We're using consultants widely --  
11 cardiovascular pathology, neuropathology particularly.

12 Our forensic pathologists are phenomenal  
13 at looking at a wound and telling you what caused it  
14 and why that killed them. But in a natural death where  
15 you may have an infectious process or you may have a  
16 real subtle histological sort of thing, it gets beyond  
17 the level of expertise of the general forensic  
18 pathologist pretty quickly. And because these are  
19 high visibility cases, we're taking no chances and  
20 sending them to the consultants.

21 And then we're also collecting tissue on  
22 these cases for histology, which we'll do immediately,  
23 and then also for later analysis, we're just storing  
24 them informally, in case a question should come up  
25 down the road, we can take a look at them. Next

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1 slide.

2 I can't present to epidemiologists without  
3 having a case definition. What we're using is an OIF  
4 death case definition is that they died in Iraq or in  
5 the supporting areas, that would be Quatar, Kuwait,  
6 one of the ships that's in the Gulf that's assigned to  
7 OIF, and that they died within 120 days of returning,  
8 from a condition that they got in theater. So if they  
9 were in a motor vehicle accident, for instance, and  
10 got severely injured and then they died at Walter Reed  
11 three months later, we would still consider that an  
12 OIF death. 120 days is arbitrary, it's not my number.

13 I picked that up from DIOR and they're the official  
14 source of all casualty information dating back to the  
15 Civil War, and it seemed to make sense to use their  
16 definition for comparability.

17 I do take one exception to the way they  
18 report and that is with suicides. They do not  
19 consider a suicide, regardless of whether there was  
20 mental health issue in theater before they died, to be  
21 combat-related or to be OIF-related. So you can step  
22 off the plane with a PTSD diagnosis, kill yourself and  
23 it would not be considered an OIF death under DIOR,  
24 which makes looking at mental health issues  
25 historically very, very difficult because that data is

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1 just not rolled into it. And we think it's important  
2 and we're tracking it.

3 All right, we're getting into data. As  
4 you can see, we're up to 529 deaths. This is as of  
5 the 31st of January. We've certainly had quite a  
6 number since then.

7 At the beginning of the war, it was evenly  
8 split between the Army and the Marine Corps and now it  
9 is predominantly Army, over 90 percent of the  
10 fatalities are in the Army, overall it works out to  
11 about 83 percent Army. Next slide please.

12 If you look overall at why people die in  
13 theater, what you're going to see is trauma, trauma,  
14 trauma, trauma, trauma, trauma, more trauma and still  
15 more trauma -- far and away what is killing our  
16 soldiers in theater is traumatic injuries.

17 I opted to compare our data with Desert  
18 Storm data and this was the data that was published by  
19 Jim Ryder, John Brundidge and Bob Dufretes back in  
20 '96. And they used a one-year time frame, from August  
21 '90 to July '91. And that time frame is pretty close  
22 to where we are right now for OIF.

23 What you see is that we have more deaths  
24 and two-thirds of the deaths from this conflict are  
25 hostile fire deaths as opposed to only 40 percent in

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1 the first Gulf War. Another huge difference is the  
2 proportion of accidents that you saw with Desert  
3 Storm. We're down to a quarter right now. Other  
4 issue, natural deaths, eight percent for them but only  
5 three percent for us. So there's really been a shift  
6 in what is killing the folks in the combat  
7 environment. We still have a few that are outstanding  
8 pending, and the suicide percentage is approximately  
9 the same. Next slide please.

10 If you look over time -- DNBI is disease,  
11 non-battle injury. That is everything that is not  
12 hostile fire lumped together. What you see is that  
13 combat was a big factor early on in the war before  
14 hostilities were declared ended on the first of May  
15 and we had a huge spike in November and even January  
16 was not at all a quiet month. The hostile deaths have  
17 not stopped.

18 DNBI deaths, in contrast, have been, if  
19 anything, declining. They're not going up, which is  
20 good, and there aren't a lot of peaks and valleys,  
21 it's fairly stable.

22 All right, I was asked to address  
23 specifically disease, non-battle injury and  
24 specifically medical causes of disease, non-battle  
25 injury, not your accidents and things that would be

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1 covered by safety, which limits what I'm looking at an  
2 awful lot.

3 Disease, non-battle injury overall is, not  
4 surprisingly, ground transportation, 30 percent;  
5 rotary mishaps and those are tied with suicides which  
6 is another major cause of disease, non-battle injury.

7 Natural deaths, which would be your  
8 medical causes of disease, non-battle injury, we're  
9 looking at 16 cases. It's that three percent of  
10 what's in theater. So what I'm left to talk about is  
11 a really small subset of everything that's going on in  
12 theater. I'm not saying it's not important, but it is  
13 important to recognize that there's a lot bigger  
14 picture going on through this.

15 All right, as I was saying, you take out  
16 the safety ones, the motor vehicle accidents, and the  
17 helicopters and you're left with considerably fewer  
18 deaths. I'm going to talk about most of these in more  
19 depth since that was my request. I think it's  
20 important to notice that of the ones that are pending,  
21 eight of them are gunshot wounds, so we don't have  
22 this burden of natural disease that we haven't  
23 unpended yet. It's a fair mix of everything else  
24 that's out there. Next slide.

25 Suicides, that's the big one. What you're

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1 going to see is that these numbers don't match. This  
2 one is 23 and this one is 26. This reason for that is  
3 a couple of late breakers that fell into the post-OIF  
4 category, that I didn't find out in time to update my  
5 data set. These are predominantly the Army, these are  
6 non-OIFs, these are OIFs. Of all of the suicides in  
7 DOD for the same time period, a reasonable percentage  
8 is OIF, but there's a lot more going on that's not  
9 OIF-related. So when the media is talking about all  
10 the OIF suicides, it's not a sudden jump. What you'll  
11 see over time, we had two in April, May, June, July  
12 was five, every other month two, two, two, all the way  
13 along, zero in January. So we do not have a spike in  
14 suicides.

15 We did look for methoquin (ph.) and  
16 because we've done toxicologic testing in every OIF  
17 fatality, that wasn't that hard to do. We went  
18 downstairs and we found that only one of those folks  
19 had taken methoquin, which raises the other issue why  
20 aren't they taking their anti-malarials.

21 (Laughter.)

22 MAJ PEARSE: We do have some further  
23 testing going on on about five of those cases where  
24 they only screened urine, and methoquin, because of  
25 its very long half-life is poorly detected in urine.

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1 So they're retesting those specimens on spleen and  
2 liver and we'll see what comes up. That should be  
3 ready later this week.

4 The heat injury deaths. We've had six.  
5 One of them occurred after running in July in Iraq and  
6 I won't go into the wisdom of that. The other five  
7 were clustered over a very short period of time. The  
8 ambient temperatures were extremely high during that  
9 entire week, it was 130 degrees ambient temperature.  
10 I put 120 because that's as high as we can document.  
11 When you do the WBGT, the dry thermometer only goes up  
12 to 120 and they were pegged, so it was very, very hot  
13 in theater.

14 These folks, four of them were found dead  
15 in bed. They had been complaining about not feeling  
16 so good when rested and did not wake up. Two of those  
17 were found with core temperatures of greater than 105  
18 degrees. What we don't know is whether that's  
19 equilibration. Usually when someone dies, they cool  
20 off. When the ambient temperature is 130 degrees,  
21 were they just equilibrating? We don't know the  
22 answer to that. They called them heat stroke, just  
23 because definitionally that's what you could call heat  
24 stroke, but that's an unanswered question. The other  
25 two, we did not have core temperatures at all on.

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1           One of them reported with a seizure, he  
2 was walking around and seized. He did have a core  
3 temperature that would be consistent with  
4 hyperthermia, but he also had a history of  
5 hyponatremia. What we have verbally is that he had a  
6 sodium of 108 at presentation to the TMC. I do not  
7 have that in writing and I've not been able to confirm  
8 that and by the time he got to us, we could no longer  
9 do valid electrolytes. He did, a month prior to his  
10 terminal event, have an admission for mental status  
11 changes with a documented sodium of 122, which begs  
12 the question did he have SIADH, we don't know. But he  
13 was different from the other four and it's important  
14 to bring that up.

15           All of them were negative for toxicology,  
16 they weren't taking antihistamines or anything else  
17 that would make them more susceptible to being a heat  
18 injury.

19           And we controlled the cardiovascular  
20 pathology on all of them. Three of them had some mild  
21 cardiac changes that would perhaps trigger an arrhythmia  
22 but none of them were what our pathologist would  
23 consider a smoking gun, none of them had a definitive  
24 cause of death other than heat. So according to the  
25 National Association of Medical Examiner Guidelines,

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1 they were considered to be heat-related deaths similar  
2 to what you would have in Chicago or in France when  
3 you have these huge clusters of people dying in the  
4 heat. Next slide please.

5 Our natural deaths. We've had six heart  
6 attacks, atherosclerotic cardiovascular disease.  
7 Interestingly, four of them were not in Iraq proper,  
8 they were in support areas and four of them were  
9 National Guard or Reserve. It was not the regular  
10 troops, these were older folks. I kind of hesitate to  
11 say that -- 38 to 46. There was an outlier that was  
12 56.

13 (Laughter.)

14 MAJ PEARSE: These were not 18-year-old  
15 kids that were out dropping dead with heart attacks.  
16 They all had extensive disease on autopsy. One of  
17 them had evidence of a prior heart attack with large  
18 areas of fibrosis in his heart. Three, vessel disease.  
19 When I looked at medical records, which were available  
20 for three of these deaths, they had hypertension, on  
21 meds, all three. Two of the three were smokers, all  
22 three had hyperlipidemia, two of them were on  
23 medication for it. So these were not surprise cardiac  
24 deaths, these were folks with a lot of risk factors  
25 for disease.

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1           The pneumonia deaths, there were two of  
2 these. Those were the two natural deaths, if you  
3 will, from infectious causes.

4           I'm going to summarize just the deaths, I  
5 believe you're getting another presentation on the  
6 overall OIF pneumonia situation, I know you've heard  
7 about it before, so I'm only going to focus on these  
8 two deaths and what we know about them.

9           The first case was in June and he had a  
10 rapidly culminating course, three days of mild  
11 symptoms which then suddenly progressed to  
12 tachycardia, tachypnea, oxygen requirements,  
13 intubation and he did not survive for transportation  
14 to Germany.

15           The second case was a more sudden onset  
16 but a slower death. He presented and was intubated  
17 within hours and he did get Medivac'd to Landstuhl  
18 whereupon he developed multiple organ system failure,  
19 Klebsiella sepsis and then expired.

20           Anatomically, at autopsy, with histology,  
21 they both had diffuse alveolar damage. One of them  
22 had pulmonary eosinophilia, the other one did not.  
23 Both of them had pulmonary edema and effusions. The  
24 second case in addition had clear evidence of multiple  
25 organ system failure with liver changes, cerebral

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1 edema, pericardial effusion and anasarca. Next slide  
2 please.

3 We sent one tissue to pulmonary pathology  
4 at AFIP and their diagnosis was acute phase diffuse  
5 alveolar damage that had not progressed to  
6 consolidation, on both cases. They looked for  
7 specific cytological changes that you would see with  
8 adenovirus and some of the other specific viruses, did  
9 not find them. They were absolutely insistent that it  
10 was not hypersensitivity pneumonitis. That is a  
11 specific triad of pathological findings and they had  
12 none of those three findings. What they said is it  
13 was consistent with eosinophilic pneumonia. And they  
14 do make a very clear distinction between the two  
15 entities. And the second case clearly showed  
16 Klebsiella.

17 And they felt that the etiology in these  
18 two deaths was most likely to be infectious although  
19 we hadn't found an agent. Next slide please.

20 As you can imagine, we tested the heck out  
21 of thee specimens. We sent them internally to the  
22 Armed Forces Institute of Pathology, pulmonary path,  
23 environmental path, infectious disease departments, we  
24 sent them to WRAIR, USAMRID, Mayo Clinic, CDC, Duke  
25 and NIOSH. Duke and NIOSH were both specifically

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1 looking at environmental toxins or particles rather  
2 than infectious agents.

3 The only thing that came up was Klebsiella  
4 and Candida in the second case of the two. And the  
5 Klebsiella because it was associated with multiple  
6 organ system failure was felt to be a terminal event.

7 It was not felt to be the primary insult.

8 The environmental study for Duke, we  
9 actually did informal case control study. We found  
10 lung tissue from other soldiers who had died in a  
11 similar region during the same time frame and sent it  
12 with the case tissue, so that they could look at  
13 comparison. Because everybody in Iraq is breathing  
14 junk. The dust in the air is awful. So we wanted to  
15 look at what's baseline junk and what is making them  
16 really sick junk. They found that the controls looked  
17 worse and they definitively stated that there was no  
18 evidence that the lung injury was due to inorganic  
19 particulate matter.

20 The NIOSH results are still pending and we  
21 haven't heard back yet. Next slide please.

22 All right, this is outside of the scope of  
23 what I was asked to talk about, but I thought it was  
24 really cool and interesting.

25 Drowning in the desert, I know Dr. Mallak

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1 probably presented some of this, the numbers keep  
2 increasing. We're up to 31 deaths now from drowning.

3 Most of those are associated with vehicles, primarily  
4 ground vehicles, although we've had a number in  
5 helicopters that have flipped. And we've had four  
6 from guys that went out swimming and four that went  
7 out during operations. They're actually on river  
8 boats and when they fall off the river boats in full  
9 armor, they sink and we've had two of those.

10 From a preventable standpoint, all four  
11 swimming incidents were in Army folks after the worst  
12 of the hostility settled off. And we haven't had any  
13 since the hostilities have picked up again. As people  
14 are more focused on combat, they're not messing  
15 around. Next slide please.

16 All right, the strengths about what we're  
17 doing, we've got complete capture of everybody that  
18 has died in-theater. We've got good visibility on  
19 everybody that dies in DOD. We've had tremendous  
20 support from GEIs, both financially as well as  
21 intellectually, where we send specimens and even some  
22 moral support and we've had good command support.  
23 Next slide.

24 We've had some pretty serious limitations.  
25 Ante-mortem information, very hard to come by.

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1 Trying to get a good line into country and then  
2 getting the information back without CIPR access. We  
3 do not have secure internet in our office at this  
4 point. Hopefully in the next six months we'll have  
5 that, but for right now, it has really limited our in-  
6 theater communication.

7 In-theater medical treatment records.  
8 Frequently the only thing -- our only clue that  
9 someone went to a medical treatment facility before  
10 they expired and came to us is that they've got an ET  
11 tube sticking out of their throat or a chest tube  
12 that's still in place. They don't come with records.  
13 We've attempted to address that and it's still not  
14 quite fixed.

15 Post-mortem micros, that's a real problem,  
16 particularly in the summer time because we have  
17 decomposition and it's not like they died in the  
18 hospital and we can just do a standard panel of  
19 microbiological testing and expect anything to grow  
20 that's meaningful.

21 Missed autopsies. These folks that have  
22 come back from Iraq and then did in the civilian  
23 sector, I find out about it, but because I find out  
24 through the casualty reports, frequently they've  
25 already been released. We've actually gone to funeral

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1 homes and taken a body back to do an autopsy. We have  
2 missed a couple that have been released to the family  
3 and we were unable to do an autopsy on those cases.

4 We have posted to the name list serve that  
5 if there's any civilian provider out there, medical  
6 examiner/coroner type that sees somebody who has been  
7 in Iraq, to please call us and we can either take  
8 jurisdiction of the case or tell you what specimens to  
9 get to send to us, but that's still a voluntary  
10 effort. If it lands in a civilian jurisdiction,  
11 there's very little we can do about it.

12 And then finally, it's really hard to nail  
13 down denominators for theater. I feel horrible  
14 presenting all these numerators to all these  
15 epidemiologists without solid rates, but for the most  
16 part, in-theater denominators are classified. They  
17 don't want us to talk about them right now. That will  
18 settle down, but for right now, it's very difficult to  
19 give you a solid rate. We've done some estimates off  
20 of pay files, looking at who is getting hazardous duty  
21 pay and the combat tax exclusion out of the Defense  
22 Manpower Data Center and we're working on some proxy  
23 files. I got those numbers Friday and they're not  
24 ready for presentation.

25 So, pending any questions, that's what I

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1 have.

2 DR. OSTROFF: Thank you very much for a  
3 very comprehensive presentation. I can just imagine  
4 all of the work that went on to gather this type of  
5 information and on behalf of the Board let me  
6 congratulate you as well as the rest of the team  
7 that's doing all of this.

8 Let me open it up to ask if there are any  
9 questions or discussion points.

10 Dr. Gray.

11 DR. GRAY: MAJ Pearse, in the 1991 war  
12 where there was quite a bit of concern about  
13 fratricide, I wonder if you could talk about that a  
14 little bit.

15 MAJ PEARSE: In the first Gulf war, there  
16 were two major incidents that accounted for an awful  
17 lot of the fratricide. We have not had any major  
18 incidents that results in multiple casualties. We  
19 have had one soldier from Fort Campbell that threw a  
20 grenade in a tent and then shot somebody else coming  
21 out. Those are being prosecuted as homicides, that's  
22 not really fratricide, as you're asking it -- friendly  
23 fire, if you will. We have had two aviation incidents  
24 that were hostile fire that are included in our combat  
25 numbers and then there's one incident that is under

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1 investigation still that I can't talk about yet that  
2 may or may not turn out to be. We're just not sure at  
3 this point.

4 Yes?

5 COL RIDDLE: COL Riddle. Part of the  
6 question was to look at and assess DOD's capability at  
7 medical surveillance to look at these incidents as  
8 sentinel events. Could you go a little bit and  
9 explain you all's role in the pneumonia and the  
10 pneumonia fatality and what role AFIP had in that  
11 cascade of events investigating those cases and then  
12 two deaths and X number of pneumonia fatalities, and  
13 then similarly where you had two pulmonary embolisms.

14 One might think that those potentially are sentinel  
15 events also, and anecdotally, I know that Walter Reed  
16 has seen a number of PE cases that have been evacuated  
17 out of theater, and if there's a similar epi  
18 investigation looking at those, and whether or not you  
19 think your capabilities are good, if these are  
20 sentinel events, to cascade backwards and initiate  
21 looking for root cause analysis.

22 MAJ PEARSE: Because we're autopsying  
23 every case, we have good visibility up front for when  
24 there might be a problem. We knew when we saw that  
25 first pneumonia case that there might be a problem.

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1 And that case was initially autopsied in Germany and  
2 they did a really thorough microbiological workup  
3 initially with PCRs for viral agents and significantly  
4 more than you would expect for an in-hospital  
5 pneumonia, for instance.

6 That's an example. Because we're looking  
7 all the time, I think we're well positioned to perform  
8 active surveillance on all of the deaths in theater to  
9 look for problems. The pneumonia deaths, we knew  
10 immediately there was an issue with that. The  
11 pulmonary embolism deaths, not so much. Remember I  
12 told you, there's that one guy we didn't get that was  
13 going to bite us? He's one of the pulmonary embolism  
14 deaths. His story, as best we can tell, is that he  
15 was in theater for a couple of weeks, developed  
16 pancreatitis, was medically evacuated to Spain where  
17 he developed a pulmonary embolism as a terminal event.

18 We have not been able to get records on that, he was  
19 seen by a fleet hospital and I've been chasing a  
20 nameless Navy physician for some time to find out who  
21 that is and I'm still looking.

22 The other case had been in Kuwait for  
23 several years. He was a 50-year-old with longstanding  
24 thromboembolic disease and he was on Levoquin and we  
25 knew that he had thromboembolic issues. He was not a

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1 sentinel event, if you will.

2 COL RIDDLE: How about the number of cases  
3 evacuated out that are being seen at Walter Reed, are  
4 you working with them on that?

5 MAJ PEARSE: Sure. Of the fatalities, we  
6 have actively looked for fratricide liden (ph.) and  
7 any of the deficiencies that we could get, have not  
8 found them. We do have two other pulmonary embolism  
9 deaths that aren't classified as pulmonary embolism  
10 deaths, one of them because his initial incident was  
11 improvised explosive device and he had massive trauma,  
12 and that was his primary cause of death. The  
13 immediate cause of the pulmonary embolism and he had  
14 undergone extensive medical therapy and certainly was  
15 at risk for pulmonary embolism because of that.

16 There was a second death that is a little  
17 less comprehensive of a story and isn't finished yet.

18 That was a young lady who was running in Iraq, and I  
19 still say that's a bad idea, who fell down and broke  
20 her patella, was immobilized and died with a pulmonary  
21 embolism at Walter Reed. Initial neuropath results  
22 suggest that she might have had amyloidosis and we're  
23 still processing tissue to finalize that. So she  
24 might have had a risk factor, we're still looking.

25 COL RIDDLE: And the second question is

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1 you said in Desert Shield/Desert Storm only 20 percent  
2 but now you're doing 100 percent. Was there a policy  
3 change that directed you to now do 100 percent or is  
4 that still an issue that's a personal choice by AFIB?

5 MAJ PEARSE: I do not believe there was a  
6 policy change. There certainly was a medical examiner  
7 change and a change in philosophy. Certainly we saw  
8 what happened after the Persian Gulf I with Gulf War  
9 illness. So I think we're better positioned to know  
10 what can happen if we don't look. But no, I don't  
11 think there's a formal policy directing us to do this.

12 COL GIBSON: This is COL Gibson.

13 You gave us a real nice breakdown of OIF  
14 and made some good comparisons back to the first Gulf  
15 War. Do you have a sense for OEF, how it breaks out  
16 proportionally and in particular the issue of suicide?

17 MAJ PEARSE: You're going to get me in  
18 trouble doing numbers without looking, right off the  
19 top of my head. They have not had a lot of suicides,  
20 I think they've had one. They also do not have as  
21 many people on the ground. They have approximately  
22 7500, as opposed to 130,000. There's a huge  
23 difference in denominator, so I'm not sure we can make  
24 any statements at all about that.

25 As far as overall why people die in OEF,

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1 it is different. Two-third of those are DNBI and most  
2 of those are transportation and predominantly  
3 aviation. The helicopters have had a really hart time  
4 with the altitude apparently.

5 DR. PATRICK: Kevin Patrick.

6 Clarification question. OEF is Operation  
7 Enduring? And what defines that?

8 MAJ PEARSE: Operation Enduring Freedom is  
9 based out of Afghanistan and is specifically anti-  
10 terrorist as opposed to OIF, which is Iraqi-based.

11 DR. PATRICK: Understood. Got a question,  
12 and it may relate to the denominator issue you're  
13 talking about. I am wondering about the suicides, the  
14 22 and then the overall 144 in the non-OIF. Perhaps  
15 the first can't be responded to in terms of  
16 denominator issue but I assume that the denominator  
17 for the 22 was much smaller than the denominator for  
18 the 144; is that correct?

19 MAJ PEARSE: Yes, sir.

20 DR. PATRICK: And if that's the case, I'm  
21 wondering how the 144 compares to the general  
22 population, general population rates of suicide.

23 MAJ PEARSE: I think I'd have to defer to  
24 my mental health colleagues.

25 MAJ GEN KELLEY: About half to two-thirds

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1 of the age-based general population.

2 DR. PATRICK: So it's better, the rates  
3 are better.

4 MAJ GEN KELLEY: That's correct.

5 DR. PATRICK: But I'm wondering -- trying  
6 to kind of triangulate onto the OIF, the 22 just seems  
7 like a high number then, but it's probably not?

8 MAJ GEN KELLEY: It's probably not.

9 VOICE: About the same as -- I think in  
10 trying to look at the denominators, it's probably  
11 about the same as the non-OIF and that's about half to  
12 two-thirds of this comparably aged civilians.

13 DR. PATRICK: Does it hold up for gender  
14 analysis as well?

15 VOICE: It's difficult to make  
16 comparisons, but -- I can't answer that.

17 MAJ GEN KELLEY: Actually, the Army has  
18 been asked these questions recently and had the  
19 opportunity to explain it and I know GEN Farmer might  
20 want to come out and talk to you and give the whole  
21 presentation, but essentially the suicide rate is  
22 lower by age-group comparison and I believe it's  
23 gender comparison too.

24 VOICE: It's age and gender comparison.

25 MAJ PEARSE: They're struggling with the

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1 same denominator issues that we are.

2 DR. OSTROFF: Well, let me just say that  
3 even if it is lower, I assume -- and you know, reading  
4 the newspaper -- that there's been a lot of attention  
5 given to these particular fatalities and, you know,  
6 from the perspective of the Board as epidemiologists,  
7 it's the issue of is there something preventable here,  
8 even though the numbers may be lower than the age-  
9 matched populations in the civilian sector, are there  
10 some characteristics here that are potentially  
11 preventable and predictable in terms of the  
12 circumstances of these particular suicides that might  
13 be amenable to some potential intervention.

14 MAJ PEARSE: We have not addressed that in  
15 a formal way, but what we have done is looked at the  
16 folks that have died and asked why. We have a  
17 forensic psychiatrist on staff, who is just getting  
18 his feet on the ground to look at some of these  
19 issues. And one of the things we found is they have  
20 the same issues that everyone else does -- marital  
21 issues, money issues, legal issues. We're not seeing  
22 the "I hate the Army" issue so much. It's the same  
23 basic factors that we see in the state-side  
24 population.

25 MAJ GEN KELLEY: Again, there has been a

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1 lot of analysis and programs done and so I would say  
2 that we probably should have the Army experts come.  
3 If you're interested in that, that would be a good  
4 presentation to have them explain to you what the  
5 programs are. I mean each of the services has a  
6 program.

7 DR. OSTROFF: COL Gardner first and then  
8 Dr. Cline and Dr. Poland and then Dr. Shanahan.

9 COL GARDNER: Let me just clarify for a  
10 minute the policy question you asked and then I have a  
11 question for Lisa.

12 In '98-'99, there was -- it's hard to say  
13 there was a policy change, but there was a change in  
14 the law which was pushed up through by DoD to give the  
15 medical examiner broader jurisdiction over military  
16 deaths, especially those that occur in civilian areas.

17 And at the same time, in '98-'99-2000 time frame when  
18 we were trying to establish the DoD medical mortality  
19 registry in the medical examiner's office, at that  
20 time we were looking at the cases -- the philosophy --  
21 there wasn't really a policy change but there was a  
22 procedural change and a philosophical change, and the  
23 change was -- the previous philosophy was we do  
24 essentially 100 percent, 95 percent autopsies on  
25 everybody we find out about. But we don't actively go

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1 out and look for cases, we simply wait for people to  
2 call us. And in '98-'99 time frame, with the  
3 establishment of the mortality registry, we changed  
4 that process so that we actually went out and looked  
5 for every single death. And Lisa, since she got there  
6 in 2001?

7 MAJ PEARSE: 2001, yes.

8 COL GARDNER: -- solidified that process  
9 and firmed it up so that there's much better  
10 identification of every single death at the time it  
11 occurs, so now that the medical examiner has the  
12 opportunity to intervene on these cases and do the  
13 autopsies, and there's still a very high, roughly 95  
14 percent, autopsy rate on all military deaths, then  
15 when OIF started, he -- Dr. Mallak insisted on 100  
16 percent autopsies for all OIF cases. And that process  
17 has changed without really a policy change. It's been  
18 more a philosophical and procedural change.

19 Now the question I had for Lisa is, you  
20 described the process of all the information that you  
21 get in from the primarily Army CID and CIS, which is  
22 the Navy investigative service and then OIS which is  
23 the Air Force investigative service. And that's where  
24 you get the information on the circumstances of the  
25 deaths. Something the Board might be able to help

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1 with is -- and needs to get a sense of -- is how good  
2 is the cooperation with all these organizations to  
3 consolidate the investigative information at the  
4 medical examiner's office so that you can get a  
5 complete picture of every death eventually and also in  
6 a more timely way?

7 MAJ PEARSE: I guess my answer for that is  
8 we have the CID agent that is part of our office and  
9 he goes with us to the morgue and he's actually helped  
10 us initiate a protocol to look at armor and we  
11 actually pull out the armor plating and look at what  
12 the serial number is and the make and model of it when  
13 it does arrive with the body so that we can do an  
14 analysis of how protective that is, and we're looking  
15 at the wound entry patterns to see how it relates to  
16 that. He is absolutely key in that process because  
17 the docs don't know anything about armor.

18 He's got good communication with OSI and  
19 NCIS. Those ties are less strong, because they aren't  
20 in our office, but we're able to get what we need.

21 We're not doing full investigation with  
22 full information from the investigators on every case  
23 in DoD, however. That's really reserved for the in-  
24 theater deaths and the cases that have a special  
25 interest -- potential homicide, legal investigation,

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1 overdose, things like that.

2 DR. OSTROFF: Dr. Cline.

3 DR. CLINE: You mentioned that you do a  
4 full pathological analysis on all the deaths.

5 MAJ PEARSE: Yes, sir.

6 DR. CLINE: And it's obvious that the  
7 ground transportation-related deaths are substantially  
8 the highest category. Could you tell us something  
9 about any analysis of those two sets of data -- drugs,  
10 alcohol, any --

11 MAJ PEARSE: No, we are not seeing any  
12 alcohol, we are not seeing illicit drugs in theater.  
13 And I have to qualify that because we started seeing a  
14 small quantity of illicit drugs in the late fall,  
15 early winter. We're seeing a few cases now where  
16 people are coming up high. We saw absolutely zero  
17 until then though.

18 DR. OSTROFF: I forget the sequence. Dr.  
19 Poland was next?

20 DR. POLAND: Going back to what Dr.  
21 Ostroff said about, you know, let's look at the things  
22 that potentially are preventable. Could you say a  
23 little more about the heat injury and heat-related  
24 deaths? I realize that it's a different environment  
25 than recruit training where a lot of attention has

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1       been focused on preventing this, but knowing we don't  
2       have all the details here, but perhaps you do, is  
3       there anything there that is potentially preventable  
4       in terms of, you know, four young men found dead in  
5       their cots?

6                   MAJ PEARSE: We've certainly looked and we  
7       don't have a take-home message on it. The guy with  
8       the hyponatremia was clearly drinking water. The guys  
9       who were just found dead, we don't have enough history  
10      to be able to assess their water intake before they  
11      died. Could better water discipline have made a  
12      difference with them? I don't know. Their  
13      electrolytes, by the time they got to us, there was  
14      enough decomposition that we really couldn't say very  
15      much about them.

16                   MAJ GEN KELLEY: How about the temperature  
17      in the tent?

18                   MAJ PEARSE: They were actually -- they  
19      weren't all in tents. Some of them were actually in  
20      palaces, they were open air. None of them had access  
21      to air conditioning.

22                   DR. OSTROFF: Dr. Shanahan.

23                   DR. SHANAHAN: Dennis Shanahan.

24                   A little change in where we've been, but I  
25      was focused kind of on the limitations issue and Dr.

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1       Pearse's first two points as far as ante-mortem  
2       information and the lack of in-theater medical  
3       treatment.

4                   Comparing that to what Ms. Embrey has  
5       charged us to do and particularly in her item 2, which  
6       is assess DoD's current medical surveillance  
7       capabilities which apparently is a real problem. I  
8       know it's a problem that's been worked on for many,  
9       many years, at least 10 years that I'm aware of. And  
10      I wonder if any of the preventive medicine officers or  
11      anybody else has information on where the automated  
12      processes stand? We were doing a substantial amount  
13      of work to try to automate medical records and have  
14      them transfer with the individual into theater and  
15      outside of theater. And I think in order to answer  
16      question number 2, we're going to need to know the  
17      status of those issues.

18                   COL GARDNER: This is COL Gardner. I  
19      guess I'm the one that has to answer that, because  
20      I've been the one working those surveillance issues  
21      the most.

22                   With the onset of the war, we implemented  
23      an electronic medical records system. The Air Force  
24      had already pretty much throughout the Air Force their  
25      GEM system for electronic medical records. The Navy

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1 had shipboard medical records system, HEALTHSAMS for  
2 shipboard medical care, basically a computerized  
3 patient log. And DoD or Health Affairs, TMA, whoever  
4 you want to call it, has been working for many years  
5 on the CHCS-2 and the TMED process and they were ready  
6 to field on a beta test basis what they call CHCS-2  
7 Theater, which is the outpatient medical record  
8 enhancement. And they were starting to try to field  
9 that.

10 And so what happened is a very rapidly  
11 pulled together interim process using a joint medical  
12 workstation to be a central server to collect the  
13 information on -- electronic information on visits  
14 from GEMS, from SAMS for ships assigned to OIF and  
15 Army midstream literally tried to start implementing  
16 the CHCS-2-T for electronic medical records there to  
17 bring those in. And that system started in January-  
18 February and has collected individual encounters for  
19 probably nearly all of the Air Force visits, the  
20 shipboard Navy visits and probably a small portion of  
21 the Army medical visits and none of the Marine Corp or  
22 land-based Navy visits.

23 In addition to that, we implemented in the  
24 same process an electronic reporting for the disease,  
25 non-battle injury rates, which is a weekly summary of

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1 patient visits for new conditions. And that started  
2 coming in too and we've tracked that very closely  
3 through the same system and we felt that we had about  
4 50 percent reporting from the medical units, an  
5 average of 50 percent reporting from medical units.  
6 We think 70 or 80 percent were report, but not all of  
7 them every week and in terms of visits for disease --  
8 new visits for DNBI conditions.

9 And in addition to that, the theater  
10 implemented a daily reporting in five categories for  
11 DNBI type conditions to try to look for bioweapons,  
12 biochemical weapons type conditions.

13 So we've tracked all of that stuff. Our  
14 implementation of full electronic medical records is  
15 still just beginning and CHS-2 now started their 30-  
16 month rollout process in January, so 30 months from  
17 now every MTF in the military will have full  
18 electronic medical records. TMED started its rollout  
19 during the war and it's still going and that'll take  
20 several years to get -- these are the block 1  
21 capabilities. So that process is ongoing and finally  
22 starting to happen after years and years and years of  
23 anticipation.

24 DR. SHANAHAN: What can we do to re-  
25 energize that process, to try to help energize that

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1 process?

2 DR. GARDNER: I think it's being pushed as  
3 hard as it can be pushed.

4 DR. OSTROFF: Dr. Shamoo.

5 DR. SHAMOO: Thank you.

6 I want to go back to the suicides. I  
7 think comparison with the general population is  
8 fraught with problems because the conditions are so  
9 different, not just age, living conditions, et cetera.

10 But what I wanted to refer to is -- from the Israeli  
11 Army, there have been two studies. The entry mental  
12 status of the soldiers when they enter the service  
13 versus mental illness and suicide rate and they have  
14 found some correlation. I read this a couple of years  
15 ago, for example.

16 The question to you is, Lisa, has there  
17 been any comparison to the entry, when they entered,  
18 to their mental status when they entered the service?

19 Is that information available?

20 MAJ PEARSE: I don't believe it's readily  
21 available and I don't think it's being done at this  
22 time. It would be an interesting study to look at in  
23 the future though.

24 VOICE: Let me add to that a little bit.  
25 We don't typically -- we have not typically in the

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1 past collected mental health status at time of entry.

2 The recruit assessment program, which is a baseline  
3 health surveillance instrument which will be applied  
4 to every new recruit, new officer, is in -- as I said  
5 yesterday during a discussion, we're about at the end  
6 of the second term in delivering this baby. We've got  
7 just one more trimester to go and we should have a  
8 product that will be deployed across the Department of  
9 Defense. It's going to be the same instrument for all  
10 the services, applied in the same way. The data will  
11 then be rolled up and provide a baseline -- this is  
12 exactly what we --

13 DR. SHAMOO: There will be mental status  
14 assessment?

15 VOICE: Yes, it will have a number of  
16 health questions that are answered by the ...  
17 professional, et cetera.

18 DR. SHANAHAN: Thank you.

19 DR. OSTROFF: So that we can try to go  
20 through exactly these types of questions.

21 VOICE: Yes, this is exactly -- the Armed  
22 Forces Epi Board recommended a little over a year ago  
23 that we push this forward and we've been working very  
24 hard to do that. Our biggest problem lately is trying  
25 to get this instrument as a common agreed upon

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1 instrument with all the services. A lot of different  
2 opinions on what it needed to look like as we stood it  
3 up. And then there's a process to get it rolled out  
4 and get the policy done.

5 DR. OSTROFF: And maybe as a new Board  
6 member, what we should do is at least share with you a  
7 copy of the instrument so that you can take a look at  
8 the types of questions it is asking at baseline. And  
9 the whole concept behind it is can you potentially  
10 determine predictors of subsequent outcomes that you  
11 might see amongst the military population. We, for a  
12 long time, felt that it was absolutely essential to  
13 try to have this type of baseline information so that  
14 we can do exactly the type of thing that you're  
15 talking about.

16 Dr. Gardner and then Dr. Berg.

17 DR. GARDNER: Pierce Gardner.

18 The group of us who met on the phone for  
19 awhile about the pneumonias had the problem that  
20 you're having of the sparse ante-mortem information.  
21 We were -- largely these folks were getting the first  
22 real workup or evaluation of information coming to us  
23 in about five to seven days after they'd been on a  
24 cocktail of antibiotics for awhile and no specimens.  
25 And when you're trying to evaluate a patient with

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1 pneumonia, the initial evaluation is really important.

2 Some of the patients were febrile, some of them  
3 weren't. Some of the patients -- we often did know.

4 In your case, you noted on one that they  
5 had a productive cough, and another one, you didn't.  
6 So the person presenting with infiltrate and no fever  
7 or production -- and we were focused on things like  
8 smoking and other things. For the folks who came in  
9 with more traditional pneumonias, we were thinking  
10 more bacterially. About half the patients had  
11 eosinophilia either ... documented five or six days  
12 into their therapy, so we didn't know whether it was a  
13 response or a primary. And in your autopsy, you had  
14 one with and one without.

15 I think the biggest problem for all of us  
16 was trying to get a better sense of what the folks who  
17 made the initial evaluation thought and did and what  
18 they received, and that I think is an area that I  
19 guess Dennis is getting a look at. I think we're all  
20 stuck until we can solve that problem.

21 MAJ PEARSE: One thing that was initiated  
22 fairly recently was a FRAGO, which is an operating  
23 instruction and order in country to prepare an  
24 executive summary -- and this is on the physician --  
25 that goes with the body that describes their clinical

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1 course and the treatment that they received before  
2 they expired. We haven't started seeing those yet,  
3 but that should help improve some of the information  
4 we're receiving.

5 DR. OSTROFF: Dr. Berg.

6 DR. BERG: Lisa, I have three comments.

7 First of all, would it be of any help if a  
8 blood sample were taken in theater after death and  
9 some serum separated and sent back to you? That might  
10 let you get electrolytes and perhaps cardiac enzymes  
11 and other things?

12 MAJ PEARSE: That's not a bad idea. In  
13 fact, that's one of the whole points of the question  
14 to the Board, is what could we be doing that we're not  
15 doing, what would be smart to be doing. We've got  
16 autopsy material. We can collect it, potentially we  
17 can collect it from the field before they get to us.  
18 What else should we be doing.

19 DR. BERG: And my second question is when  
20 you're looking at the suicides, do you have this  
21 broken down by the type of unit that they are? I  
22 remember a year or so ago, there was a lot of concern  
23 about stress and behavioral problems among Army  
24 Special Operations Forces. I realize the whole  
25 theater is very stressful, but are perhaps some units

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1 are under more stress than others. Have you looked  
2 into that?

3 MAJ PEARSE: I haven't looked into it. We  
4 have the data, but I have a lot of data that I haven't  
5 gotten to yet, and there is a whole mental health  
6 assessment team that is spending full time looking at  
7 the suicides, so I backed off of them quite honestly.

8 DR. BERG: Okay. And then my third  
9 thought is do you have any thoughts as to the  
10 practicability of screening people, particularly  
11 reserves and guard personnel before they go overseas?

12 You know, there are 16 cardiovascular deaths -- or  
13 excuse me, six. And you indicated nearly all of them  
14 had a number of significant risk factors and there's  
15 been concern about the fitness of reserve and guard  
16 units. Does that offer any sort of handle  
17 potentially?

18 MAJ PEARSE: I know they fill out a pre-  
19 deployment questionnaire screening and they receive a  
20 physical exam when they come onto active duty. The  
21 details of what's included in that exam, I don't know,  
22 and what would be a show stopper, what would trigger  
23 prevention of a deployment is something else I don't  
24 know.

25 DR. BERG: Thank you.

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1 DR. ZAMORSKI: Mark Zamorski, Canadian  
2 Forces.

3 I think it's important to find out that  
4 those are prevalent risk factors in general. I mean  
5 you have men who smoke and have hypertension and  
6 hyperlipidemia, so it's not so much a question what  
7 the prevalence of those risk factors were in the  
8 people who died, it was, you know, what was the  
9 prevalence of risk factors in all those people who  
10 didn't die, in a sense. I'm not sure for that  
11 particular illness that screening on the basis of risk  
12 factors is going to be terribly helpful.

13 DR. BERG: It may or may not be, but one  
14 of the charges is to sort of figure out are there  
15 things we can do. And the effort may come to nothing,  
16 you may be absolutely right.

17 COL GARDNER: This has been a big issue,  
18 the pre- and post-health assessments and there's been  
19 tremendous effort on this.

20 The real emphasis really didn't start  
21 until February-March after a lot of people had gotten  
22 over there, but that pre-deployment health assessment  
23 is where you sit down with an individual and determine  
24 that they're -- and every one in theory has to be  
25 signed off by a medical provider to say that he is

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1 able to go. And so if they're pregnant or if they're  
2 HIV-positive or if they have serious medical  
3 conditions, they wouldn't be allowed to go. In the  
4 reserves, about 10 percent weren't allowed to go,  
5 through the pre-deployment process.

6 We know there are slipups, we know there  
7 are people who arrived -- and fortunately most of  
8 those people who arrived inappropriately were screened  
9 on the other end when they got there and turned around  
10 and sent right back. Somebody who arrived with their  
11 chemotherapy in hand or two most post-heart surgery  
12 was immediately sent back.

13 The problem is this is not a medical  
14 decision. The medical review and pre-deployment  
15 assessment is a recommendation to the commander. When  
16 the unit commander says this guy is my executive  
17 officer and I can't live without him, he's going  
18 anyway, then we can't stop it. Of course, when they  
19 get on the other end, the command -- the theater  
20 commander says no way, we're not taking him and sends  
21 him back. So that process has worked fairly well.  
22 But about 10 percent of the reserves were screened  
23 out.

24 Coming home, I guess we enhanced the  
25 process of screening people coming home so that they

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1 now have a longer -- a mandatory visit with a medical  
2 provider to review an extensive list of questions and  
3 issues and make sure that they get into proper medical  
4 follow-up. And we've now tracked about 300,000 of  
5 these post-deployment health assessments as they come  
6 back.

7 COL UNDERWOOD: Yes, thank you. COL  
8 Underwood.

9 We're also working at the service level  
10 and the DoD level on quantifying the individual  
11 medical readiness parameters, which includes dental  
12 readiness, includes vaccine status, includes physical  
13 readiness. And also Kelly Woodward sits on that DoD  
14 level, he might comment about that.

15 But you're probably well aware of what  
16 happened at Fort Stewart, that was very much in the  
17 news in terms of the large medical hold population.  
18 COL Gardner referred to this in terms of reserve and  
19 national guard coming to be deployed, who were  
20 subsequently found not fit. And then initially they  
21 were not able to be sent back home, they had -- were  
22 kept on active duty until their medical problems could  
23 be resolved, but this was very much in the news in  
24 terms of the large population that was there with pre-  
25 existing medical conditions which made them unfit for

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1 deployment.

2 COL GIBSON: This is COL Gibson. Can I  
3 add one other part to that. The members of the  
4 reserve sign a certificate -- they have to certify  
5 their fitness for duty on an annual basis. Until  
6 recently, I thought that we had -- the bulk of the  
7 problems there were people who didn't identify that  
8 they had a problem, because if they did, they would be  
9 removed from their billet. I've since found out,  
10 sitting on a couple of other committees, that in some  
11 cases these individuals do report that they have a  
12 physical problem and their commanders, the personnel  
13 system, leaves them in that billet because they need  
14 to stay at 100 percent or 95 percent of capacity, et  
15 cetera.

16 So this is a complex issue. There's a lot  
17 of attention being brought to it right now within the  
18 personnel community, as to how to properly deal with  
19 these things.

20 DR. OSTROFF: Other comments?

21 DR. PATRICK: I'm struggling with this  
22 notion -- get back a little bit I guess to what Dennis  
23 was talking about, and that is the second point,  
24 assess the current medical surveillance capabilities  
25 on early and complete assessment.

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1           And in part, what I want to envision is a  
2 model by which each one of these components that's  
3 potentially -- that can potentially be improved, from  
4 ante-mortem data to medical records and whatnot, is  
5 somehow displayed and then broken down in a way that  
6 we know how to essentially tackle the particular  
7 issues that are within each one.

8           Who is responsible for developing such a  
9 model and essentially portioning out the authority and  
10 responsibility to tackle the surveillance and then  
11 intervention strategies that might be embedded within  
12 such a model? I'm hearing bits and pieces in various  
13 places and lots of important information, but is it  
14 your office, John?

15           COL GARDNER: Yeah, I'm the one that  
16 always seems to end up getting --

17           DR. PATRICK: Our only way to assess this  
18 would be to look at that model and then get some  
19 estimation of the level of fidelity or the level of  
20 quality that each one of the components of that is  
21 being addressed at a point in time and then, you know,  
22 when one works from those kinds of things, you think  
23 well, what's possible, what will we really see as an  
24 ideal here in terms of the -- even the length of time  
25 that we would like to have the fatality information

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1 back, fed into the system, so that we can actually say  
2 whoops, that might be a sentinel event because there's  
3 a pattern emerging.

4 So I'm wondering if we can ask as a Board  
5 to really see that and then ask well, how are we doing  
6 on each of these components.

7 COL GARDNER: I've been working on that  
8 very issue for a year and a half and trying very hard  
9 with a team to try to deal with the issues of  
10 integrating the whole surveillance capabilities. And  
11 each service has their own ways of doing things and  
12 there are dozens of different systems out there doing  
13 lots of different things and I've been working to try  
14 to integrate that with a team and I've got a report  
15 we're just finalizing right now that makes  
16 recommendations of how to pull it together and I'll  
17 give you a copy.

18 But in spite of the system not being  
19 perfect and being disjointed, there's still a lot  
20 going on. For example, in June -- you mentioned the  
21 stress issues, in June we noticed the mental health  
22 visits for DNBI jumping 10, 20 fold and once that was  
23 looked into, it turned out that this was a localized  
24 problem in one division that had been told they were  
25 going home at the end of June and then mid-June, they

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1 were told guess what, you're not going home for two or  
2 three more months. And suddenly the mental health  
3 visits skyrocketed. And they sent mental health teams  
4 over to try to deal with those issues and so on, and  
5 they started an R&R policy and so on in response.

6 So there are a lot of problems, it's  
7 disjointed but there's still a lot going on and  
8 there's a lot of -- this stuff is really being tracked  
9 fairly closely even though we don't have at our  
10 fingertips the data that we need. It's kind of ad hoc  
11 at times and we're trying to pull that together.

12 DR. PATRICK: Well, it seems to me that by  
13 definition, this is going to be something that's going  
14 to be very hard to sort of wrap our minds around.

15 COL GARDNER: It's really complex.

16 DR. PATRICK: But I think seeing at least  
17 a first draft of what the various components are --  
18 because I heard the comment from what Bill had said,  
19 you know, would it be helpful to draw blood tests and  
20 get serum values -- well, yeah, that's exactly the  
21 type of advice we need. But this is one of those  
22 things that just has way too many variables to contain  
23 in your head and you basically have to depict this,  
24 break it down and then look at each one of these  
25 components I think in a way. So I think it would be

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1 very instructive as a Board, if we're to answer this  
2 question, we need first to describe what the process  
3 is and then figure out what components could be  
4 improved.

5 At the next meeting, if we could see,  
6 maybe you could take a stab at okay, this is what it  
7 looks like end to end and these are the components and  
8 these are the people who are responsible for it. That  
9 would be very instructive.

10 COL GARDNER: I think you've brought --  
11 the question that came forward was just related to  
12 mortality and my answer was related to everything  
13 else. I think that mortality is where we have done  
14 extremely well and Lisa just -- I mean there's nobody  
15 in the world who can match 100 percent accountability  
16 and 100 percent autopsies, 100 percent investigative  
17 reports. We've done extremely well. It's in the  
18 other areas that we haven't done as well. Now we do  
19 track, as I said, DNBI, we do track vacs out of  
20 theater and we do track, you know, the wounded in  
21 action and the safety stuff. So there's a lot of  
22 stuff being tracked but there are a lot of holes that  
23 we have to have ad hoc solutions to, and that's what  
24 we're trying to fix.

25 DR. OSTROFF: And that would be my sort of

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1 follow-up comment, is that your data I think are  
2 spectacular and I think that they are largely  
3 believable. I don't see anything in the mortality  
4 data that really stands out in terms of particular  
5 sentinel events that would cause us to make  
6 recommendations or make suggestions that there are  
7 some unusual patterns of illness and injury going on  
8 in the DNBI category. The problem is that mortality  
9 in this circumstance is always a relatively  
10 insensitive way to be able to determine if there is  
11 some particularly problematic pattern of illness going  
12 on. And I certainly would like to hear a little bit  
13 more about the types of things that you were just  
14 describing, to give us a better sense as to whether or  
15 not there may be something going on in theater that,  
16 from our perspective, would allow us to develop the  
17 sort of intervention that would help minimize that.

18 COL GARDNER: I would welcome your support  
19 in that process. We really need to generate the  
20 political will to make things happen. There's a lot  
21 of stuff going on piecemeal, but bringing it  
22 altogether requires a unified approach that has buy-in  
23 from all sectors. And getting that buy-in from all  
24 sectors is not easy.

25 DR. OSTROFF: It's the issue of are there

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1 a lot of medivacs for cardiac related difficulties and  
2 if you're just looked at the six atherosclerotic  
3 related fatalities, you may well be missing a fairly  
4 large problem.

5 COL GARDNER: We just commissioned three  
6 studies. One that we're at the beginning of is what  
7 Dr. Pearse has done with deaths and one is the track  
8 and review in more detail all the DNBI data from the  
9 war and all of the medical evacuations. We have  
10 roughly 500 deaths, we have roughly 2500 non-fatal  
11 injuries, wounded in action, safety accident cases and  
12 then we want to look at each one of those individually  
13 and look at the medical and circumstantial issues for  
14 each of those. And then we have roughly 12,000  
15 airvacs from theater and we want to look at each one  
16 of those individually and look at the medical issues  
17 related to those too. And so we've just commissioned  
18 those studies to be done over the next six to twelve  
19 months.

20 COL RIDDLE: I think one thing, Dr.  
21 Patrick, is last year, remember the Board made  
22 recommendations on a standard investigative protocol  
23 to include non-attributional investigation of leave  
24 circumstances surrounding medically related fatalities  
25 when we were looking at that sickle cell trait issue.

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1       And probably it would be good to see what work has  
2       been done on that, to take a look at it, to address  
3       the issues like you and Dr. Berg brought up, and when  
4       we're just specifically looking at medically related  
5       deaths or death investigations, are we getting the  
6       right samples at the right time to be able to answer  
7       the questions.

8               I'll check with Commander Mallak to see  
9       what progress that they've made, to see if we can get  
10      a copy of that and make sure that it's codified in  
11      policy as opposed to at the discretion of one medical  
12      examiner.

13             DR. PATRICK: Part of my question also is  
14      how timely and if we're looking at sentinel cases and  
15      attempting to determine -- sort of close the loop  
16      fairly quickly in sort of a quick epi analysis, that's  
17      part of the dimension, is time. So again, you know,  
18      you build those systems based upon how quickly do you  
19      think we can get it and you feed it forward based on  
20      your best estimates, because I think this is something  
21      that's going to improve over time and we just have to  
22      start someplace.

23             COL GARDNER: Can I just make one  
24      clarification? Whenever I quote those numbers, they  
25      always get misinterpreted, so I think to clarify that.

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1 We have roughly 500 deaths, we have roughly 2500  
2 wounded, official wounded in action. Of those, a  
3 third were returned to duty within 48 hours and so in  
4 terms of serious injury, we're well below 1500. We  
5 have roughly 12,000 medical evacuation from theater.  
6 Only 300 or 400 of those were urgent evacuations and  
7 1000 were immediate evacuations. The rest were  
8 routine. We've had the press accuse us of hiding  
9 12,000 serious injuries from the war because we don't  
10 announce those, and in fact people need to understand  
11 that airvac out of theater is routine medical care for  
12 us. Some of those are women who had a Pap smear  
13 before they went and then they got the results back  
14 that it was abnormal and need to be worked up. We  
15 can't do that in theater, we've got to vac them to  
16 Landstuhl and send them back. So the airvac out of  
17 theater to Landstuhl is -- at least 1000 of those went  
18 back, right back to theater. And that's kind of no  
19 different than you being sent to a specialist across  
20 town, for us.

21 DR. OSTROFF: Well, I think that the Board  
22 would be very interested in some of the -- we need to  
23 be briefed on some of the analyses that are being  
24 done, particularly around the significant ..., so I  
25 would make a request to both COL Riddle and COL Gibson

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1 that we try to arrange ....

2 Thanks very much for your presentation and  
3 for all the good work that you're doing.

4 Before we break and then go to executive  
5 session, I'd like to make a little observation of the  
6 schedule. We're going to do this later on in the  
7 afternoon, but I think it's best that we do it before  
8 everybody breaks.

9 There are three members of the Board for  
10 which this will be their last meeting. As is  
11 traditional for our Board at our meetings, when we  
12 have members that are departing, we do acknowledge  
13 their good work and the effort that they've put  
14 forward. There are two of the three departing Board  
15 members that are here -- I'm sorry -- two of the three  
16 departing Board members are here and we'd like to do  
17 the presentations now. The third, Linda Alexander,  
18 couldn't make it to this particular meeting, and we'll  
19 make sure that we get her the appropriate  
20 acknowledgement after the fact.

21 The two members of the Board that are here  
22 are Dr. Gardner and Dr. Berg. So let me head up to  
23 the podium where COL Riddle is and we'll do the  
24 presentation.

25 COL RIDDLE: Dr. Berg, on behalf of the

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1 Armed Forces Epidemiological Board, we'd like to  
2 present you with this plaque in recognition of your  
3 outstanding service to the AFEB, and as a member of  
4 the AFEB from March 2000 to March 2004.

5 (Applause.)

6 COL RIDDLE: We also have a Certificate of  
7 Appreciation signed by The Honorable Dr. William  
8 Winkenwerder, Jr., Assistant Secretary of Defense for  
9 Health Affairs.

10 For exceptionally meritorious service and  
11 outstanding contributions as a Member of the Armed  
12 Forces Epidemiological Board from March 2000 to March  
13 2004. As an AFEB member, your superb leadership,  
14 excellent organizational skills, and outstanding  
15 professional knowledge contributed significantly to  
16 the promulgation of numerous important policy and  
17 program recommendations for the Department of Defense.

18 Your contributions have significantly enhanced the  
19 health and wellbeing of soldiers, sailors, airmen,  
20 marines, DoD civilians, and their families.

21 (Applause.)

22 DR. OSTROFF: Lastly, you will get a coin  
23 and we'll guarantee that after you leave we'll make  
24 sure that we keep the Navy on their toes in terms of  
25 their surveillance data because we knew every meeting

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1 that you came to, that was always an issue for you.

2 DR. BERG: I've gone through one Navy  
3 representative and I see we have a new one, so I was  
4 going to ask a question. Of all the committees, task  
5 forces, work groups, et cetera that I've been on, this  
6 has been the most outstanding one. It has brilliant  
7 people on it who roll up their sleeves and know what  
8 to do and despite all of the complexity we sometimes  
9 get into, I get a tremendous sense of satisfaction out  
10 of what we produce. And I think that is recognized by  
11 the award we got last year.

12 So it has been a wonderful privilege and  
13 honor to work with all of you.

14 DR. OSTROFF: Thanks, Bill.

15 (Applause.)

16 DR. OSTROFF: Next we have Dr. Gardner,  
17 another member of the Board who has made outstanding  
18 contributions over the last several years. Our  
19 veritable font of knowledge concerning vaccine issues  
20 and we will dearly miss you.

21 COL RIDDLE: Dr. Gardner, on behalf of the  
22 AFEB, we present you with this plaque in recognition  
23 of our outstanding service to the Board, serving as a  
24 member from March 2000 to March 2004.

25 We also have a Certificate signed by The

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9 the promulgation of numerous important policy and  
10 program recommendations for the Department of Defense.

11 Your contributions have significantly enhanced the  
12 health and wellbeing of soldier,s sailors, airmen,  
13 marines, DoD civilians, and their families.

14 (Applause.)

15 COL RIDDLE: And Dr. Gardner, being a  
16 glutton for punishment, has actually volunteered to  
17 come back as a consultant and we hope to bring him  
18 back and help out with addressing our issue on  
19 multiple immunizations.

20 DR. OSTROFF: Any comments?

21 DR. GARDNER: I certainly thank you. It's  
22 good to go out with Rick, I think he's done such a  
23 terrific job, I'm in good company and Steve and Rick  
24 have really made this just a great pleasure to be here  
25 and I think we -- I find great pleasure in the fact

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1 that we've worked so well together.

2 Thanks so much.

3 DR. OSTROFF: We'll miss you.

4 (Applause.)

5 DR. OSTROFF: Besides COL Riddle, there's  
6 one more individual for whom this is their last  
7 meeting and that's COL Jones. For the last couple of  
8 years, he's done an able job representing the joint  
9 staff and we'd like to take the opportunity to also  
10 acknowledge you and we have a plaque and a certificate  
11 for you as well.

12 (Applause.)

13 DR. OSTROFF: And you get a coin too.

14 COL RIDDLE: So Dave, certainly on behalf  
15 of myself and the Board, we present you with this  
16 plaque and certificate in recognition of your  
17 outstanding service to the AFEB, a friend to the AFEB  
18 and a friend to us all.

19 We wish you well. I think Dave's going to  
20 retire, come back down to Florida, leave the joint  
21 staff and retire down here with his family. He served  
22 the Board from May of -- actually from May of 2001 to  
23 March 2004 and again, please accept our deepest  
24 appreciation for the outstanding contributions. Thank  
25 you.

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1 (Applause.)

2 DR. OSTROFF: And just to close the loop,  
3 even though we acknowledged Rick earlier in the day,  
4 we also have a plaque for you.

5 (Laughter and applause.)

6 DR. OSTROFF: I'll miss you.

7 Okay, why don't we go ahead and take a  
8 break and then we'll come back in executive session  
9 which is for the Board members as well as the  
10 preventive medicine liaisons and why don't we plan to  
11 be back here in 15 minutes, five minutes to five.

12 (Whereupon, the session was concluded at  
13 4:40 p.m.)

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