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ARMED FORCES
EPIDEMIOLOGICAL BOARD
AND
NCID BOARD OF SCIENTIFIC COUNSELORS

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CAPITAL HILL REPORTING
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1 DR. HENDERSON: We have some handouts
2 going around. We would like to introduce Dr.
3 Zajtchuk, our host, I guess, and would like to say a
4 few words and thank you very much for inviting us
5 here.

6 DR. ZAJTCHUK: I would like to welcome you
7 all here and to thank you for all the support and
8 getting it passed.

9 And I'm very much familiar with it, since
10 I helped edit the two textbooks, books, on
11 epidemiology board that some of you may have seen
12 and to thank you in advance for continuing to help
13 us.

14 We are looking forward to the expectation
15 of you helping us in this particular issue, which
16 has to do with smallpox and many other issues.

17 We appreciate that you give us guidance as
18 to where we should be going in the future.

19 I know there is a difference of opinion
20 about this particular subject matter that we are all
21 meeting about. I have my own personal feelings.

22 I happen to be familiar not just to what I
23 read in the papers, unclassified or classified, but
24 otherwise, if you destroy the smallpox vaccine here,
25 that this doesn't necessarily mean you will

1 eliminate it from the world market. I'm sure you
2 are familiar with all of that.

3 But that's for you to decide and give us
4 the advice and to Dr. Joseph who is very much
5 interested in the subject matter.

6 So again, I am going to go into -- we are
7 going to bring you up to date with all that is going
8 on over here.

9 But again, many thanks to you. But please,
10 whatever we can do to make your visit here
11 comfortable and interesting, if you have some time
12 and want to visit our other areas here, we are quite
13 very active now in advanced technology and internal
14 medicine.

15 And there is an office here which deals
16 with all of that. You are welcome to go and visit
17 that, if you have some time.

18 So thank you again, and I will keep in
19 touch.

20 DR. HENDERSON: I think the choice to put
21 the classified briefing first, without the
22 scientific presentation, was successful.

23 But we really now want to turn to the
24 keynote of the morning in terms of Dr. Mahy's
25 remarks, filling us in on all the background we have

1 not heard so far, I would hope. Thank you.

2 DR. MAHY: Okay. I've chosen not to
3 present slides and just do a board here, if you are
4 going to take any notes.

5 What I would like to do is just go back
6 over the history of where we are now and why we are
7 in the situation and what we are discussing and give
8 you some idea of why the HHS perspective developed
9 the way it did.

10 Some of you will know a lot of this, and
11 some of you won't. But please interrupt, if there
12 is anything you want to know.

13 The last case of natural case of smallpox
14 occurred in Somalia in 1977. That was a culmination
15 of essentially a ten-year campaign of eradication in
16 which several people here, particularly D.A.
17 Henderson, was very closely involved.

18 And it is fair to say, I think, that the
19 entire cost of that smallpox eradication campaign
20 was saved with a single year's vaccine cost in the
21 USA alone. So it is quite dramatic.

22 The economic effect of eradicated a
23 disease, a vaccine-preventable disease, is
24 astounding. I could give you similar figures for
25 polio, which is currently in progress now. And

1 measles is also scheduled hopefully for eradication
2 to follow on polio.

3 So there is enormous benefit in
4 eradicating a disease and an enormous economic
5 benefit. One of the problems arose a year after
6 eradication had been completion.

7 It was in Birmingham in England, where
8 Dr. Henry Bendson had a laboratory that was working
9 on smallpox in the University of Birmingham.

10 It was visited by an MRC committee, who
11 advised him that the conditions of the laboratory
12 were not really adequate to contain smallpox. But
13 nevertheless, he was continuing doing some last
14 minute experiments.

15 And in a very dramatic and very nasty
16 incident, which occurred in 1978, in fact
17 immediately prior to the International Congress of
18 Biology that was held in the Hague that year, the
19 virus infected a person in a room somewhat distant
20 from the laboratory in which work was going on.

21 The explanation as to how this occurred
22 has never been entirely satisfactory, but it's
23 likely to have been transmission of the virus
24 through air ducts. And that person, Janet Parker,
25 eventually died of the disease.

1 She infected her father, who died probably
2 not of smallpox but of another condition, and her
3 mother. And her mother was the last person that we
4 know of to have been infected with smallpox, and her
5 mother survived.

6 The tragedy, of course, was that Henry
7 Bendson himself committed suicide actually before he
8 had even -- before Janet Parker died, as soon as he
9 realized what had happened.

10 What that illustrated, I think, to
11 everybody was the extreme difficulty of maintaining
12 work on a virus that is very highly infectious in
13 laboratory conditions that were not adequate.

14 And so WHO over a period of four years or
15 so recommended that there should be consolidation of
16 the smallpox virus stocks that were held. And at
17 that time, there were 17 to 20 laboratories around
18 the world that were actively working with different
19 repositories and strains.

20 And the number of repositories was
21 gradually reduced until eventually it was agreed
22 that there would only be two repositories, one in
23 Moscow, where a lot of work had been done during the
24 smallpox campaign led by Dr. Maranikova (phonetic)
25 that we've already heard mentioned this morning, and

1 one in Atlanta, where Jim Nacarno, who was Joe
2 Esposito's predecessor, was running a smallpox
3 laboratory there.

4 And those two sites were chosen, I think,
5 partly because of their great expertise in the area,
6 but I think also they represented in some way the
7 East/West difference at that time.

8 The Moscow laboratory eventually acquire a
9 number of collections, including collections from
10 Asia and from related states and a number, if you
11 like, Eastern Bloc states.

12 And the collection that came to Atlanta at
13 that time primarily included the collections from
14 the Netherlands, from Japan and from the United
15 Kingdom.

16 There was some resistance for a while by
17 the Department of Defense in releasing their stocks,
18 but they eventually were moved also to Atlanta to
19 the repository.

20 And subsequently, the American type
21 culture collection also deposited their smallpox
22 strains in the repository in Atlanta. So all of the
23 U.S. stocks were put into that repository.

24 The nature of the division and the way it
25 was done at the time certainly was one in which the

1 collection that we have in Atlanta is essentially an
2 internationally controlled and monitored collection.

3 And I think it is probably wrong to think
4 of this conceptually as being the U.S. stock. It
5 essentially is a collection of viruses that was put
6 there by WHO and which has been subsequently always
7 monitored by WHO.

8 So this essentially was the two
9 repositories.

10 In 1986, there was an important meeting of
11 the committee of WHO that deals with smallpox, which
12 is known as the Committee on Orthopox Virus
13 Infections.

14 And at that meeting, there was a lot of
15 consideration given to some new technologies that
16 have been developed, especially by Joe here, Joe
17 Esposito and his group at CDC.

18 I passed out two manuscripts relating to
19 this. And this was when restriction mapping had come
20 in, and it was possible to use certain enzymes, such
21 as ND3.

22 So that you could begin to differentiate
23 quite easily the viruses which were highly virulent,
24 the variola-type viruses, from those other viruses,
25 such as vaccinia. And Joe did a lot of very elegant

1 mapping studies in which he showed that this was the
2 case.

3 This was, I think, partly the basis for
4 the committee decision in 1986. They made the first
5 recommendation that all the stock should now be
6 destroyed because the techniques for diagnosis were
7 now adequate.

8 And if the virus was to appear somewhere,
9 we would be able to detect it by this procedure. At
10 that point, there was a recommendation made to
11 destroy these virus stocks as soon as possible. It
12 was recommended destruction at that time.

13 In 1989, I came to the CDC, and one of the
14 first things I did was to meet with D.A. Henderson,
15 Tom Monoth (phonetic), a number of other people that
16 were concerned at the time in a group that was
17 essentially a joint U.S./USSR group of academy
18 scientists.

19 We had a meeting, and we discussed the
20 feasibility at that time that rather than continuing
21 to rely on the restriction mapping techniques that
22 Joe had developed, that we should actually determine
23 the complete sequence of the virus.

24 And that having done that, we would have a
25 much better record of smallpox before it was finally

11
1 destroyed.

2 That was, I think, a very useful meeting.

3 It was attended by several Russian heads of
4 institutes, as well as people like Joshua Lederberg
5 was there. And we all agreed that once we had this
6 genetic sequence, it would be a good idea to destroy
7 the virus.

8 I also came at that time here to this
9 conference room and gave a presentation about what
10 we intended to do and what our outline was in terms
11 of sequencing. And this was really when the
12 sequencing project was conceived.

13 Then in 1990 at the World Health Assembly,
14 Secretary Louis Sullivan made an announcement which
15 essentially had developed through our discussions
16 with James Mason, who was the Assistant Secretary
17 for Health at the time.

18 And he had persuaded Louis Sullivan that
19 the time was right for us to stand up and say that
20 we were going to destroy the smallpox virus. And we
21 essentially invited the USSR to do the same thing.

22 So that was a very critical time. That
23 was -- and that was at the WHO in Geneva. And this
24 was the announcement by Louis Sullivan to destroy
25 the virus.

1 Now, that essentially has remained the
2 position, the official position, if you like, of
3 Health and Human Services since that time.

4 And it's clear to say that his statement
5 that he invited the USSR to do the same was followed
6 up with an attempt on the part of us at CDC to
7 collaborate closely with those people in the USSR
8 who were involved in work with small pox. And it
9 turned out that other than the repository, which was
10 maintained under admittedly bad conditions -- I
11 think all of us have been over there and seen that
12 repository.

13 And those of you who got that article I
14 put out from The New York Times can see some
15 pictorial information -- it was a pretty rundown
16 place in Moscow with poor security.

17 There was a lot of subsequent letters from
18 people in The Chicago Tribune and elsewhere about
19 the fact that this is not a good facility.

20 But at the time, it turned out that the
21 genetic group that we wanted to collaborate with on
22 sequencing was the group in Koltsovo Institute in
23 Novo-Sibirsk.

24 And we became in contact with those
25 people, and we began to develop a collaboration

1 which involved partly the Institute for Virus
2 Preparations and partly those people in Koltsovo.

3 I want to just give you some idea of how
4 we conceived the project at the time. I know it's
5 only five years ago, but it was really quite a
6 formidable task we were undertaking, because we knew
7 that we were talking about determining about 200,000
8 base pairs of DNA, and at the time only one or two
9 herpes viruses in sequences. And that would have
10 taken quite a number of years.

11 But we estimated that we could do this one
12 in three years, and a date was essentially put on
13 the destruction by committee that met later that
14 year in WHO. On December 31 -- they set a date of
15 December 31, 1993.

16 That was the WHO Orthopox Committee that
17 considered our scheme, considered what we might be
18 able to do. And we have that today.

19 We collaborated with the -- Joe Esposito
20 spoke to Dave Botski (phonetic) and other people who
21 were involved in the human genome project.

22 And we got in touch with Craig Venter
23 (phonetic), who at the time was working at the
24 National Institutes of Health and was probably the
25 most advanced in terms of automated sequence

14
1 analysis.

2 So we collaborated with him. He has
3 subsequently, I think most people know, left the
4 government and now has his own institute, the
5 Institute for Genomic Research, in Gaithersburg.

6 But we collaborated with him throughout
7 the project, and certainly at many of the early
8 stages, they were able to transfer technology,
9 particularly to Joe's lab.

10 And we ended up with a very, very nice
11 transfer of sequencing, which in fact has had
12 effects in the whole of our division at CDC.

13 Obviously, we do work with many, many
14 other viruses and smallpox, but there has been a
15 tremendous advantage, I think, in getting that
16 technology brought over. So that was one very good
17 plus from the project.

18 The project went extremely well. And by
19 the time Craig Venter was leaving the government, we
20 were already almost finished the complete sequence
21 of a strain that had been agreed by WHO as the first
22 one to do. And this was a strain that is known as
23 the Bangladesh 75.

24 And the reason for picking that strain was
25 that it was the last well-documented strain isolated

1 fairly near the end of the smallpox era in 1975,
2 which was known to be highly virulent and under the
3 name of virulent major strain.

4 We had a certain list of priorities that
5 we agreed at that WHO meeting, and we agreed that a
6 good idea would be to compare this strain with a
7 minor strain. The sequence of vaccinia, which is
8 the vaccine for smallpox, of course, was already
9 determined by Enzo Piretti's group in Troy, New
10 York.

11 So a second strain that we agreed to try
12 to sequence was a strain called Garcia. It has
13 already been mentioned this morning.

14 And the Garcia strain, it was agreed that
15 the Russian group would take that as their primary
16 responsibility. And subsequently, it took nearly
17 two years in order to get the DNA of that strain to
18 Novo-Sibirsk.

19 And in the meantime, the Russians were
20 working with another strain, which was called India.

21 We know it as India 1967. And they had already
22 obtained a lot of sequence analysis by a very, very
23 laborious method nowadays, known as the Maxim-
24 Gilbert method.

25 And they had essentially gone into an

1 enormous amount of work obviously in doing this, but
2 they had produced a strain.

3 And the person who was primarily involved
4 in that work was a man called Sergei Shchelkunov
5 (phonetic).

6 DR. CASSELL: Was the choice to do the
7 Indian strain -- this was a recommendation, also, by
8 the

9 DR. MAHY: No.

10 DR. CASSELL: -- this was just --

11 DR. MAHY: No. The India strain we always
12 knew would be likely to be somewhat similar to the
13 Asia strain. And had we gone -- this strain, for
14 example, represents a Latin American strain, a South
15 American strain. So this is Asia and this is South
16 America.

17 We were trying to get some geographic
18 information. Here we are back to Asia again. So
19 our recommendation was to go to African strains as
20 also of interest.

21 And there are several of those that have
22 been looked at. One for sentimental reasons is the
23 Somalia, the last strain, which Joe can tell you a
24 lot more details about this, but it is not important
25 here and now.

1 There was a strain also from Sierra Leone,
2 and there were several strains that had already been
3 cloned in sequence but where the origin was a little
4 bit unclear.

5 And we were concerned that we -- we wanted
6 to a well-documented strain. There is one called
7 Harvey -- that would be a minor strain -- and
8 Butler. And these strains were strains that had
9 been isolated that had, if you like, a complicated
10 history.

11 We weren't absolutely certain exactly
12 where they originated, but we have seen -- they had
13 originated in Africa. I think Harvey was actually
14 acquired from somebody in Gibraltar.

15 So anyway, the India strain came in
16 because it was already being worked on and because
17 they already work continuing. And we worked with
18 this man, Sergei Shchelkunov, and he has been a
19 frequent visitor to CDC.

20 And, in fact -- if you want to put that
21 one out, Joe -- we have a recent publication, which
22 is a direct comparison of these two strains.

23 From the point of view of technical
24 sequence information, I would point out that this
25 strain finally turned out to have 186,103 base

1 pairs. And the India strain was never totally
2 completed.

3 The only strain we have completed was the
4 one done in Joe's lab, because the ends of the virus
5 are very, very hard to sequence. Those are very
6 difficult.

7 So they have about 185,778 base pairs from
8 India, which essentially contained all of the
9 essential parts of, you know, all of the codings,
10 and all of that virus.

11 And so this is a recent publication that
12 came out this month with the people in Novo-Sibirsk,
13 which essentially compares those two sequences. And
14 as you can imagine, they're pretty similar.

15 There has also many, many other
16 publications on the India strain. Most of them are
17 listed in that article, so you can get them from
18 there.

19 Now, the other work that has been done is
20 to -- because the Garcia strain was a request of WHO
21 and because there was no money, we were asked on
22 several occasions to fund work in Novo-Sibirsk on
23 this Garcia project.

24 And finally, CDC put together \$75,000,
25 which we sent to WHO. And WHO then meted it out to

1 the institute in Russia on basically a nucleotide
2 cost basis.

3 So we said, "Well, if you would do another
4 1,000 nucleotides, you will have" --

5 DR. RUSSELL: Base by base. Well, how
6 much per base was it?

7 DR. MAHY: So that is the way Garcia has
8 been done. I don't want to go into a lot more
9 detail on that.

10 DR. CASSELL: Can I just -- for
11 clarification purposes, you are saying that there
12 were sufficient monies to continue to work with the
13 Indian strain but not the Garcia strain at the WHO
14 requested that the work be done on?

15 DR. MAHY: Well, I mean, they have
16 continually complained of not having any funding.
17 And we have had all sorts of requests from them.
18 Dr. Nedasov (phonetic) has been over several times
19 to see us, and we have had a lot of contact with
20 people there.

21 But essentially, for smallpox the requests
22 have come mostly through especially Morris Hillerman
23 at MERC (phonetic), who several times went over to
24 Novo-Sibirsk and was interested in their research
25 and was trying to help them get funded.

1 DR. HALVORSON: Brian, if they had had the
2 Garcia strain, do you think they would have started
3 on that earlier?

4 DR. MAHY: If they had not had this, you
5 say?

6 DR. HALVORSON: Yes. You said they did
7 not have it for several years. It took several
8 years in order to get the DNA sent over.

9 DR. MAHY: Yes.

10 DR. ESPOSITO: They initially -- we
11 produced some clones in collaboration with Horton
12 Laboratory in England.

13 DR. MAHY: Right.

14 DR. ESPOSITO: So part of the genome was
15 available in the way of clones. Peter Greenway
16 provided those clones to them early on, so they had
17 some starting material.

18 What we did was then to produce some DNA
19 so the entire genome so that both of us would have
20 the entire genomes involved. They did have some
21 material in the way of cloning.

22 DR. MAHY: I think another thing that
23 illustrates is that that was -- that growth of
24 virus, in order to produce that DNA occurred in 1991
25 and essentially was the first time for certainly

1 seven years, six or seven years, that we had
2 actually grown any virus at CDC.

3 And since that time, we have not had a
4 major growth of -- in order to prepare stocks of
5 DNA. So in other words, the repository has been
6 largely dormant.

7 Now this information is still going on,
8 still be accumulated with one or two other
9 collaborators around the world, especially Jeffrey
10 Smith at Oxford.

11 He started sequencing the African strain,
12 which we had already done some sequencing on, the
13 Congo, which Joe has cloned.

14 So there's been quite a lot of information
15 which is still being produced. And one or two
16 laboratories around the world are working with DNA
17 clones.

18 There is a record at WHO of which
19 laboratories have clones of the DNA. And there are
20 certain rules and regulations, such as you are not
21 supposed to have any work with vaccinia virus going
22 on, obviously, in the laboratory in which the clones
23 are used and so on.

24 DR. RUSSELL: How many laboratories are
25 there, do you think, that have clones? Half a

1 dozen?

2 DR. MAHY: We can give you a list, but I
3 think it's about six or seven.

4 DR. ESPOSITO: Seven or eight, yes.

5 DR. MAHY: It is not very many. And the
6 funding for this, again, has partly been from CDC.
7 We have funded to some extent Jeff Smith's work and
8 so on as much as we can.

9 We essentially have no more money now, but
10 we have been trying to get as much information as we
11 could.

12 DR. CASSELL: Brian, you said that you
13 cannot have vaccinia work going on in the same lab
14 where you are doing the sequencing.

15 DR. MAHY: Well, it's clear that
16 introducing virulent strains of smallpox into
17 vaccinia would be perhaps the easiest way to
18 construct a dangerous virus.

19 How you would test it, how you would
20 examine its virulence is not at all clear,
21 but -- so the possibility of that occurring
22 essentially accidentally, as well as experimentally,
23 is obviously something that WHO wants to rule out.

24 DR. ASCHER: Can we go back? Are you at a
25 pause right now, or are you going to continue with

1 anything?

2 DR. MAHY: We can come to that a bit
3 later, but essentially the amount of government FTEs
4 that are devoted to this project is Joe and his
5 technician. There are two people only.

6 And unless the friends over here wish to
7 support some work, we have really no -- we don't
8 have enough expertise to do more than a minimal
9 effort.

10 And we are devoting it at the
11 moment -- let's talk about that later, but our
12 interests are more in other things, such as
13 monkeypox and other perceived dangers than they are
14 in smallpox at the present time.

15 DR. HENDERSON: Brian, if I may, I think
16 the original decision in 1986 to destroy the virus
17 was to destroy it when certain actions had been
18 taken to assure that we would be able to retain the
19 information.

20 And similarly, that point was never
21 reached before you went on to say we're going to
22 sequence and then destroy at the end of sequencing.

23
24 So the decision to destroy was at the end
25 of sequencing, which should have come at the end of

1 December 1993, but it was not completed at that
2 time. It was delayed from there.

3 So that we came then to a point of
4 September of last year, where the group was convened
5 again to review how much information is now
6 available, is now the time to do it, is there enough
7 information to proceed. So that is the sequence of
8 events.

9 DR. ASCHER: One of the common threads
10 here, in terms of this history to date, is you are
11 talking about evolving technology.

12 DR. MAHY: Right.

13 DR. ASCHER: And you are going from RFLP
14 to eventually automated sequencing to now PCR. And
15 one of the questions that we would like to address
16 is how much of that technology, how much of your
17 position as to where you were going was based on the
18 current technology.

19 Let me re-ask the question. If you were
20 to be asked today of how to go about getting
21 reference information from the available stocks,
22 would you be using both the virus cloning or would
23 you be going straight to PCR? And my view is you
24 would probably go straight to PCR.

25 DR. MAHY: Well, if you wanted to do what

1 we wanted to do, which was to get a blueprint, the
2 whole sequence of the genomes, our strategy now
3 would be to shotgun the genome and to assemble by
4 computer.

5 DR. ASCHER: Right.

6 DR. MAHY: And Craig Venter has told me
7 now that he can do a poxvirus genome in four months
8 in his current technologies.

9 DR. ASCHER: But that does not require in
10 the same sense growth as the earlier procedures or
11 even availability of live material in the same sense
12 as five or six years ago.

13 DR. MAHY: Right. I mean, so that if we
14 had the viruses cloned and we wanted to get all the
15 sequences of them, we could certainly sequence in
16 that way.

17 DR. ASCHER: Right. So one thing that we
18 talked about last night, and it has been discussed,
19 I guess, elsewhere -- and I would like to know what
20 the discussion was -- is destruction of the virus,
21 in changing it to a non-infectious material for the
22 purpose of molecular procedures, ever been discussed
23 as an alternative?

24 And in terms of what would happen to the
25 existing strains --

1 DR. MAHY: Yes. The WHO committee
2 considered that, and in fact one of the
3 recommendations in their report, which I gave you
4 copies of, was that we should keep a cloned DNA
5 repository in both Novo-Sibirsk and here, or at the
6 time in Moscow and Atlanta.

7 DR. ASCHER: Well, that is the second
8 question.

9 DR. MAHY: So that once you have a cloned
10 DNA repository, of course, the question then is:
11 How much do you want to do? How much do you want to
12 clone? How much do you want to grow?

13 But there is no question that you could
14 destroy all the infectious virus, and you could keep
15 quite a large selection of viruses in the form of
16 DNA clones.

17 DR. ASCHER: What about not as clones?

18 DR. MAHY: Well, the --

19 DR. ASCHER: Just as the --

20 DR. MAHY: Well, yes. I mean, that
21 also -- it is a question --

22 DR. ASCHER: I mean, clones is a little
23 further along in the genetic engineering --

24 DR. MAHY: Yes, it is.

25 DR. ASCHER: -- phase of --

1 DR. MAHY: The deterioration is not going
2 to be very great. There is always the problem of
3 cloning introducing artifacts and so on.

4 But either way, I think you could -- if it
5 was decided to destroy the virus but to keep
6 information, that could be done. Although, again,
7 it is a matter of time, because each of these
8 materials, I think, would probably need to be grown.

9 DR. ASCHER: But the decision to retain
10 the clones --

11 DR. MAHY: You would be happy with that,
12 wouldn't you, Joe? I mean, you wouldn't want to --
13 you said you wouldn't want to simply penalize what's
14 there.

15 DR. ASCHER: The decision to retain the
16 clones was made at a time when that was basically
17 the only strategy which would allow you to keep
18 material for the future given the technology.

19 DR. MAHY: Right.

20 DR. ASCHER: What I am saying now is that
21 the decision to retain the clones might also be on
22 the table in the sense that if you eliminated the
23 clones and kept phenol (phonetic) preps, you
24 probably could still go back in the future and
25 reconstruct anything you needed to know using PCR

1 without having to either the grow the virus or have
2 something you can clone.

3 And so I am wondering why we would retain
4 the clones in 1995 in terms of public perceptions,
5 given what we will hear later about the potential of
6 clones to reconstitute.

7 So I would raise for the committee's
8 discussion of destroying the clones as an additional
9 recommendation.

10 DR. MAHY: Well, the clone issue was --
11 the clone issue has gone both ways.

12 DR. ASCHER: Right.

13 DR. MAHY: In the 1990 meeting, the
14 decision was made to destroy all the clones and not
15 to retain any clones at all.

16 In 1994 when we met, a lot of people said
17 we really wanted to keep these clones to get some
18 more sequence information, things like that, but we
19 would like to eliminate any complete genomic DNA.

20 And what you are talking about essentially
21 is maintaining complete genomic DNA in phenol. And
22 the WHO decision was not to do that simply on the
23 grounds that this allowed the possibility of
24 recreating relatively easily the virus, as compared
25 to clones where the agreement was that no more than

1 20 kb of any one clone would be in any one
2 laboratory at any time. And everybody has agreed to
3 that. Investigators are all quite happy with that
4 arrangement.

5 DR. ASCHER: That is a point of
6 clarification, the size of the clones.

7 DR. MAHY: So that is the clarification on
8 that.

9 DR. ASCHER: Got you.

10 MR. BAILEY: Is there an East African
11 strain on that last?

12 DR. MAHY: Sierra Leone.

13 PARTICIPANT: Somalia. That's West
14 Africa.

15 DR. MAHY: Somalia, I suppose it would be.
16 Somalia would be East Africa.

17 This is not an exhaustive list. I mean,
18 there are one or two others.

19 But what you could, Joe, is put out that
20 list of the sequences.

21 DR. ASCHER: And the bottom line on the
22 differences is very, very extreme similarities, at
23 least in this one paper, with the nuances being in
24 the hard-to-sequence regions.

25 DR. MAHY: Yes. I mean, I think -- I

1 don't personally think that this meeting has time
2 for a detailed discussion, but you have Joe here who
3 can tell you -- I mean, the most interesting paper,
4 I think, is the one in virology, which gives the
5 complete analysis of the genome.

6 But it's a highly complicated subject,
7 which I think, just for the moment, I will leave
8 aside. But I think if you want to ask Joe specific
9 questions on that, you could do that.

10 DR. ASCHER: But just for the record, this
11 is not like HIV or Hanta (phonetic) virus, where you
12 can get tons of sort of geographic biogenetic tree
13 information and establish complete evolutionary
14 histories based on this. These are very, very small
15 differences.

16 DR. MAHY: Well, I think the answer is we
17 don't know. And Joe was telling me earlier this
18 morning that in terms of the HA sequences they have
19 done so far, which is in the order of 20 or 30,
20 there is some semblance of at least -- you would say
21 to this -- until we do a lot more, we can't tell.
22 But Joe will present that when he gives his talk.

23 I think the point I wanted to make here,
24 though, is that the project was successful. The
25 reason for the delay from December 31 was actually

1 not that the sequence wasn't completed, because we
2 published in Nature the entire sequence, which I
3 have given you the paper of, in December of 1993.

4 But there was a technical committee that
5 had been set up by WHO to analyze our work we were
6 doing. And that technical committee, which included
7 people like Bernie Moss, David Boyle from Australia,
8 Jeffrey Smith from Oxford and so on.

9 They met in January, and it was in January
10 that I suppose we got the official ratification that
11 sufficient sequence information had been obtained
12 and the quality was good.

13 And we also brought Dr. Shchelkunov from
14 Novo-Sibirsk, and we compared both of the sequences
15 at that time and had, I think, an excellent meeting
16 of the technical committee in January of 1994.

17 So at that point, we were set for -- so at
18 that point, a meeting was convened for September of
19 1994, which was the Orthopox Committee. And at that
20 September 1994 meeting -- the report is here, and I
21 think it has been given out to you.

22 Does everybody have that? And you can see
23 that almost all of the issues that -- I would say
24 all of the issues that you are talking about around
25 here were discussed at some considerable length.

1 But, of course, this was a group of people
2 that had met on several previous occasions. And
3 it was agreed then to set a date for discussion of
4 the members of the committee. Two people on the
5 committee argued for a five-year stay of execution,
6 but they wanted to destroy the virus after that
7 time.

8 And the rest of the committee felt that it
9 should take place as soon as possible. And so we
10 agreed on this date of June 30, 1995, to destroy it.

11 Now one of the critical points here was,
12 first of all, can we detect the virus adequately,
13 and I would like Joe to address that issue, because
14 he is going to show you the actual data.

15 We believe now at least that we have good
16 diagnostic tests, and we are working with Peter. We
17 want to try and transfer these so that at least they
18 are available in as many laboratories as possible.

19 And the paper describing those tests, Joe
20 can give you these two manuscripts. We want to make
21 sure you have all the information.

22 These are both in press and both
23 confidential, but they are going to be coming out,
24 the first one in the Journal of Clinical
25 Microbiology, I think, the other one in a book.

1 DR. ESPOSITO: This one is going to be on
2 the Internet.

3 DR. MAHY: A book on the Internet. So
4 this is -- it is widely disseminated information as
5 to how you diagnose smallpox and how you can tell
6 smallpox from, you know, minor strains from major
7 strains and so on.

8 The other issue that was considered at
9 very great length was the question of the vaccine at
10 that meeting, and it was agreed that there should be
11 a repository of seed vaccine that was maintained
12 essentially in the Netherlands. And it was also
13 agreed that stocks of vaccines should be maintained
14 for emergency purposes.

15 On the question of hidden stocks, whether
16 or not there was a permafrost victim or whether
17 there was a hidden stock that was held by a
18 terrorist group or by a country that wanted to use
19 it for biological warfare, I think the committee
20 feeling, if I could summarize, that, first of all,
21 the existence of those stocks makes no difference to
22 the requirement or not for infectious virus in the
23 WHO stock in Atlanta.

24 There is nothing that we could conceive
25 that you would require infectious variola virus for.

1
2 If such a think occurred, if a virus did
3 appear, it could be rapidly diagnosed, rapidly
4 isolated, characterized and destroyed. And that is
5 the general argument. The other is much more
6 detailed.

7 And then in addition to that, the
8 committee considered very carefully, I think, what
9 the impact of this would have in general terms.

10 And I think the view of the WHO committee
11 is that once destruction has taken place officially
12 -- and I would say that it was always agreed that
13 they should be in both repositories simultaneously,
14 and the WHO committee included two Russian
15 representatives.

16 And once that had happened, that any
17 further stocks that were revealed would obviously be
18 illegal and in breach of international authority.

19 And the original idea of Dr. Sullivan,
20 this whole thing being keeping with the Biological
21 Toxic Weapons Convention in 1972, would be
22 fulfilled. So there is a moral high ground issue,
23 though there did not seem to be any practical issues
24 in terms of diagnosis.

25 And on the question of more information

1 about the virus, the committee felt, I think very
2 strongly, that this was the best argument for
3 retaining it, in terms of the possible need for more
4 understanding of smallpox virus, more understanding
5 of how the virus interacts with the immune system,
6 which is particularly interesting. And while you
7 can study that in terms of gene products, you cannot
8 -- there are certain things that you may only be
9 able to do with the virus itself. However, we do
10 not have an adequate animal model.

11 It is very difficult to conceive how you
12 would get much information about the human immune
13 system by studying the system in mice, for example,
14 if you were to make transgenic (phonetic) mice,
15 which has been suggested by some groups.

16 And on balance, I think the committee felt
17 overwhelmingly that the advantage of destruction far
18 outweighed any advantages that might come from
19 research on this virus when there were many other
20 viruses, first of all that we know nothing about,
21 that we have not had time analyze, but also viruses
22 that are related that could be used as models that
23 would tell us about smallpox.

24 DR. RAUCH: Brian, I have a question.
25 Louis Sullivan's position back in 1990, the position

1 as late as September 1994 -- obviously, Louis
2 Sullivan's position was an HHS position. That's
3 obvious. Was it a U.S. government position?

4 DR. MAHY: It was because the World Health
5 Assembly representative represents the government.
6 And I would say that -- in fact, you might pass that
7 out, Joe.

8 Around that time, the Secretary of Defense
9 signed his agreement for the destruction of the Army
10 stocks at CDC. The ATCC agreed to destroy their
11 stocks held at CDC.

12 And numerous other bodies, which are
13 listed here, agreed that the virus should be
14 destroyed. So that there was no -- there is no
15 question, I think, that inasmuch as DOD is
16 represented by the Secretary of Defense -- and I
17 don't know how much that can be representative, but
18 in terms of health matters -- that they agreed to
19 that.

20 DR. HENDERSON: There was a formal
21 memorandum of understanding signed by the Assistant
22 Secretary in HHS and DOD with regard to destruction
23 of the virus in 1991.

24 DR. RAUCH: In 1991.

25 DR. MAHY: Right. So the position

1 is -- I think the only thing that has changed the
2 position that we can conceive is that subsequent to
3 the September 1994 recommendation, there was a move
4 by the United Kingdom to raise the issue of the
5 necessity for --

6 DR. RAUCH: Was the movement of the stock
7 to the other facility in reference to the
8 destruction process? In other words, were they
9 starting to
10 prepare -- was the Russian government starting to
11 prepare for the destruction, assembling the
12 inventory, getting the stocks together?

13 And what level of cooperation was WHO
14 going to get on that end in terms of verification or
15 any of the things that we --

16 DR. MAHY: You have touched on an
17 important point here, because Dr. Sandakchiev -- I
18 mean, one of the things we did during this
19 intervening period which I have not referred to, we
20 did make a lot of attempts, CDC particularly,
21 without WHO's approval, to try to publicize the
22 issue, what was going to happen because we see this
23 as a momentous thing from the point of view of
24 medicine and biology and so on.

25 So a number of debates took place. And I

1 was chairman of the International Congress of
2 Virology in Glasgow in 1993, so I specifically
3 arranged for a roundtable on this issue.

4 And that was a particularly important
5 forum, I think, in which this was discussed. So
6 that there was an opportunity at that point for many
7 -- I also went to the ASM. I went to different
8 places and said what we're going to do and asked the
9 people's opinions.

10 So over this period, a lot of discussion
11 took place. And Dr. Sandakchiev, who is the
12 director of that institute, came out against
13 destruction of the smallpox virus.

14 Now at that time, of course, he didn't
15 have the virus in his institute. The virus, so far
16 as we know, was in Moscow.

17 After this decision was taken place, we
18 had a man sitting here, Dr. Kaborivetz (phonetic)
19 who was one of the ministers from the Ministry of
20 Health, who sat at the September 1994 meeting and
21 never said a word. Dr. Marinkoble (phonetic) was
22 also there.

23 But soon after the meeting, the virus was
24 moved. I would say about October the virus was
25 moved from Moscow to Novo-Sibirsk ostensibly to give

1 it better security.

2 DR. WOLFE: What was the date of the
3 signing of this?

4 DR. MAHY: Those are different dates.
5 That's just a list of different people at different
6 times. But it was over that period. Most of it was
7 around 1993, 1992. I can give you the individual
8 document. That's just a list of the --

9 DR. ASCHER: But were there any stated
10 reasons or any reasons stated to that this was part
11 of the process to arrange for the eventual
12 destruction? Were they on the same time line? Were
13 they beginning this process?

14 DR. MAHY: No. I mean, I would say that
15 we have never at CDC been given any encouragement,
16 if you like, about that issue. But at WHO it's
17 always been said -- it was always agreed.

18 But, of course, what happened in between
19 1990 and here was, of course, USSR disappeared and
20 Russia appeared. And so -- and with all their
21 problems in health and trying to cope with
22 diphtheria and everything else they have to do, I
23 don't quite know where this fits in.

24 But there is no question that the
25 representative that in 1990 agreed to destroy the

1 virus was a representative of the USSR, who was
2 subsequently then replaced. And the person in
3 September 1994, to my knowledge, didn't voice an
4 opinion that I heard on the issue.

5 PARTICIPANT: Brian, I think you may have
6 some conflicting evidence.

7 DR. MAHY: On the time line?

8 PARTICIPANT: I think you and Charlie are
9 kind of at odds here.

10 PARTICIPANT: Well, the evidence presented
11 earlier was in direct conflict to the statement you
12 just made.

13 DR. MAHY: Well, I am saying what --

14 PARTICIPANT: I can't go on because it is
15 an open session now.

16 DR. MAHY: I know. But all I'm saying to
17 you is what the WHO -- I mean, Uri Genden (phonetic)
18 is, as you know, a Moscow virologist, who WHO has
19 been dealing with a lot of this issue. And the
20 statement has always
21 been -- and in fact he works in that institute.

22 I would like to just give you an idea from
23 the Russia point of view just who we have at CDC
24 now. Probably the most important person from the
25 original institute is a man called Vladimir Loparev,

1 and he is still working with us at CDC on sequencing
2 smallpox.

3 He is from the Moscow Institute of Virus
4 Preparation. So that's where the original -- so he
5 has firsthand knowledge exactly of what was in the
6 Moscow Institute of Virus Preparation.

7 He confirmed for us the fact that the
8 virus had been moved. We called his director, and
9 we got this confirmation.

10 Now, before him we had a man who worked on
11 the project in the early stages who left, Nik
12 Selivanov. And you will see his name on perhaps
13 just the one paper there. He went back, and I don't
14 whether he has come out again or not.

15 Now the group in Novo-Sibirsk, of course,
16 was doing biological warfare, not only -- I mean,
17 the biological warfare that I have been most in
18 contact with is in relation to Marberg (phonetic)
19 and things of this sort.

20 They have published numerous papers on the
21 ability of these viruses to infect primates and so
22 on. And most of those workers became redundant
23 essentially when the USSR disappeared. So we have a
24 lot of those people working with us now.

25 And probably one of the most important

1 people is Vladimir Chizikov. He is leading the
2 sequencing of Hanta viruses at the current time,
3 working the Hanta virus group. He is basically a
4 direct colleague.

5 He led some of the sequencing originally,
6 I think, of the India strain, and he is very closely
7 connected with Dr. Nedasov, who will be coming to
8 see us in June and spending a week with us at CDC.

9 DR. CASSELL: Just out of curiosity, do
10 these people go through any type of security
11 clearance that are working on these projects at CDC?

12 DR. MAHY: No. CDC is an open
13 organization. CDC does not classify or restrict.
14 You know, we don't work on anything of that nature
15 at CDC. And there is no formal procedure. We
16 welcome people from any country to come and work
17 with us on research.

18 We have several other people that are in
19 the group. There is a Dr. Kosorov, whose first name
20 I can't remember. I think it's Michael. He is from
21 Novo-Sibirsk.

22 And then we have several others who are
23 working on the sequencing with Sergi Morzunov.
24 These people are all working in the Hanta virus
25 group.

1 And I could go on listing names. I would
2 say maybe 15 or so Russia people currently working
3 in the division on different aspects of virology.

4 DR. CASSELL: Just again another curious
5 question in terms of the security of the smallpox
6 stocks and other things at CDC. Could you just
7 comment on that and where they are housed?

8 DR. MAHY: Those are areas where I think
9 perhaps I could fall behind security, because I
10 don't think our public relations people are keen on
11 this information being made widely available.

12 But, you know, I can certainly -- if
13 people feel that they would like me to talk about
14 this, I can, but I think it's not an issue that I
15 would like to go into in detail.

16 But at the request of the -- what I can
17 say in this group is that at the request of the DOD,
18 there are two completely separate repositories which
19 are situated quite a number of miles apart. So
20 there is a duplicate set, if you like, to the
21 original set.

22 DR. ASCHER: There are several aspects of
23 a brain drain like this. One is the visiting
24 scientists, the other is the Wernher Von Brauns of
25 the world.

1 DR. MAHY: Well, most of these people
2 never go back, of course.

3 DR. ASCHER: Is that your intention? I
4 mean, is that their intention?

5 DR. MAHY: Well, we have -- I mean, for
6 example, I have a group from Russia who are working
7 on hepatitis.

8 And Michael Kosorov just left yesterday to
9 go back to Turkmania (phonetic) for some
10 investigations with the chief of the hepatitis
11 branch.

12 But that's -- I mean, they go back and
13 forth to collect samples and things of that sort,
14 but not otherwise.

15 DR. CASSELL: Brian, the Russian scientist
16 that indicated to you that the stocks had been
17 moved, did he also give a reason as to why they had
18 been moved?

19 DR. MAHY: We have never been, I think,
20 given a reason other than it was ordered by the
21 chief medical officer of the minister of health or
22 whatever you call him.

23 DR. HENDERSON: They have talked
24 privately. You know, security is a big issue. Plus
25 they cannot work on that virus at Moscow, because

1 the facilities are just not available to them.

2 DR. MAHY: But by the same token, though,
3 that facility in Novo-Sibirsk has never been
4 approved by WHO for work with live smallpox virus.

5 Whereas, the CDC, at least -- for many,
6 many years now, we have been able to work with live
7 viruses at CDC, but Moscow was prevented by WHO from
8 actually using live virus.

9 DR. WOLFE: Brian, in relation to the
10 Russians who are coming here and then going back, as
11 opposed to emigres, do we have any comparable
12 American scientist working in Russia or any of the
13 former Soviet Union on such things as tick-borne
14 encephalitis, Congo-Crimean --

15 DR. MAHY: Yes. We have a number of
16 programs, particularly -- currently, we have people
17 over there on influenza research, working in St.
18 Petersburg.

19 We have a whole team of CDC people working
20 on the diphtheria problem in Russia, which is a
21 major issue.

22 Joe has been to Novo-Sibirsk -- how long
23 were you there, about two or three weeks or
24 something -- in the institute for a visit.

25 DR. WOLFE: My point is these people are

1 getting technology that can be transferred back on,
2 let's call them, more hot-type organisms.

3 Do we have an ability to get into Russia
4 to work on their so-called hot organisms like Congo-
5 Crimean or tick-borne encephalitis to mention two
6 major ones that we have concern about?

7 DR. MAHY: They would be absolutely
8 delighted if we did that. We have sent from Fort
9 Collins -- we have an agreement with Fort Collins,
10 specifically Dimitri Lvov and Sergei Lvov, his son,
11 who is working on tick-borne viruses and has been
12 back and forwards with the Fort Collins group.

13 But most of that collaboration has been
14 more the question of the guys from CDC/Fort Collins
15 go over there, and they get out into the field.

16 And they collect a lot of ticks and a lot
17 of insects and so on, take them back, and then the
18 work is done in Fort Collins.

19 DR. WOLFE: How about plague? Is there
20 any exchange work with plague?

21 DR. MAHY: I don't think even at CDC, we
22 don't have a very strong capability. But Fort
23 Collins, again, is the place.

24 DR. WOLFE: At Fort Collins, I mean.

25 DR. MAHY: But there is nothing that I

1 know of in plague that's directly going on.

2 DR. JAHRLING: Did I hear you correctly
3 that you said that CDC would have two sets of virus?

4 DR. MAHY: Right.

5 DR. JAHRLING: So it's not just in one
6 physical location.

7 DR. MAHY: There are two repositories of
8 virus. They're not absolutely identically the same,
9 but they certainly originally were.

10 I think you would say that they were
11 originally divided up essentially at the time they
12 were put in there. And obviously, both repositories
13 would be destroyed if we go ahead and destroy them.

14 DR. ASCHER: One of the concerns is that
15 we are now in the era of molecular engineering, and
16 it really is clear that if times were different,
17 people coming over and learning this would pick up a
18 great deal here compared to what we would pick up
19 over there in terms of some of the new technology.

20 DR. MAHY: Oh, yes. I mean, that's always
21 been the case. I mean, we don't go send people to
22 work in Africa or Sierra Leone in order to -- and
23 currently in Russia, I would say that if anybody, if
24 Joe wanted to go to work for six months or a year or
25 two years in Dr. Sandakchiev's institute, they would

1 welcome him with open arms. Wouldn't they, Joe?

2 DR. ESPOSITO: I'm sure.

3 DR. MAHY: But, I mean, it isn't so much
4 that there -- I don't think there is any barrier.
5 It's just that we have to consider our program and
6 what we will gain from any exchange, and we don't do
7 that.

8 DR. RAUCH: For my own understanding, the
9 WHO agreement to destroy --

10 DR. ASCHER: Recommendation.

11 DR. RAUCH: Yes. Well, yes.

12 DR. ASCHER: It's only that.

13 DR. RAUCH: Right. Right. What is the
14 legality? I mean, what is the legal -- I mean,
15 international law is kind of all over the place.
16 Are there any verification measures built into this
17 proposed resolution?

18 DR. MAHY: It's an area that is very
19 difficult. And, you know, the ASM -- I currently
20 sit on the Public and Scientific Affairs Committee
21 to ASM. They are looking very much into this.

22 They are trying to develop systems for
23 edification. We have had some very interesting
24 stuff in relation to Sedlov (phonetic) outbreak and
25 so on.

1 I believe that in any field -- it doesn't
2 matter whether it's medical, science or any other
3 field -- international legislation is extremely
4 difficult.

5 I mean, look what is going on Croatia. I
6 mean, it's just impossible to be sure about this.
7 But the question is, I think what we have to ask
8 ourselves here is: Is the U.S. -- first of all,
9 does it need this virus, these infectious virus
10 stocks, for some purpose that is related to this
11 aspect or for some other purpose?

12 And the second question is: Should we
13 really be seen, when we have the WHO stocks here, to
14 be going against the decision of the WHO committee
15 about destroying them?

16 They don't belong to the U.S. I mean,
17 they are an international -- if the Russians don't
18 destroy theirs, that's another issue that I think
19 needs to be dealt with by a different set of
20 factors.

21 But if we come out at that World Health
22 Assembly and we say that we have changed our view
23 and are going to keep them --

24 DR. ASCHER: Don't question. You just say
25 that the Russians --

1 DR. MAHY: There are 180 countries going
2 to vote, and the question is: What are they going
3 to do?

4 DR. ASCHER: If the Russians don't decide
5 to destroy -- you have said that the Russians on the
6 Advisory Committee have been in favor, but there
7 have been voices within Russian that have been
8 against.

9 DR. MAHY: Yes. I mean, it's safe to say,
10 without mentioning any names, that one of the
11 members of the -- one of the people who wanted to
12 delay destruction for five years was one of the
13 Russians, but I don't think that that was related to
14 any political end or something.

15 DR. ASCHER: What is your current view of
16 the likelihood of everything goes forward and the
17 WHO recommendation proceeds and the United States
18 destroys its virus that Russia will follow? What is
19 the probability of that in your mind?

20 DR. MAHY: I think the pressure would be
21 absolutely enormous. If Russia is intending to
22 remain any credibility in the World Health Assembly,
23 I think the pressure for them to at least, you know,
24 go through the motions of destroying it would be
25 very high.

1 If it is retained essentially legally,
2 according to international law, then they are in a
3 lot of trouble. They are going to be treated the
4 same way Iraq is treated or other countries. So
5 it's going to be very difficult to maintain
6 relations.

7 DR. ASCHER: Is there any negotiating
8 point by WHO where they could get the two
9 governments together and do the joint agreement and
10 then really do it, or is it going to be independent?

11 DR. MAHY: I mean, what we said was
12 simultaneous. So we will do it in the afternoon,
13 and they will do it in the morning, so it will be at
14 the same time.

15 DR. ASCHER: But we don't know that they
16 will agree.

17 DR. MAHY: Well, I mean, if the World
18 Health Assembly agrees to do this, the ratification
19 system that we set up was not a political one. It
20 was a laboratory one at the level of heads of
21 institutes.

22 If the head of institute -- it has been
23 agreed by WHO that the head of the institute is
24 ultimately responsible to see that that destruction
25 takes place.

1 Joe is the chief fact totem in destroying
2 our stocks and will be there and will have to sign
3 off, and it will be essentially recorded. Now all
4 this is laid down in that document I gave you. So
5 you can read what is supposed to happen.

6 DR. CASSELL: Brian, I hate to curtail the
7 discussion, but given that you do have some time
8 constraints as far as a flight this afternoon, maybe
9 we should try to stick to the science --

10 DR. MAHY: We should move on a bit.

11 DR. CASSELL: -- and move on and finish
12 the summary and then come to the CDC's answer to the
13 last series of questions, if we could.

14 DR. MAHY: Well, if you like, I can go
15 through the CDC's position now and then Joe can
16 follow, or otherwise Joe can give the diagnosis --

17 DR. CASSELL: Well, I think that we should
18 probably finish with the science first and have Joe
19 --

20 DR. MAHY: Right. Well, is it all right
21 if Joe does that, and then I will come on afterwards
22 and do the agency positions.

23 DR. CASSELL: Sure. I don't mean to be
24 too hard on you, but I know you have a plane to
25 catch --

1 DR. MAHY: No. You are absolutely right.

2 DR. CASSELL: -- and I don't want to lose
3 your expertise before we get down to business.

4 DR. ESPOSITO: I am just going to update
5 you on our modern technology of fingerprinting
6 orthopox viruses and identifying and differentiating
7 smallpox virus. So if I can have the first slide.

8 (Slide.)

9 This is a picture of smallpox, which you
10 all should be familiar with. The next slide.

11 (Slide.)

12 This is variola major. You have already
13 gotten this slide, so I won't go through it except
14 to say that for smallpox sequences, we have nearly
15 700,000 base pairs in the process or actually in the
16 database right now.

17 So it represents the largest single virus
18 set of information that is in the gene bank right
19 now. There is no other virus that has this much
20 accumulated information.

21 This lists the strains. We are on the
22 last 15 kilobases of the Garcia strain, and we
23 should finish that up sometime this summer.

24 Then we will have 3 complete genomes in
25 the database, as well as the left and right ends of

1 the various other strains that Brian talked about.

2 As well, we have focused on two genes, the
3 hemagglutinin of the orthopox viruses -- and by
4 definition a virus is an orthopox viruses
5 hemagglutinates red cells. No other poxvirus will
6 hemagglutinate.

7 So that was the marker that we chose to
8 use to start developing our fingerprinting PCR chain
9 reaction diagnostic test.

10 The other one that we use is a tumor
11 necrosis factor receptor. This is a very important
12 gene. It's felt to be one of the key regulators of
13 virulence of the virus.

14 So therefore, if someone made a mutant
15 virus, for example, and deleted this gene, we
16 wouldn't be able to pick that up by PCR, number one.

17 Secondly, that virus would be severely attenuated.

18 Therefore, the likelihood of it causing severe
19 disease would be greatly reduced.

20 This gene is not presenting vaccinia
21 virus, the vaccine. This gene has a homolog in
22 vaccinia virus.

23 The next slide.

24 (Slide.)

25 These are the two genomes on a physical

1 linear map of the DNA, and the colored areas show
2 you the areas of DNA difference between vaccinia
3 virus, which is at the bottom, and smallpox virus
4 from Bangladesh, which is at the top.

5 And you can see the major areas of
6 difference between the two viruses are at the ends
7 of the DNA. The central part of the DNA is highly
8 conserved. Obviously, the vaccine worked.

9 The next slide.

10 (Slide.)

11 This takes that linear map that you just
12 saw horizontally and it places it vertically down
13 the side. We have the alphabetical designations.
14 And the number of proteins that we can identify that
15 would be coded in that DNA would be approximately
16 188 proteins.

17 And we compared the amino acids of these
18 proteins between variola and vaccinia virus, and you
19 can see that 151 of these 188 are virtually
20 identical. They have greater than 90 percent
21 homology.

22 Then we looked at another region of
23 differentiation between 30 and 90 percent homology
24 between the two viruses, and we find there are 25
25 genes that have that degree of homology. And then

1 there are 12 genes which variola virus has that are
2 totally dissimilar or not present at all in vaccinia
3 virus.

4 So future efforts at diagnostics could
5 focus on these other distinctive genes, one of which
6 is the tumor necrosis factor receptor. And we have
7 identified several other proteins, which in fact,
8 using cowpox model systems, are actually produced by
9 orthopox virus.

10 Next slide.

11 (Slide.)

12 PARTICIPANT: Joe, how many vaccinia genes
13 are not found in variola?

14 DR. ESPOSITO: How many vaccinia genes are
15 not found in -- the other way around.

16 PARTICIPANT: It's a bigger genome.

17 DR. ESPOSITO: Yes. I think -- let's see.
18 I have the slide on that. I think there are a half
19 dozen, something like that.

20 Vaccinia virus contains an IL-1 receptor
21 and smallpox doesn't. And if you delete that gene
22 from vaccinia virus, you can make vaccinia virus a
23 little bit more virulent.

24 Next, please.

25 (Slide.)

1 These are methods of detection and
2 differentiation of orthopox viruses. Brian
3 mentioned to you in the late-seventies, actually, to
4 mid-eighties, we determined using restriction and a
5 nuclease mapping, one, that there was no -- we
6 helped to determine that there was no animal
7 reservoir from the virus using DNA mapping studies
8 of monkeypox and variola virus.

9 The other was that variola virus could not
10 be a progeny, a natural progeny, of monkeypox virus.

11 And those restriction maps are also diagnostic.

12 Then we began our sequence determination
13 and began developing flemorase (phonetic) chain
14 reaction tests based on the HA sequences, as well as
15 the tumor necrosis factor receptor sequences.

16 Now we are focusing on an Eliza (phonetic)
17 serologic identification, looking for particularly
18 IGM, which would be the early antibody produced
19 after a poxvirus infection, and trying to design a
20 genetically engineered protein, which would be able
21 to be identified in an IGM Eliza acid, for example.

22 So right now, we are -- and I will show
23 you that later.

24 Next.

25 (Slide.)

1 Okay. This is a phylogenetic (phonetic)
2 tree of the hemagglutinin, and you can see that we
3 have three orthopox viruses that are indigenous to
4 North America and the United States. There's one
5 from a raccoon from Aberdeen, Maryland, a mole from
6 the San Francisco area, and a skunkpox, which is
7 indigenous around the Washington State area.

8 The other viruses are the Old World
9 orthopox viruses from Eurasia and Africa, and you
10 can see listed here the different ones.

11 And you can see that HA sequences can be
12 differentiated into these different clades
13 (phonetic), and we can actually separate these by
14 looking at the sequence, per se. So that's
15 diagnostic.

16 In order to -- sequencing is a little be
17 laborious, so we can develop other tests to look at
18 this same type of result.

19 Next, please.

20 (Slide.)

21 And that flemorase chain reaction -- and
22 the other thing we have in terms of sequence
23 information, we have gone into the repository and
24 gone into scab specimens, extracted the DNA from
25 those in the P-4 facility, sequenced the

1 hemagglutinin.

2 And what we are now starting to see are
3 the clades or the phylogenetic relationship of
4 different strains of smallpox.

5 And you can see here, for example, these
6 are variola minor or lastram (phonetic) strains.
7 These are variola major.

8 We are now in the process of going back to
9 the literature and looking at the case fatality
10 rates of these different ones to see how that pairs
11 up with the sequence to see if the sequence of this
12 HA is in fact reflecting something about the virus
13 that we know about and the epidemiology.

14 DR. ASCHER: This was all done without the
15 requirement for live virus is what he is saying.

16 DR. ESPOSITO: This is a PCR directly from
17 scab material DNA, which we extracted
18 with --

19 DR. ASCHER: No culture, no growth, no
20 nothing.

21 DR. ESPOSITO: No culture, no growth.
22 This is from something the size of a head of a pin.

23
24 DR. CASSELL: From all data, with respect
25 to animal models, taking into account the

1 phylogenetic data, I mean, is there any information
2 with respect to, say, for example, gerbils?

3 DR. ESPOSITO: There is no -- humans were
4 the stripped host for smallpox virus. If you look
5 at other genes, smallpox fits in a category which
6 differentiates it.

7 We don't know what the host strain genes
8 are. Camelpox, for example, is smallpox in camel.
9 It only infects camels.

10 There is -- there never has been a
11 suitable animal model system for studying smallpox
12 so that one could do experiments like differentiate
13 strains in animal model systems. Is that --

14 DR. CASSELL: I guess the question --
15 understand that I am not a smallpox virologist or a
16 virologist period, but, I mean, how extensive have
17 there been attempts formally to look at
18 accessibility of different animals?

19 DR. ESPOSITO: That goes back before my
20 time. Perhaps D.A. can answer those kinds of
21 questions. If those were done in the sixties, when
22 smallpox was still around --

23 DR. ASCHER: Well, ectromelia is --

24 DR. ESPOSITO: Well, ectromelia is a
25 hematotropic (phonetic) disease.

1 DR. CASSELL: Well, so what I'm getting at
2 is that that search would have been, I think, very
3 narrow, because clearly things -- I mean, the number
4 of animal species used for animal models formerly
5 were extremely limited, very poorly defined.

6 DR. MAHY: I think that's not true,
7 though, if you look in that book there. It has a
8 lot of information on what -- it's just exhaustive
9 on anything that was ever done. And I think it's
10 pretty wide ranging the number of species that they
11 looked at.

12 DR. HENDERSON: There were. There were a
13 lot looked at. And I think we have evidence from
14 natural infection of chimpanzees and orangutans
15 exhibiting apparent smallpox after contact.

16 Those are the only simians that we have
17 known got infected. But they have really not been
18 successful in inoculating other animals.

19 There was quite a lot of work done, as you
20 say, in the early sixties by the Germans continuing
21 on in Munich in the sixties and seventies.

22 MR. BAILEY: D.A., one of the -- I was
23 just going to comment that one of the papers that I
24 saw trafficking around made the comment that strains
25 of variola were tested in monkeys, for example, and

1 who were later found out to be contaminated with
2 monkeypox or other poxviruses. So this was, I
3 gather, a fairly common problem.

4 DR. MAHY: It was a problem. Particularly
5 in the Russian collection, there were some viruses
6 that were contaminated.

7 But also, the -- I mean, there is also
8 evidence that monkeypox, which is commonly believed
9 to be essentially a rodent-borne
10 virus -- but when this gets into monkeys, especially
11 orangutans, and monkey species, we get a very much
12 smallpox-like disease.

13 Actually, true monkeypox appears to
14 be --

15 DR. RAUCH: Let me clarify just a bit
16 further. We were concerned about monkeypox, which
17 does infect humans. It can transmit from human to
18 human, at least over a couple of generations, before
19 dying out.

20 And in Moscow, they were getting specimens
21 from humans and animals and testing these for
22 monkeypox. They are, of course, smallpox. They
23 then found that they were getting smallpox. They
24 were identifying isolates from monkeys.

25 And this gave us some real concern,

1 because if we had smallpox in monkeys, then we had a
2 natural reservoir.

3 It was not until the restriction into
4 nuclease test came along that they were able to take
5 this apart and discover that these were all
6 laboratory contaminants.

7 So that the so-called whitepox were
8 laboratory contaminants. Monkeypox was quite a
9 different piece altogether and behaved it.

10 PARTICIPANT: Can you give me a sense of
11 the -- what is the temporal sequence of your PCR and
12 (inaudible) detection (inaudible) How long does
13 this take?

14 DR. ESPOSITO: If we have the primers in
15 hand, the primers take a day for our core facility
16 to produce. If we have the primers in hand, we are
17 talking about an hour.

18 This is a demonstration which shows --
19 here in the first two lanes we have the Bangladesh
20 strain and the Garcia strain. Using a set of
21 flemorase chain reaction primers, we can amplify the
22 hemagglutinin gene.

23 It's about a kilobase in size, and you can
24 see that this set of primers works on all of the
25 Eurasian/ African orthopox viruses. We have another

1 set of primers that will amplify the DNA of the
2 North American species.

3 And here, for example, you can see when we
4 take that product, the DNA product, that we
5 amplified from the geno DNA, that when we cleave
6 that with a restriction enzyme called tap one, then
7 that cleaves it at a specific site in the DNA. Then
8 we get two bands produced with both major and
9 lastram virus.

10 Here, for example, in these two tracks,
11 you see a human monkeypox and a monkey-monkeypox.
12 And you can see right here there are several bands
13 produced with those. I am not going to call out all
14 of these, except the vaccinia camelpox and here some
15 cowpox.

16 So we can differentiate these quite
17 readily using the hemagglutinin as the marker.

18 Next one.

19 (Slide.)

20 We have also gone in and determine whether
21 we could do this. We had DNA preparations in the
22 laboratory. We had clone material. We had material
23 in the repository.

24 So we went in and took some crust
25 material, and you can see here that we can readily

1 identify the virus directly from scab material.

2 We took some scratchings of the ice and
3 the frozen material of the corelontope (phonetic)
4 membrane of chicken eggs. As well, we took some
5 scratchings off the ice that is frozen in the
6 repository. And we are able to diagnose it from
7 cell culture material.

8 So the method of extraction that we are
9 using to get the DNA out, to make it suitable for
10 flemorase chain reaction seems to work with all
11 sorts of specimens that we have.

12 DR. RUSSELL: The cell culture band is
13 pretty heavy. How much -- what were the tighters
14 (phonetic) those cultures?

15 DR. ESPOSITO: Well, yes. These -- I
16 couldn't say offhand. This is just material in the
17 repository.

18 I would say in tissue culture, if it's
19 passaged a couple of times, you can get a smallpox
20 virus stocks. And it grows pretty much as well as
21 vaccinia virus does, tissue culture.

22 So I would say that this culture probably
23 represents -- the corelontope membrane material here
24 is just one little dime-sized spot on a much larger
25 surface.

1 So therefore, when we scratch the ice, the
2 probability of hitting that little dime-sized spot
3 is -- you know, we would probably have to thaw it
4 out, and we didn't want to do that.

5 So you can see with the corelontope
6 membrane material. I am sure if we thawed it out
7 and smushed it up a little bit, we could probably
8 get out enough DNA that would give us bands of this
9 nature.

10 Now, this is the tumor necrosis factor
11 receptor. We have biological information now by
12 expressing this in a bacteria and testing it in a
13 tissue culture system.

14 This protein will actually bind tumor
15 necrosis factor. It will also bind lymphotoxin.
16 These are key players in the immune response to
17 diseases, particularly the inflammatory response.

18 So deletion of this in a construct has
19 been made, for example, in a rabbit poxvirus called
20 myxoma virus. It has a 40-percent homolog of this
21 protein that is an orthopox virus.

22 But when the deletion was made in myxoma
23 virus, myxoma virus virulence was attenuated very,
24 very much.

25 So we feel --

1 DR. RUSSELL: What is the homology between
2 that and any mammalian genes?

3 DR. ESPOSITO: Forty percent.

4 DR. RUSSELL: Between that and human TNF
5 receptor?

6 DR. ESPOSITO: Right. And it's also 40
7 percent between the orthopox and the laporipox
8 (phonetic).

9 DR. RUSSELL: Okay.

10 DR. ESPOSITO: But they are essentially
11 structurally -- they are structurally the same.
12 What they are is that they have the binding domain,
13 but the amino acids that fall in between the binding
14 domain are suitable enough to cause that structure.

15 DR. RUSSELL: The fold is the same.

16 DR. ESPOSITO: Even though the amino acid
17 sequences are only 40 percent, it still falls
18 together the same way. We would love to crystalize
19 it and answer your question.

20 DR. RUSSELL: Where did the gene originate
21 from?

22 DR. ESPOSITO: That's a matter of
23 controversy right now. Some people say that
24 poxviruses can grow in the same cells that
25 retroviruses can grow in.

1 And therefore, it may be, because what we
2 find in a poxvirus is a full-length gene, not
3 spliced. There's no splicing in poxviruses. And
4 the human gene product is a product of splicing.

5 So what would have to have happened, the
6 theory is that the messenger RNA in the cytoplasm
7 somehow had to get into recombining into the
8 poxvirus. And one way that that could happen is if
9 a retrovirus or a reverse transcriptase were present
10 in the same cell as a poxvirus.

11 I am not aware of anybody actually
12 analyzing poxviruses for reverse transcriptase
13 activity, but I know in Australia right now one very
14 interesting finding has emerged in the sequencing of
15 wild type isolates of fowlpox virus. They found
16 integrated into the wild type fowlpox virus genome
17 entire avian retrovirus genomes are integrated into
18 that genome.

19 So that's an amazing finding. It means
20 the viruses are probably in the same cell. It was
21 fortuitous that the entire genome of a retrovirus
22 got into one.

23 DR. RUSSELL: Not a retrovirus --

24 DR. ESPOSITO: Other strains of fowlpox
25 are showing bits and pieces of retrovirus. We have

1 no -- when we found that out, we immediately went
2 back to the sequence and looked.

3 Do we have retrovirus in smallpox or
4 monkeypox and what sequences are available?

5 We really, I think, need to look at some
6 of this question in terms of the sequence of
7 monkeypox. If we can get the analysis of that
8 sequence, because that is the thing that is in the
9 monkey where we know there are retroviruses in
10 primates, of course.

11 But in smallpox, there doesn't seem to be
12 retrovirus homologs like they are seeing in fowlpox.

13 So I think it's important in terms of
14 understanding the biology of these viruses how they
15 get these genes. There are at least a dozen genes
16 that poxviruses have that mimic cytokine (phonetic)
17 binding proteins.

18 And these are proteins that are regulating
19 the immune system.

20 So how smallpox evolved to overcome the
21 immune system, we are now learning how to do that in
22 tissue culture, how to answer that question by
23 expressing the protein and looking at the binding to
24 the cytokines. I mean, we are taking this one step
25 further.

1 DR. RUSSELL: Have you got data on the
2 differences between the alastrim and major strains
3 with regard to this side of genes?

4 DR. ESPOSITO: Yes. The alastrim -- we
5 expressed -- Vladimir Loparev was doing these
6 experiments. What he did -- and I have a slide in
7 here which I can show you.

8 But he has expressed a tumor necrosis
9 factor receptor for alastrim, for Bangladesh virus,
10 for two strains of monkeypox and a couple strains of
11 cowpox virus and camelpox virus.

12 And the TNF receptor that he has expressed
13 in the bacteria -- and that is only the binding
14 domain. We have a problem expressing the part that
15 gets integrated into lipid membranes.

16 But just expressing the binding domain of
17 that protein, the authentic protein is on the
18 surface of an infected cowpox cell or infected
19 camelpox, infected cell. That protein is actually
20 on the surface and has a long tail that goes into
21 the cytoplasm.

22 DR. RUSSELL: Have one transmembrane
23 domain?

24 DR. ESPOSITO: Yes. And that long tail
25 that goes in the cytoplasm is what signals all the

1 processes that are being affected by TNF binding to
2 that. It is called signal transduction.

3 Okay. So that tail exists on the smallpox
4 one. The myxoma virus one, on the other hand, is
5 secreted. It's not on the cell surface. It has a
6 truncated tail.

7 Smallpox and camelpox have long tails on
8 them and they, therefore, are capable on the cell
9 surface of being involved in signal transduction.
10 And that's what we are aiming to find out.

11 We are trying to apply this technology of
12 using this TNF receptor. For example, we have set
13 up a model system with cerebral malaria, and we are
14 trying to intervene in cerebral malaria, because
15 that's an inflammatory process. And one of the
16 theories is that TNF is produced.

17 And so we think that these proteins,
18 interleukin receptors, interferon gamma receptor,
19 which is what the lab at Novo-Sibirsk is working on,
20 all these types of cytokine receptors have very good
21 potential for therapeutics or even learning
22 mechanisms of different types of genes. We may --

23 DR. ASCHER: It is also the whole cotexin
24 (phonetic) family of cancer and AIDS and everything
25 else.

1 DR. ESPOSITO: Right.

2 DR. ASCHER: That's the other big issue.
3 It's the same mechanism over a longer period of
4 time.

5 DR. ESPOSITO: Okay. So we focused, just
6 in our PCR analysis and in also our bacterial
7 expression, we are expressing the HA, and we are
8 expressing the TNF receptor, and we are looking at
9 the biologic activity of those molecules that we are
10 expressing.

11 We want to actually express some of these
12 in ucariout (phonetic) systems, and we are setting
13 up collaborations to do that, to get more authentic
14 versions.

15 But we have -- we have a bacterial
16 expressed TNF receptor that binds equal to human TNF
17 receptor that's available commercially, which they
18 both will bind TNF 100 percent.

19 And they will interfere with lysis of L-
20 cells, which have a receptor on their surface. It
21 will also bind lymphotoxin in a fluorescent cell --
22 so this protein is a little bit promiscuous now that
23 we are finding out, and there are others. The other
24 ones that we know of in poxviruses.

25 Ones that block interleukin converting

1 enzyme are also involved, for example, in stopping
2 program cell death.

3 What happens when a virus goes into cell,
4 the cell begins to die, so that you can clear that
5 dead cell.

6 Poxviruses are putting out proteins to
7 retard that program cell death. So that's another
8 thing that viruses, the viruses that we are using as
9 a strategy to survive, until they can get a light up
10 and become systemic. And the more efficacious that
11 process is, the more effective a pathogen it
12 becomes.

13 DR. RUSSELL: Joe, you said that deleted
14 TNF receptor would attenuate the virus, and that's
15 likely since a lot of genes to which you do that,
16 with the exception of (inaudible). Do you have
17 direct evidence of that?

18 DR. ESPOSITO: No. We have not said they
19 have knocked out in monkeypox or cowpox and actually
20 done the experiment. Those knockouts are available.

21 The cowpox ones are -- we are collaborating now.

22 We have actually identified three key
23 different TNF receptors in cowpox virus, which are
24 variance, and we are working with people at Duke
25 University, Bill Gogritz (phonetic), formerly Bill

1 Gogritz Laboratory in particular.

2 And he and I are developing a
3 collaboration with Vladimir Loparev to look into
4 this whole issue of what's going on with different
5 ones.

6 For example, ectromelia micepox virus does
7 not have this gene. You don't see ectromelia up
8 here. The gene is deleted from ectromelia. So
9 ectromelia doesn't have this, but it turns out it
10 still binds TNF.

11 It has another one, and the other one is
12 one that's analogous to the second one that we found
13 in cowpox virus.

14 So all told, we have identified so far in
15 different orthopox viruses three different TNF
16 binding proteins. So we think it is very crucial
17 that one, it really wants to keep this TNF binding
18 capability.

19 DR. RUSSELL: Is this one of the genes
20 that Enzo Piretti deleted from Copenhagen to make
21 Nivac (phonetic)? He took --

22 DR. ESPOSITO: This one is not a vaccine.
23 Vaccinia has a vestige of this one here. It's just
24 a truncated version.

25 DR. RUSSELL: It has the short one.

1 DR. ESPOSITO: Yes. You can see right
2 here. But what happens in vaccinia is the
3 truncation leads to a DNA frame shift, and that
4 causes just a small truncated protein.

5 We don't even know if it is produced or
6 not. But the sequences are there. I mean, one
7 theoretically could go into vaccinia and engineer
8 it.

9 Our next slide just simply slows the PCR
10 analysis similar to what you saw. Here we have
11 variola strain here, based on the TNF receptor gene.
12

13 And we have equally been able to
14 differentiate orthopox viruses. But here we are
15 keying on a virulence gene.

16 We are now accumulating sequences of a
17 seree (phonetic) protease inhibitor-like gene, which
18 we think is involved in transmission and cell-to-
19 cell spread of the virus.

20 So it's another gene that probably the
21 virus is going to have to have to be an effective
22 pathogen. And we have some sequences on that, and
23 we are now developing biogenetic trees for all that.
24

25 It's called the spy three gene, because it

1 resembles a serine protease inhibitor, but it doesn't
2 function in that capacity. It seems to be
3 functioning in cell and tissue formation or fusion
4 of the membranes of the affected cells so the virus
5 can travel around.

6 And that may be one of the mechanisms of
7 how it is carried around the body, also.

8 DR. ASCHER: Some of the enormous leaps in
9 molecular biology, you have shown us the three
10 generations of technology. And of course HMA is the
11 fourth.

12 And it would seem that if you wanted to go
13 into every single reference strain that you have and
14 even do classification for phylogenetic purposes,
15 you could do that in six months.

16 DR. ESPOSITO: Yes. I mean, the
17 technology is moving fast, and we get the
18 experiments done. That takes --

19 DR. ASCHER: Brian's history had some kind
20 of a time constraint of technology, and I think that
21 has kind of gone away. So that's very important to
22 reference.

23 In other words, they gave it three years
24 because that's how long it was going to take to
25 sequence it. In this case, if you used HMA, you

1 could knock these off in six months.

2 DR. ESPOSITO: Yes. I mean, it was not
3 long ago we were growing chicken eggs for --

4 PARTICIPANT: It's budget related as well.

5 DR. ASCHER: Well, exactly.

6 DR. MAHY: I think the other thing about
7 technology is that a lot of this stuff Joe is
8 talking about -- of course, the majority of it, any
9 virus -- but it's telling us a tremendous amount
10 about TNF receptors and --

11 DR. ASCHER: And does not require the
12 retention of live virus for the future.

13 DR. MAHY: -- which will all be done by
14 expressed proteins. At some point, you have to go
15 into the model, but the question is: Are you better
16 to go into an ectromelian mouse model rather than
17 going into something where there is really no --

18 DR. ESPOSITO: This is our first attempt
19 at an Eliza test. We have taken very finely
20 diverged viruses, vaccinia and raccoon/fox virus. I
21 mentioned this, and we were expressing this in a
22 bacteria.

23 And we can see with anti-serum against
24 each that we can differentiate these better than you
25 can with tissue culture cell material.

1 So we are pursuing this course, developing
2 diagnostics based on the HA protein that we would
3 eventually like to make an IGM test out of this on a
4 dipstick or something like that. So we are
5 proceeding along that technology right now and
6 expressing these genes.

7 DR. ASCHER: Brian, what is your time
8 constraint today?

9 DR. MAHY: I need to make it 1:00.

10 DR. ASCHER: Oh, okay. Fine. We have a
11 little more time.

12 DR. MAHY: We have another hour or so.

13 DR. ASCHER: Peter, I am going to ask you
14 to do your own introduction. I have the handout,
15 but the transition to your presentation is sort of
16 unclear, other than this is part of the overall
17 picture and more background information.

18 It is not a formal response to anything at
19 this point. It is just another bit of information.

20 DR. JAHRLING: Okay. In the interest of
21 time and Brian's schedule, among others, I am going
22 to present just a barebones -- I should not call it
23 a proposal so much as a strawman to address some of
24 the vulnerabilities that we in DOD still perceive to
25 exist.

1 And I think we all understand that the
2 urgency of today's meeting is driven by the pending
3 destruction, decision to destroy variola. It is an
4 irreversible step, of course. And reasonable people
5 will argue over whether the world is truly going to
6 be a safer place following this ceremonial
7 destruction.

8 And other people might also ask why, at
9 the eleventh hour, is the DOD coming back and
10 arguing for retention of variola. And speaking only
11 for myself, I can say that some of the information
12 which has recently become available, as you heard in
13 the classified briefing this morning, was very
14 compelling.

15 It at least compels us to reassess our
16 defensive posture against a real biological warfare
17 threat and ask some simple questions which may not
18 have simple answers.

19 We have raised these before, and they will
20 be raised later. But let me just frame what I think
21 is the essential questions for this group to deal
22 with right now.

23 How effective is the available vaccine
24 against aerosolized variola? Everybody think it's
25 effective, but nobody knows that. I would like to

1 know.

2 How are we going to treat biological
3 warfare casualties on the battlefield or in civilian
4 populations if they should become exposed, and what
5 are the scenarios? How would we even recognize a
6 variola attack unambiguously and rapidly?

7 I think you would agree that these are
8 legitimate concerns of the DOD. They are a little
9 bit different from the concerns of the Public Health
10 Service. And we would be irresponsible if we did
11 not address those deficiencies and propose
12 solutions.

13 We feel that some of these solutions
14 entail critical tests with variola itself. Reliance
15 on surrogate viruses and markers might seriously
16 compromise the development and validation of
17 effective countermeasures. So we have developed
18 this three-part proposal to address the critical
19 questions.

20 I have distributed copies of that proposal
21 to the advisory board. All three aspects of the
22 proposal require the use of infectious variola
23 intermittently over a three-year period.

24 The specific goal of each project is to
25 develop confidence in the use of other orthopox

1 virus strains to replace or act as surrogates for
2 variola in future development to diagnostic vaccine
3 or therapeutic strategies.

4 So I can show you the essence of that
5 proposal in a few overheads.

6 (Slide.)

7 Basically, we are talking about three
8 different things. One is to determine the protected
9 efficacy of vaccinia, either the Wyatt (phonetic)
10 stockpile, which is maintained at CDC, or the new
11 cell culture derived vaccine that is being readied
12 by the DOD as we speak, against aerosolized variola
13 in a valid animal model. And for that we mean
14 primates.

15 There has been some discussion about
16 whether there is in fact a valid primate model. We
17 have heard information this morning that is
18 testable, and we propose to test whether the model
19 that has been proposed in the classified briefing is
20 in fact the valid model.

21 There is also literature dating back to
22 the forties by Dr. Hanour working the DOD, where he
23 aerosolized variola and infected the periodic table
24 primates.

25 The numbers are very low, threes, twos,

1 that kind of thing. But whatever macaque-irus
2 (phonetic) is, which I don't believe is a
3 macaque -- I believe it's a podus (phonetic) monkey.
4 But in his hands, it was very susceptible to
5 aerosolized variola.

6 But we do have one lead of a readily
7 available primate that if we can confirm it to be a
8 valid model, both immunologically and virologically
9 compatible with what we believe to be human
10 smallpox, we will have a model in which we can test
11 that very critical question of whether the vaccine
12 does in fact confer protection against an
13 aerosolized challenge.

14 We would also like to evaluate antiviral
15 drugs for their ability to inhibit orthopox
16 replication, both in vitro and again in an animal
17 model.

18 And we have talked about transferring and
19 augmenting existing orthopox diagnostic capability
20 from CDC. It's very good to keep Joe Esposito's
21 number in our phone book. Joe is not going to be
22 there forever.

23 I think the feeling within DOD is that we
24 need to have our own capability. We probably won't
25 come close to matching your capability down there,

1 but at least a stand alone capability to rapidly and
2 unambiguously identify these viruses.

3 Could I have the next overhead?

4 (Slide.)

5 Okay. To get down in the weeds just a
6 little bit, and let me say, John Huggins was here to
7 talk about the antivirals. We have Joe, and Alan
8 Schmaljohn can talk about diagnostics efforts that
9 we are already beginning to develop.

10 Let me simply say from the standpoint of
11 animal model development and utilization, we propose
12 to look at susceptibility of readily available
13 primates, including rhesus and pseudocercopithecus (phonetic)
14 macaques, as well as baboons, to moderate
15 aerosolized doses of variola and to measure the
16 standard virologic and immunological parameters and
17 to compare the pathogenesis with the pathogenesis in
18 humans and, based on that data, select the most
19 valid model for efficacy trials.

20 Then we propose immunizing the animals
21 with vaccinia, either Wyatt or the cell culture-
22 derived vaccine, challenge after a moderate period
23 of time with aerosolized variola, and to cross-walk
24 these studies with monkeypox infections of primates
25 to determine if in fact we will feel comfortable

1 using monkeypox in primates as a surrogate for
2 variola in future development efforts.

3 Next.

4 (Slide.)

5 From the standpoint of determining
6 effective antiviral therapeutics against smallpox,
7 there is no commercial market for this. Nobody is
8 testing it.

9 However, people are developing antiviral
10 agents with efficacy against other DNA viruses that
11 act in ways that one would expect to be effective
12 against orthopox viruses as well, that being
13 inhibitors of DNA polymerase or cap methylation
14 inhibitors. And John Huggins may address those
15 issues in detail, if you wish.

16 We would propose looking with vaccinia at
17 monkeypox in vitro and screening assays and put the
18 reserve variola for critical evaluations.

19 Also to determine the therapeutic efficacy
20 of drugs that come through that screen against
21 variola and eventually monkeypox in a model, to
22 complete the preclinical microbiological section of
23 the new drug application and, of course, to maintain
24 a tech watch for potential new drugs, by that point
25 using variola surrogates.

1 And one more slide.

2 (Slide.)

3 Okay. Actually, Dr. Esposito has given a
4 terrific overview of the development of diagnostic
5 systems based on PCR. We are talking actively about
6 transplanting that capability to USAMRIID or
7 elsewhere.

8 I would say just at the bottom here, after
9 development we feel that methods must be calibrated
10 for sensitivity and specificity using clinically
11 relevant materials, and also to determine our
12 diagnostic capability in artificial mixtures in
13 various orthopox viruses and variola mixed with
14 other potential BW agents. This again is a question
15 a little bit different from the one which CDC has to
16 grapple with.

17 Dr. Russell asked a question about
18 basically what is the sensitivity and specificity of
19 the method, and that's a testable question.

20 We can get the answer easily, but we feel
21 more comfortable knowing what the limit of
22 sensitivity is of the PCR or whatever PCR capability
23 is.

24 And last.

25 (Slide.)

1 I just want to reiterate that all three
2 aspects of this proposal entail the use of variola
3 over a three-year period. The specific goal of each
4 project is to develop confidence in other orthopox
5 strains through variola in future development
6 efforts.

7 We also recognize that the potential
8 ramifications of the DOD facility working with
9 infectious variola at this point in time could be
10 very damaging to the reputation of USAMRIID, as well
11 to ongoing international negotiations regarding
12 nonproliferation.

13 The critical facet in the successful
14 execution of these proposal will be active
15 collaboration with our colleagues in the Public
16 Health Service, specifically the folks that are here
17 today from the maximum containment lab of the CDC.

18 That is a very broad overview of the
19 proposal that we would like to put on the table.
20 And if there are specific questions, I will be glad
21 to answer them or refer them to people with the good
22 answers.

23 DR. ASCHER: How important is the lead
24 that we heard about on the primate model to this
25 whole plan? And if you deleted that from your

1 consideration, would you be talking about this at
2 all?

3 DR. JAHRLING: I think it is still
4 reasonable to go look at readily available primates.
5 We have virologic and immunologic tools that didn't
6 exist back in the forties, when that study was
7 really last done systematically. So that it is
8 reasonable to think a model might be developed.

9 But I think that information you just
10 alluded to is critical. It looks like there is a
11 very real possibility that a valid model exists.

12 DR. ASCHER: So that raises your
13 plausibility.

14 DR. JAHRLING: Yes.

15 DR. MAHY: Peter, where does this fit into
16 your priorities? Have all the other agents that
17 troops might encounter, for example, in South
18 America or in Africa and other countries where we
19 have a variola virus -- we have no vaccines.

20 We have many hemoratic fevers (phonetic)
21 now. I mean, a good job has been done with -- but
22 there are plenty of other viruses that need to be
23 looked at. I just wondered where this --

24 DR. JAHRLING: Okay. Well, that list, of
25 course, is always evolving based on threat

1 assessments and what have you.

2 I think the threat assessments are
3 sufficiently credible that we have to seriously
4 consider them and maybe nudge this agent a little
5 bit higher on our list of priorities.

6 It will have an impact on other
7 requirements, on BL-4 space. Something is going to
8 drop off the bottom of the list.

9 But my personal feeling is that the
10 evidence I have heard has been telling us or leading
11 me to believe that maybe something does need to fall
12 off the bottom of the list.

13 DR. RUSSELL: What is using BL-4, BL-3 and
14 4 capability now?

15 DR. JAHRLING: We have a big effort of
16 fuella (phonetic) viruses, Marberg and ebola
17 (phonetic), of course. We still have an ongoing
18 tech watch with the urana (phonetic) viruses.

19 Some of the Hanta virus work is still
20 requiring BL-4, that work going on in animals. We
21 also have ongoing efforts with tick-borne
22 encephalitis virus. Am I leaving one out?

23 DR. MAHY: Congo-Crimea?

24 DR. JAHRLING: Congo, yes.

25 DR. HALVORSON: Do you have an ongoing

1 effort in Congo?

2 DR. JAHRLING: Yes. It's a sporadic
3 effort. There is nothing going on specifically
4 right now with Congo, but there are -- actually,
5 that is the one that is in the wings waiting for
6 availability of --

7 DR. MAHY: We have just had the largest
8 outbreak of Congo in many years, as you know, in
9 1988.

10 DR. JAHRLING: Right.

11 DR. MAHY: Thirty-five cases and fifty
12 percent death.

13 DR. HALVORSON: You have given us a list,
14 an appendix of materials. Do you want to test it?

15 DR. JAHRLING: Those are the antiviral
16 drugs that Dr. Huggins compiled.

17 DR. HALVORSON: Could you comment briefly
18 on opportunities within these?

19 DR. JAHRLING: John, I think maybe that is
20 one for you.

21 DR. HUGGINS: Okay. Let me introduce this
22 with a little bit of why we think that -- we are
23 fortunate in a couple of things.

24 First of all, viral DNA ratification is
25 fundamental to the virus replication cycle.

1 Inhibition of it clearly stops virus replication.

2 Our advantages of the DNA called alphas
3 share in common a number of conserved sites among
4 all DNA replication viruses commonly designated as I
5 through XI.

6 Of these, there is a separate agent area
7 called Region A, which is where the drugs bind. And
8 it shares no sequences with the human alpha, which
9 just means that it doesn't hit the normal
10 replication enzymes.

11 And it is very homologous to herpes
12 simplex virus, which has been the lead virus in this
13 area. It in fact shared sequence homology with HSB,
14 EBV and others.

15 And in the critical areas of the binding
16 domains, there is essentially homology with the A,
17 the 2-3 and the 5 regions, which are where the drugs
18 bind.

19 Therefore, the DNA replication for
20 vaccinia is inhibited by the same classes of
21 compounds that work against HIV, for which herpes
22 simplex is in fact the lead.

23 Next one.

24 (Slide.)

25 Because of this, we have been able to look

1 very rapidly to see that the development of drugs
2 against herpes simplex, CMV, VZV and EBV, is quite
3 advanced.

4 That means there are several compounds
5 already approved for clinical use against herpes and
6 CMV. And there is a large number currently in phase
7 two, phase three clinical trials.

8 The vaccinia and the variola DNA called
9 alphas also are very close to each other. Ninety-
10 eight percent identities, ninety-nine percent
11 conserve changes, one deletion.

12 All of the critical areas, I through XI,
13 are homologous between vaccinia and variola and
14 also in the critical A, 2-3 and 5 domains between
15 even HVS herpes. Therefore, the homology, even
16 though they are only 30 percent or so, mean that we
17 have a very conserved area.

18 Next.

19 (Slide.)

20 What this has done has meant that a large
21 class of compounds working against viruses that are
22 in clinical development by a large number of
23 pharmaceutical companies are known to inhibit either
24 vaccinia or closely related analogs.

25 These include the acyclic guancic

1 (phonetic) analogs, such as gancyclovir (phonetic).

2 They include BVDU. They include a new drug called
3 HPMPC, which has now been given the name cydobovir
4 (phonetic) by Iliad (phonetic) Scientific, which is
5 in phase three clinical trials for CMV.

6 These compounds, along with some older
7 compounds like PAA and phoscarnate (phonetic) are
8 known to inhibit a number of animal models.

9 I think I will jump to a little bit of a
10 change on this thing, and that is to say that there
11 are some vaccinia animal models available using the
12 skid mounts.

13 And here you see one of those compounds,
14 HPMPC, which is in phase three clinical trials, in a
15 study in which you are looking now at the survival
16 of skid animals infected and treated for a period of
17 only five days.

18 And you can see the comparative control
19 animals, treating for only a five-day period with
20 increasing doses, causes a significant increase in
21 mean time to death. And treating on a twice weekly
22 basis for twenty weeks causes significant extension.

23 The other thing we know about this study
24 is the cause of death for those animals has not been
25 determined, but they appear to die without vaccinia.

1
2 So that may have simply been a laboratory
3 animal room and the infection that killed them.

4 But if we go on and look a little farther
5 at that, looking at this drug, treating only for a
6 total of five days, the first five days of the
7 study, looking at various organs, liver, kidney -- I
8 have trouble reading the top one -- what you see is
9 that there is a significant inhibition in viral
10 replication for a significant washout period.

11 The drug probably washes completely out
12 within a week. And you see that there is an
13 inhibition of virus replication followed by a slow
14 regrowth.

15 This can be looked at even a little
16 farther. In this case, looking at prophylactic
17 treatment either at day minus seven or minus one
18 with 100 milligrams per kilogram per day, looking at
19 either a tail lesion score on day seven or eleven,
20 where you count the number of tailpoxes, or looking
21 at mean time to death, you see that in this case of
22 a single growth dose treatment, you get a
23 significant increase in the survival of these
24 animals.

25 The other thing we see is if you delay

1 treatment in this model even out as late as six
2 days, you still get a significant increase in mean
3 time to death with this particular drug.

4 This is not necessarily being the best
5 drug against vaccinia. This ends up being a drug
6 that for reasons that Eric likes to work on these
7 various compounds has been tested in a vaccinia
8 model.

9 Most of the drugs in this category have
10 not been adequately tested, and there is a whole
11 series of compounds that show activity here.

12 So what we end up with is, along with the
13 compounds you see in the first list of things that
14 are known to have vaccinia activity, you see
15 structural analog targeting this enzyme that are
16 also likely to have activity, belcyclovir,
17 pencyclovir, gancyclovir.

18 In other words, there are a lots of
19 compounds in clinical development which certainly
20 fit into the category that inhibit the enzyme that
21 we are going to target.

22 There are other classes of those compounds
23 to be looked at, but I think because of the clinical
24 development of these compounds, this is clearly
25 where we would want to start.

1 DR. ASCHER: Dr. Halverson, was there
2 anything more? Did you have any more questions
3 on --

4 DR. HALVERSON: No, no. I want to get a
5 sense of which of these that are coming are new,
6 that are deriving, that have not been going through
7 a system.

8 DR. HUGGINS: HPMPC is probably the newest
9 hot compound for CMV. What we end up with is a
10 spectrum of compounds with increasing ability to
11 inhibit both the enzyme and with a little bit of
12 additional toxicity, although we now have cyclic
13 HPMPC, which is perhaps 50-fold even less toxic than
14 HPMPC and which may only need to be dosed weekly.

15 So that's a new compound, and there are
16 even newer compounds in phase two clinical trials.
17 Most of these compounds have occurred in the last
18 five years and are now into phase two and three
19 clinical trials for either CVM, VSV.

20 Herpes, I think there is less effort on it
21 because CVM and now gancyclovir has sort of tied
22 that market up. But certainly, these are being
23 developed against some of the more severe diseases
24 because there are market niches for them.

25 DR. RUSSELL: How does their in vitro

1 inhibitory capability compare with the (inaudible)?

2 DR. HUGGINS: Those have only really been
3 looked at in a very limited case, but they appear to
4 be much better inhibitors; that is, in inhibition
5 assays, they can completely shut down viral
6 replication.

7 I think the viosemi (phonetic) carbosomes
8 had only a moderate to very weak therapeutic index
9 ratio. That is, there was a lot of toxicity
10 associated. We had to dose them nearly to toxic
11 dose.

12 Whereas in these compounds, certainly for
13 CMV retinitis and seminated (phonetic), there's a
14 significant therapeutic index there.

15 So I think what we have here are compounds
16 that not only inhibit virus replication very well,
17 but have a very wide safety margin compared to the
18 old compounds.

19 DR. ASCHER: And the anecdotal experience
20 with even acyclovir in chickenpox and zoster is very
21 good.

22 I don't think that that has been submitted
23 for licensure modification, but once you license a
24 drug, of course, it's used for everything. But all
25 the referral cases we see of severe chickenpox on

1 acyclovir.

2 And I think if somebody showed up in a
3 hospital right now in the United States with
4 smallpox, they would get acyclovir for chickenpox.
5 And I suspect it would work.

6 We would really not have a clue until you
7 do some of this. But the indications are that it
8 should work.

9 DR. CASSELL: John, would you like to make
10 any comments related to the importance of this area?

11 PARTICIPANT: In the whole area of
12 orthopox virology, we honestly think it is very
13 important since we have a laboratory and our program
14 is devoted to this area. I am sad that Dr. Moss is
15 not here.

16 In the area of antivirals, we along with
17 other, have been in a concerted effort to develop to
18 antiviral drugs over the last 20 years. Some of
19 these compounds -- he's right.

20 The acceptability of these drugs is much
21 better than it was with RINP (phonetic) and with
22 other substances 20 years ago.

23 And the similarity with the herpes
24 replicates is (inaudible) and would be worth looking
25 at.

1 DR. RUSSELL: How essential is the live
2 variola virus to evaluating these?

3 PARTICIPANT: I don't know. That's a good
4 question. I think that vaccinia -- from what I
5 gather from the sequence data, it is pretty similar.

6 PARTICIPANT: There is 98 percent virology
7 in --

8 DR. RUSSELL: My confidence in the
9 explanations of pharmacologists on mode of action is
10 less than 100 percent.

11 (Laughter.)

12 PARTICIPANT: But the mode of action of
13 acyclovir, for example, or AZT or chain terminating
14 is pretty well worked out.

15 DR. RUSSELL: A mode of action is.

16 PARTICIPANT: A mode of action.

17 DR. RUSSELL: Not the mode of action in
18 the live critter or in the virus cell interaction.
19 I mean, it's a lot better, I admit.

20 PARTICIPANT: But variola vaccinia --

21 DR. RUSSELL: In this case, you depend on
22 analogy in the other viruses, the vaccinia,
23 ectromelia and so forth and then have to extrapolate
24 that and then convince then convince the FDA that
25 you were right.

1 PARTICIPANT: But basically, you are not
2 really --

3 DR. RUSSELL: I am just making an
4 argument.

5 PARTICIPANT: Well, yes, but it was kind
6 of an interesting discussion, because you are not
7 going to market it for smallpox. I mean, you
8 basically would want enough information.

9 DR. RUSSELL: We didn't market
10 paradostigme (phonetic) for a nerve gas either. We
11 had a shitload of trouble using it.

12 (Laughter.)

13 DR. HUGGINS: Those letters keep coming,
14 let me tell you.

15 DR. ASCHER: John -- I mean, Brian --
16 sorry, John. You had not seen this before, then.
17 You had not seen this proposal in truth.

18 PARTICIPANT: No, I hadn't.

19 DR. ASCHER: And, Brian, had you seen it
20 at all, the proposal?

21 DR. MAHY: No, but I know that Joe has
22 been here --

23 DR. ASCHER: Gail and I would like --

24 DR. MAHY: -- independently. And I think
25 the -- I can comment on CDC's view on

1 this --

2 DR. ASCHER: Yes.

3 DR. MAHY: -- which really comes into the
4 whole question of priorities. Clearly, we want to
5 help DOD in any way we can, but we also have our own
6 priorities in relation to the P-4.

7 Would you like me to go through these
8 other points now?

9 DR. CASSELL: I think that would be good,
10 but could you maybe comment a little more
11 specifically with respect the proposal that these
12 studies be conducted over a three-year period?

13 DR. MAHY: Yes. I think the first thing I
14 would say is that I don't think -- I think there are
15 studies that we could do that might helpful which
16 would not involve the use either of live virus or of
17 our facility.

18 And I would like to see -- and I think I
19 am speaking also for Jim Hughes at the Center. I
20 think we would like to see a diagnosticator be
21 expended as much as possible so that -- we would
22 like to help to get that transferred to DOD.

23 I don't think myself that I would ever get
24 away from CDC with even getting approval for an
25 aerosolizing smallpox virus infecting monkeys with

1 this, even if I had the facility to do that. I
2 really don't think I would ever get through our
3 animal people at CDC. It's very hard actually to
4 even do essential experiments with rabies and others
5 that we have to do. And I think that would be just
6 about unthinkable.

7 So then the question arises if DOD needed
8 to do this -- of course, they don't have access to
9 virus, and the question is how would the virus be
10 brought here to do such experiments?

11 I think that is almost unthinkable, also.

12 So we are in a difficult situation in terms of
13 saying, "Well, this is a great idea, Peter. Let's
14 get on with it."

15 (Laughter.)

16 We have two parts. We have a larger force
17 than even they do here, but it's essentially similar
18 in design. And we have two separate laboratories.

19 We tend to work obviously with one agent
20 or with agents at a single time for the most part;
21 so that with antiviral polmy (phonetic) syndrome
22 work, which a considerable amount of work is going
23 on -- we now have five different antiviruses polmy
24 syndrome in the Western Hemisphere.

25 And there's a lot of work going on. We

1 want to find out transmission in rodents. We want
2 to find out ways of dealing with this to eliminate
3 this, because is a domestic problem which was on our
4 doorstep. It's dealing with -- but we don't work in
5 the same facility, for example, with ebola and
6 Marberg.

7 As I am sure you have seen, we have just
8 gotten another case of ebola from Africa, which has
9 been announced. We working with that virus. We
10 have a lot of other things going on that require the
11 other facility.

12 Now, when we close down one, we have to
13 then decontaminate for two weeks. So we can move
14 whatever experiments in one into the other, and then
15 we continue, finish that off and start something
16 new.

17 In the smallpox work, the only time that
18 we grow smallpox was the Garcia growth was at the
19 end of one of these decontaminating procedures just
20 before we -- we use them now to make these smallpox
21 viruses -- so it is very difficult for me to see
22 that I could put this as a priority at CDC over and
23 above many, many of the other things that we have.

24 We have quite a number now of new
25 arenaviruses (phonetic) from South America that we

1 are trying characterize in fairly simple terms. We
2 are working with the Yale group. We have Chuck
3 Fullhosh (phonetic) from Yale, who is almost full
4 time working with these various viruses, in
5 particular the Venezuela hemoratic fever and the
6 Brazilian hemoratic fever.

7 John Paul Gonzales, a guy who actually
8 infected himself at Yale, is with us at the moment.

9 He is not going into DSL-4, but he is working
10 there. And we are very interested in characterizing
11 that virus.

12 So with all these things, I am not saying
13 that it could not be possible, but I think the type
14 of experiment we did would probably be more limited
15 to something like something that John was talking
16 about, maybe looking at the effect of an antiviral
17 in growth cultures, I mean, that
18 sort -- I cannot conceive of experiments on animals
19 that we would be allowed to do.

20 DR. ASCHER: Be allowed on what basis,
21 Brian? Priority, space or the political issue?

22 DR. CASSELL: All the above.

23 DR. MAHY: That would be not political.
24 That would, I think, be the basic agreement of the
25 animal use. I forget the name is exactly,

1 but --

2 PARTICIPANT: Animal Care Use Committee.

3 DR. MAHY: Animal Care use Committee,
4 which basically has to approve any experiments that
5 we do on animals.

6 DR. ASCHER: Well, that is a twist I had
7 not thought of.

8 DR. MAHY: Now, over and above all these
9 factors is the fact that CDC is being reduced at a
10 very considerable rate in order to make a government
11 that costs less or works better.

12 So I am losing -- we just lost nearly 20
13 percent of our staff. We may be losing 2 percent of
14 the staff each year for the next 5 to 10 years.

15 So that we also have to then say: How
16 does this fit in with those four new hepatitis
17 viruses that we discovered last week, for example?
18 So there are many other priorities like that. But
19 over and above that, we also have to find money.
20 And we can't afford these things.

21 DR. CASSELL: Okay. I think Dr. Takafuji
22 has something.

23 DR. RAUCH: I don't understand the animal
24 use consideration. But apart from that, I think any
25 implementation of DOD's research plans at the CDC

1 really needs to engage Steve Joseph and David Sacher
2 (phonetic) or Joseph and Phil Lee.

3 DR. MAHY: Yes. You are quite right.

4 DR. RAUCH: It needs to be worked out at
5 that level. I mean, we could speculate all we want
6 to about it, but I think that because of the
7 political sensitivity of the issue, it really needs
8 to be worked out at that level, including resources.

9
10 I mean, everybody understands that you all
11 have your own domestic priorities. That's why it
12 needs to be worked out not here.

13 But now, I don't understand the animal use
14 --

15 DR. MAHY: I was referring specifically to
16 certain types of experiments. I wasn't referring to
17 -- if those are useful animal model, we could
18 investigate the interaction of a variety of their
19 uses. But there is one thing.

20 I do not think that (inaudible), either
21 smallpox virus infection of monkeys (inaudible)
22 because of a particular scenario, it is not one
23 which is what they call (inaudible). And it is
24 certainly not one that could easily be got through.

25 DR. TAKAFUJI: Brian, I would like to make

1 a few comments, if I could. There is no one more
2 sensitive to me in terms of what is happening at CDC
3 and the cutbacks that you are sustaining.

4 It is devastating, and I am very much
5 appreciative of the constraints that you are
6 operating under.

7 One issue needs to be made explicitly
8 clear, and that is the smallpox issue is not a DOD
9 issue. It's a national issue.

10 And therefore, from the standpoint of all
11 laboratories, regardless of whether they are DOD-
12 colored laboratories or they happen to be in the
13 U.S. Public Health Service or whatever they are, I
14 think it's important that laboratories need to look
15 at this as a common problem that we have to work
16 together on.

17 So I would certainly encourage some things
18 that Terry Rauch has already alluded to, and that is
19 that there is a need for a sense of cooperation as
20 we move this project.

21 The second thing is that there are some
22 projects that you have down in CDC that I suggest
23 maybe could be done up here at USAMRIID. Because
24 the dilemma that I see us facing is moving the
25 virus.

1 We can't move the virus for all the
2 political reasons that have been discussed. And
3 that is a limiting factor regardless of what we want
4 to do or not want to do or what you want to do or
5 not want to do. That is a reality that we have to
6 deal with.

7 So in terms of the priorities that both
8 your laboratory has, as well as the priorities that
9 our laboratories have, I think we need to look at
10 aspects in terms of how two laboratories could
11 collaboratively work together on not only these
12 types of disease but the Hanta viruses, ban the
13 sidsonio (phonetic) viruses and all these other
14 viruses that we need to come to common resolution
15 on.

16 So I through that out as an item of
17 discussion. The fact that laboratories cannot
18 address it is really not pertinent here. What we
19 need to do is get the board to address the issue of
20 what needs to be done.

21 And once we come to an agreement on what
22 needs to be done, then we can go from there and
23 decide where is the logical place where it can be
24 done and how we can work together.

25 DR. MAHY: I think the issue here is

1 getting a bit out of the debate. But the issue is
2 that I am currently, and all of us at CDC are going
3 through a tremendous process of cutting down.

4 We no longer have any expertise to speak
5 of in corona (phonetic) viruses, paramixa (phonetic)
6 viruses.

7 We are cutting out lots of programs, parvo
8 (phonetic) viruses, many, many things which are --
9 the public health things which we are asked about,
10 we need to provide information.

11 And I am saying that within that, as I see
12 it from my standpoint, this does not have a priority
13 that would make me welcome this proposal as
14 something that we need to do straight away. I mean,
15 this --

16 DR. ASCHER: Outside of this discussion.

17 DR. MAHY: That is all I am saying. And
18 obviously, if it was agreed at the highest level for
19 national interest that we had to have this service
20 be available, then we would cut other things out.

21 DR. ASCHER: Outside of this discussion at
22 our previous board meetings here at this institute,
23 we took tours, which indicated that Ernie's point
24 about getting together is absolutely clear.

25 BL-4 space is rate limiting for the total

1 American response to all these agents with new ones
2 coming up every day.

3 And if there is any duplication or any
4 whatever going on, it really should be Dr. Joseph
5 and Dr. Sacher's goal to have this one common
6 facility for the nation.

7 And whether the CDC is doing work in their
8 facility or doing work in CDC's facility, however
9 that works, I think that should be a goal, unless
10 you are going to get more space.

11 I mean, do you want us to recommend you
12 should have more BL-4 space because the country is
13 in a desperate shortage? I think we would do that
14 as well.

15 DR. MAHY: Well, certainly, as you know,
16 the head of our special branch came from here. We
17 are in very close contact.

18 We do -- I think it is fair to say, Peter,
19 we have a very close relationship in what we do. I
20 think the possibility of unnecessary duplication is
21 almost out.

22 But in other respects, I would agree with
23 you. And I think NIH is considering it. But where
24 are your people, John? I mean, your
25 people --

1 DR. JAHRLING: I don't know that those
2 plans have been advanced much beyond the thought
3 stage.

4 DR. MAHY: We have just had our own
5 laboratory axed by the decision.

6 DR. ASCHER: Yes. That's why I am asking.
7 I just want to get this on the table so we
8 understand. The FDA program is down, and yours is
9 next.

10 DR. MAHY: I mean, our entire laboratory,
11 our new laboratory for work has been cut by \$40
12 million. So we have no -- and our current
13 laboratory where Joe works has been contaminated.
14 So we are having a --

15 (Laughter.)

16 DR. CASSELL: And the construction monies
17 for NIH have just been cut by \$73 million. And it
18 looks like that's pretty certain that that will
19 happen.

20 Bud has had his hand up patiently now for
21 a long time.

22 DR. ASCHER: Oh, I'm sorry.

23 DR. BENENSON: I wanted to raise a very
24 unorthodox question. Why can't variola work be done
25 at class 3?

1 DR. ASCHER: That is what I wanted to ask
2 Ernie about a minute ago.

3 DR. BENENSON: Yes. You don't have to be
4 limited.

5 DR. ASCHER: With vaccinated personnel,
6 vaccinated personnel.

7 DR. BENENSON: With a properly set up,
8 tightly controlled class 3 facility and personnel
9 re-immunized, I'd say, every year, you would have
10 absolutely no hazard.

11 DR. MAHY: In previous years, we had a
12 facility. There was a facility that had essentially
13 gone into disuse at CDC, which Joe was working in,
14 which was like P-3 .

15 It was a vaccinated people only facility
16 in which we could work with the virus. In fact,
17 what happened at CDC was when came to try to reopen
18 that facility for this purpose.

19 We discovered all the pumps for removing
20 the affluent had seized up, and everything was in a
21 mess. And we finally decided to move the entire
22 operation in any attempt to grow the virus into the
23 P-4 lab.

24 You are absolutely right, but that is a
25 decision, if you like, made at the CDC management

1 level. We consider it too risky to possibly expose
2 engineers, sanitary workers, other people who are
3 not vaccinated to the risks of that type of thing.

4 It was a very different situation 10, 20
5 years ago. Now we have a large number of people who
6 have never been vaccinated before and who may come
7 in contact with this. And the easiest way to deal
8 with it is to deal with it in D-4.

9 DR. ASCHER: What I asked Ernie was that
10 the Army, or whoever built the facility at Dugway,
11 apparently a modern version of this for P-3 work,
12 particularly for aerosols -- and I don't know that
13 that has to be discussed, but there is potentially a
14 possibility, if you followed Bud's agenda to talk
15 about that, it would have to be done with a lot of
16 consultation.

17 DR. BENENSON: But the limiting factor,
18 going back to what Brian said earlier, is that we
19 can't move the virus. That's the dilemma that
20 we --

21 DR. ASCHER: Right.

22 DR. BENENSON: Politically, we can only do
23 it in one place. That's the dilemma that Peter and
24 I have talked about.

25 PARTICIPANT: And that is not going to

1 change either.

2 DR. BENENSON: And that is not going to
3 change. So we are stuck. If we are going to do any
4 work, it has to be done at CDC.

5 DR. KRIKORIAN: But it doesn't have to be
6 done in P-4 facilities.

7 DR. BENENSON: Not necessarily, depending
8 on what the study is and what the risks are. But I
9 am not going to set your priorities and your
10 concerns, because your concerns are certainly valid
11 ones. There is an element of risk that has to be
12 addressed and has to be defined, because --

13 DR. MAHY: I certainly don't think that
14 the -- I personally do not think that any people in
15 CDC at management level would agree to work with
16 smallpox outside of our P-4 facility.

17 I could be overruled on that, but I don't
18 think so, because that came down from on top to me.

19 DR. BENENSON: Well, that is your
20 decision. You see, that is your internal decision.

21 DR. MAHY: It wasn't my decision to do it
22 that way, but I think it's --

23 PARTICIPANT: I might point out that
24 trying to do an aerosol challenge experiment at
25 anything less than P-4 would be unwise.

1 DR. KRIKORIAN: At Walter Reed, at least
2 when I was there, I don't know, we immunized
3 engineer personnel and required them -- who had to
4 have access to restricted areas.

5 DR. BENENSON: You were not trying to
6 aerosolize at (inaudible) which is what would be
7 done at --

8 PARTICIPANT: I have one concern here
9 because I have to sit in with the (inaudible) and
10 that is I would like to kind of redirect us back
11 towards the science. What we are discussing right
12 now can be discussed in other forums.

13 But we have the scientific expertise here,
14 and that I think that's what we need to concentrate
15 on and trying to provide some scientific guidance to
16 those people who have to sit down and don't have the
17 expertise. I would kind of try to encourage you all
18 to turn back to that direction.

19 DR. KRIKORIAN: Well, we are going to lose
20 Brian, too, and if we don't get --

21 DR. MAHY: I think what we are talking
22 about, Debra, is that last section that was
23 concerned with what agency's responses are.

24 And I think that was the last issue I was
25 going to deal with before I leave, because that was,

1 I think, important for each agency to answer that
2 last page.

3 DR. ASCHER: Well, that is what we have
4 next. That's exactly where we are. In fact, I have
5 both sets of responses, and that is what Gail just
6 mentioned to me.

7 We are referring category three of the
8 questions on a set of questions that most of you got
9 faxes for. And Peter Jahrling has also agreed to be
10 a resource for this discussion.

11 It is not a long list, and it is not
12 nearly as complicated as the previous questions. I
13 will read the questions, if you don't have them, and
14 I have -- Brian, did you pass them out, or do we
15 have extra copies?

16 DR. MAHY: We will pass these around.

17 DR. ASCHER: John, are you prepared after
18 these two to make your comments about some of these
19 issues of the three-part questions? Okay.

20 Well, let's read the questions and then
21 see if there are any concerns. We have handed out
22 your responses, and they speak for themselves. And
23 then we will comment as we go through them.

24 DR. HUGGINS: Why don't I copy this?

25 DR. ASCHER: That's fine.

1 And the questions are obviously: How
2 frequently has variola virus been grown in the U.S.
3 over the past 15 years for the purposes of research?
4

5 The DOD's response, which you don't have,
6 it says, "Very infrequently over the last 15 years,
7 variola stocks were sent to CDC in 1981."

8 We had already heard that. And your
9 response was that the growth is only in 1980, 1981,
10 1984 and once in 1991.

11 Part B is: What facilities now exist in
12 the U.S.? And the military response is fairly
13 succinct.

14 It says, "Infectious variola research must
15 be conduct in BSL-4 biocontainment, gas-type glove
16 boxes or spacesuit labs. Only two such labs exist
17 in the U.S., one at USAMRIID and one at CDC."

18 And your response basically is the same.
19 I see nothing in conflict at all.

20 See how recent changes in the threat
21 assessment in infected plans and priorities for
22 research on variola.

23 The CDC response is very short, "Plans and
24 priorities for research have not been affected by
25 recent change."

1 And the DOD response, obviously from this
2 morning and later discussion, is a little more
3 detailed.

4 It says, "Recent changes in the biological
5 warfare threat have generated a reassessment of the
6 DOD posture against orthopox viruses."

7 Three areas of concern were identified,
8 and the research proposal we heard, referencing
9 diagnostic vaccine efficacy and chemotherapeutics is
10 then referenced.

11 I think that is consistent with the
12 presentations we have heard, both on the threat and
13 on the proposal.

14 DR. CASSELL: Could we ask Brian if he
15 would still respond --

16 DR. ASCHER: Yes.

17 DR. CASSELL: -- as C after this morning?

18 DR. MAHY: I would not see that there
19 would be any change at CDC. I mean, I think the
20 data we heard was interesting.

21 But I think the arguments which we feel in
22 terms of the need for live virus in order to respond
23 to such a threat I think remain somewhat similar in
24 that if an attack or something occurs, we would not
25 turn to our live variola stocks. We do need to be

1 ready with appropriate measures, appropriate
2 vaccines.

3 And obviously, we would isolate any virus
4 that appeared. That's our duty with any smallpox
5 situation. But I am only speaking for myself.

6 And I think it is something which, as has
7 been said before, could be talked about at a higher
8 level in terms of the importance of
9 the -- in terms of hard data that we saw. Nothing I
10 saw made me feel that there was a need to start work
11 with live variola virus.

12 DR. ASCHER: D is fairly straightforward.

13 What plans do either of the facilities have using
14 the present containment facilities for experimental
15 work?

16 We heard the DOD proposal that restates
17 that. And it is also referenced to a new cell
18 culture vaccine. And Brian's statement is a clear
19 restatement of what he said this morning, based on
20 the Garcia sequence and closing the loop.

21 This is all fairly clear, I think. I
22 don't see any problem. Any corrections or additions
23 since this was written on anybody's part?

24 And then we have talked also about what
25 level of priority do those responsible for the

1 present containment facilities assign to
2 experimental work? The two responses, again stated
3 by Brian clearly a few minutes ago, are that it has
4 very low priority.

5 The DOD basically says it is one of their
6 things they have to be concerned about, the same
7 consistent position.

8 And the last point, Brian, about a lot of
9 this can be accomplished without the live virus,
10 which I still think --

11 DR. MAHY: Right. I think it is
12 absolutely essential that we maintain a good
13 diagnostic capability.

14 I don't know how many reports we get, but
15 I think it was reported to the September meeting
16 that about 170, 180 reports have been received by
17 WHO of smallpox emersion since the eradication and
18 have dealt with -- the vast majority tend to be
19 measles or chickenpox, but there were also a number
20 -- I know Joe has investigated some bones and mummy
21 pits and so on periodically.

22 It's very important that we have a
23 capability to continue to deal with these
24 possibilities.

25 DR. ASCHER: John, is your perspective

1 similar on these questions, or did you have anything
2 you wanted to --

3 DR. HUGGINS: I have nothing to add to the
4 questions that have been -- the five questions that
5 were listed and provided. The NIH does not work
6 with variola and has not worked with variola for a
7 long time.

8 We have no capability on the campus that
9 would be comparable to the capability that exists
10 here in Atlanta. So we could not entertain even the
11 possibility of including the kinds of
12 experimentation that Peter was talking about.

13 In just thinking about question number E
14 that has been talked a little bit about here. I
15 mean, I think that Peter's presentation at least
16 made me think a little more about this issue to some
17 extent.

18 And I think that one might want to look a
19 little more seriously at validating whatever
20 surrogate model systems you are looking at in terms
21 of antivirals or other activities.

22 Some focus to animal work I think might be
23 a very reasonable thing to think about. Whether or
24 not that could be done soon or not, I don't know.

25 To what extent, I don't know either. I

1 haven't thought that much about it. That is a very
2 much a top of my head answer.

3 DR. JAHRLING: The logistics of doing that
4 kind of an animal experiment are very -- they are
5 not that formidable. We do that kind of experiment
6 all the time with -- it's just a matter of getting
7 clear.

8 DR. HUGGINS: I realize that, Peter. I
9 think it would be valuable just to know that the
10 tissue culture and surrogate systems that you are
11 working with have some grounding in a model system
12 that has some -- what do you think?

13 DR. RUSSELL: Well, there is no substitute
14 for validating models, if you are going to depend
15 mainly on surrogate systems. And the problem, of
16 course, with variola is you never can get through
17 homology.

18 You either have to have a host with the
19 variola virus in whatever you are dealing with, or
20 you have a homology between the virus and the host,
21 but it is not variola.

22 So you are stuck. And doing experiments
23 to validate all three arms of that triangle are kind
24 of important. I have been trying to think about
25 some of the experiments that are important.

1 One of the things that worries me is, of
2 course, threat assessment, how do you validate it?
3 And we have depended traditionally on experiments
4 done either recently or in the past to help us
5 assess this very, very fragmentary kind of
6 information that comes through the intelligence
7 community. They get information, and much of it is
8 experimentally testable.

9 The question of the effectiveness of
10 vaccinia against aerosolized viruses is
11 theoretically testable. Politically, I have very
12 serious doubts whether it is even remotely possible
13 to test from a political point of view.

14 The other one that bothers me from a
15 threat assessment point of view is how the hell do
16 we deal with the issue of the virus with an
17 additional gene put in, a down regulating agent of
18 some sort?

19 Could you even do that experimentally with
20 monkeypox? Could you take -- or even ectromelia?
21 Could you even do those experiments with ectromelia
22 and get an idea of whether it changes the -- I don't
23 know. These are the biggest scientific questions
24 here --

25 DR. MAHY: There are groups beginning to

1 work.

2 DR. RUSSELL: -- related to threat
3 assessment.

4 DR. MAHY: Certainly Mark Fuller, I think,
5 is beginning to work with ectromelia and looking at
6 all sorts of things. But I think it could be --
7 it's possible that NIH could direct some of this
8 work to answer these questions.

9 DR. RUSSELL: Advisory committees get
10 very, very anxious about genetic recombination which
11 results in -- probably results in up regulating the
12 virulence of any agent, whether it is a mouse agent
13 or a monkey agent.

14 DR. RAUCH: Phil, in many ways you just
15 restated the paper that Bernie Moss and Billy
16 Yockley (phonetic) and others, some of their
17 arguments for not going forward with -- I mean, it's
18 a --

19 DR. CASSELL: I was just going to say that
20 if you think that getting animal use clearance for
21 aerosolization of primates is difficult, I think the
22 animal community, with regards to mousepox and a
23 threat to the animal colonies, would also be of
24 great concern.

25 So it may not be as easy as we now think

1 it is, I mean, because this is not a trivial matter
2 in terms of containment either.

3 PARTICIPANT: We had an ectromelia problem
4 and -- so I know that they are not anxious to go to
5 --

6 (Laughter.)

7 DR. RAUCH: But politically it's a double-
8 edged sword. I mean, you asked the question: Will
9 the current vaccine protect against aerosolized pox?
10 And that is a -- you can put that into an
11 experimental design.

12 You say politically you have great concern
13 with that.

14 DR. RUSSELL: I don't have a concern. I
15 am saying that the political climate makes it
16 incredibly difficult --

17 DR. RAUCH: Okay.

18 DR. RUSSELL: -- perhaps impossible, to
19 answer the question.

20 DR. RAUCH: But on the other side of the
21 coin, if something were to occur in a BW scenario
22 and our vaccine doesn't work, think of the political
23 -- I mean, think of the political consequence of
24 that.

25 DR. ASCHER: One summary statement here is

1 that our approach today and in the next day or so to
2 come up with a summary can identify, a, do we or do
3 we not have concerns about a threat?

4 And b, do we or do we not have a plan that
5 might be put in to keep us more up to speed against
6 that threat?

7 And I guess the purpose of presentations
8 today were to show us a version of that, which is
9 what are the concerns, what are the science and what
10 could we do?

11 And if we don't think there are any
12 concerns or we don't like the science, we should say
13 that.

14 But at this point, it does then add to the
15 people who are negotiating at some level the fact
16 that we have concerns and the fact that we have a
17 plan to help resolve these concerns.

18 And it is sort of like the issue of Star
19 Wars, where we just continued to push and push and
20 push until the whole thing got so ridiculous to the
21 point where the other side said, "We give up."

22 And at this point, having a strategy is
23 like having the fantasy of Star Wars. And at this
24 point, to have the Soviet or the Russians understand
25 that we have an organized approach, we have

1 concerns, may help the future elimination.

2 So they are not in -- they are sort of at
3 cross purposes, but they could lead to the same
4 answer.

5 DR. MAHY: I think one of the critical
6 issues here is what would be the effect of a
7 decision to destroy the virus, and what would be the
8 effect on the program that may be going on. Would
9 it put pressure on that program? And what are the
10 funds that are being used to fund it and so on?

11 I mean, the answer is you have an
12 imbalance at the present time. You have a program
13 in one part of the world and not in the other part
14 of the world.

15 But I do think it needs to be weighed
16 carefully, and it is quite possible that removing at
17 least the virus at the political level would be a
18 considerable advantage in reducing the activity.

19 If it isn't destroyed, then certainly
20 there is no reason why work should not continue at a
21 pace such as we have heard.

22 DR. RUSSELL: The current level of
23 scientific endeavor in this area is far below the
24 national needs. Whether or not the virus is
25 destroyed may affect the level.

1 I could envision a decision to destroy
2 linked to a decision enhance the total level of R&D
3 directed at the issue in orthopox virus. And I
4 think that would be an interesting outcome.

5 My principal concern is enhancing the
6 total level of effort. The specifics I am not quite
7 as confident about because what are the best
8 experiments to do kind of changes over time.

9 And how to answer the question of either
10 immunologic protection or antiviral protection may
11 change in five or ten years.

12 If we have a major program and if we can
13 use whatever politics allows us to use, the clones,
14 the gene information, cellular experiments and so
15 forth, if that is allowed to move or actually
16 supported in concomitant with the level of threat,
17 then I think that might be a good outcome without
18 arguing about the specific experiments.

19 DR. HENDERSON: I think the decision has
20 to -- whatever you are looking at, there is a
21 background with this that at least I have seen in
22 the last four years, that we have had a heightened,
23 perhaps tightening, concern about biological
24 defense.

25 DR. RUSSELL: Which has resulted in

1 decrease budgets.

2 DR. HENDERSON: The difficulty is that we
3 have seen decreased budgets at NIH, at CDC, and now
4 projected for next year projected here is almost
5 draconian in the biological defense budgets at best.

6
7 So we are looking ahead to possibly doing
8 things at the same time in the face of declining,
9 markedly declining, resources, which is of great
10 concern. We would like to see it reversed, but
11 there is no evidence of this taking place at all.

12 DR. MAHY: And nothing happened when
13 budgets were better over many, many years.

14 DR. HENDERSON: Right.

15 DR. MAHY: For ten years, there was any
16 work done in this area.

17 DR. RAUCH: I just feel that I need to
18 comment, however, that 1996 is a bad year, but it is
19 a bad year for all medical research and development,
20 not just medical defense against BW threats.
21 Everything is going down, whether it be infectious
22 disease, blood substitute work, whatever.

23 So bio-defense did not take a
24 special -- any special reduction. It is a total
25 downward trend in DOD.

1 PARTICIPANT: Yes, but as a matter of
2 fact, the 1997 and out-year program has been plussed
3 up last year. So there is some emphasis added on.

4 PARTICIPANT: No. I think what I am
5 reflecting to is what Phil and I were briefed on at
6 the joint committee.

7 DR. RUSSELL: Terry, you have to admit
8 that there is a dichotomy between the budget
9 behavior of the Department of Defense and the
10 arguments about the level of threat.

11 There is a disconnect there. I see that
12 disconnect. Everybody here sees that disconnect.
13 And out-year budgets have always been discussed as
14 fantasy budgets in any real terms.

15 DR. RAUCH: They are fantasy until they
16 come into the year of execution, and then they are
17 real.

18 DR. RUSSELL: Right. And what has been
19 happening --

20 DR. ASCHER: But I suspect that the
21 volunteerism unit of the FBI has also got a 30-
22 percent cut, but that might change. And, you know,
23 it has to do with proper salesmanship.

24 DR. RUSSELL: And while the general
25 military threat to the United States is going down

1 in terms of very large wars, large scenarios and
2 global warfare, the threat of this kind of activity
3 is going up.

4 And the budgetary response at the
5 Department of Defense just flat ass doesn't respond
6 to it. It doesn't reflect it.

7 So we have a big credibility problem here.
8 If the threat is so god damn high, why don't you
9 put some money behind it?

10 DR. CASSELL: Well, I think the scientific
11 community would much better appreciate these
12 reductions if in fact you don't -- you not only have
13 a dichotomy with respect to the increase in BW
14 threats, but just the new and emerging infections
15 area in general and national security as far as
16 troop health is concerned, coupled with the issue of
17 antibiotic resistance and all these other really
18 crucial areas where the incidence is going this way
19 and the funding is going this way.

20 And it is oft compounded because of the
21 decreases in funding, DOD, CDC and NIH in
22 particular, with respect to research and
23 development.

24 DR. RUSSELL: Yes. It is not a DOD-
25 specific phenomenon. Don't get us wrong.

1 DR. MAHY: But would you not agree,
2 though, that if the decision was made to destroy all
3 of the remaining variola virus stocks in a verified
4 fashion in two places simultaneously, surely that is
5 going to reduce the threat far, far more than
6 leaving the status quo, which we have heard about
7 this morning?

8 DR. RUSSELL: An arguable point.

9 DR. RAUCH: Yes. I don't know if I agree
10 with that, Brian. I just simply don't agree with
11 that. Number one, it is not measurable.

12 DR. HALVORSON: This is not our decision
13 to make. I think we are wasting our time.

14 DR. RUSSELL: We are beyond the science
15 here, fellows. We are getting off to something that
16 we were not charged to do.

17 DR. HALVORSON: We do have other questions
18 that we were supposed to address. Are we going to
19 get to these next?

20 DR. ASCHER: Yes. We are clearing Brian
21 because he has to leave. And once we do that, we
22 will probably take a break for lunch. And then we
23 will continue on with our questions.

24 Is Joe going to be here today?

25 DR. ESPOSITO: Yes.

1 DR. ASCHER: You will be with us the rest
2 of the day.

3 DR. MAHY: If you are going to stay --

4 DR. ASCHER: Yes. Anything else you
5 wanted to say?

6 DR. MAHY: Joe can cope with all the
7 questions.

8 DR. ASCHER: You know, it is conceivable
9 in one of our statements we can make a generic
10 statement that there is a very big shortage in high
11 level containment, and any experiments of this type
12 would cause a lot of problems.

13 They might not have asked the question,
14 but we certainly can highlight it and add it to your
15 emerging infections, that here is another example.

16 DR. CASSELL: But could we just clarify,
17 is it really the lack of space or the lack of
18 personnel to work in the space that is the most
19 crucial issue?

20 DR. MAHY: Currently, it's the lack
21 of -- it's both issues really, combined with an
22 extraordinary increase in the number of agents we
23 have to deal with.

24 I mean, nobody would have said this five
25 years ago, but I cannot believe how much we are

1 seeing. And whether it is due to the factors that
2 the Institute of Medicine report dealt with, such as
3 the increased contact with areas with increased land
4 use, things of that sort, whatever reason, we have
5 more agents to deal with now.

6 There are also technological issues. Ten
7 years ago, we were not over concerned about
8 hepatitis C. Now we have something we know is an
9 absolutely major cause of chronic disease.

10 We have no way currently of treating it.
11 We want to try to look at possible therapies. We
12 want to improve diagnosis. And now we have a whole
13 lot of other agents that are probably less important
14 but nevertheless are contributing to transfusion
15 hepatitis.

16 And in many, many areas like that, these
17 are things that have come out because of technology,
18 but they need to be dealt with. And they affect
19 literally millions of people worldwide every day.

20 PARTICIPANT: So, Brian, the hepatitis
21 issue doesn't really rate itself in terms of the BL-
22 4, does it?

23 DR. MAHY: In terms of the BL-4, I think
24 the -- I am trying to be realistic. I do not
25 believe that give the fact that the U.K. and many

1 other countries that want BL-4 to do this have
2 failed to produce anything.

3 I think there should be a lot more effort
4 to try to get them in a number of places, and I
5 think we could certainly do with more space. But we
6 would also need considerable resources and
7 personnel.

8 These are very expensive 24 facilities
9 that we have to keep going. And we virtually close
10 -- we were at the point when we were going to close
11 the MCL.

12 We threatened to close the MCL because we
13 had absolutely no staff. The last couple of people
14 who worked on the antivirus went into buy-out. And
15 we were then given some new positions.

16 But for over six months now, we have been
17 trying to get OPM to fill those positions. We don't
18 have a single person hired, and that is another
19 story that I don't want to go into.

20 But, you know, we are in a crisis point.
21 Pierre Lone (phonetic) is about the only person now
22 working regularly in -- and he is going off to the
23 Ivory Coast to look at this ebola situation in a
24 couple weeks.

25 When he leaves, there is only one person

1 on hand to run the lab and so on. We are absolutely
2 on a shoestring.

3 And there are lots and lots of things we
4 are being asked to do. We want to help DOD with
5 their things. We want to help Yale and the other
6 groups.

7 DR. ASCHER: But you have to air this out.
8 The public perception is that you have this trailer
9 that you can dump in the middle of some city in
10 California, and they spent more on the sets for that
11 movie than would cover your budget and USAMRIID for
12 one year. What was the cost? \$25 million.

13 DR. MAHY: We did get a visit from Ted
14 Turner. He came to see us earlier this week, and he
15 is certainly interested in helping and maybe making
16 another movie.

17 DR. ASCHER: Maybe politically Congress
18 has to hear that that is a fantasy and it is not at
19 that level, and it is a real problem.

20 DR. MAHY: Well, we have had Congressmen
21 in the last two weeks, and they basically said,
22 well, there's nothing they can do about it. This is
23 not the time. It is cut, cut, cut and so forth.

24 I mean, much more than the BL-4, we would
25 like to retain the lab that was already planned,

1 which was going to rehouse our virology. That has
2 all gone by the wayside, so -- I am only trying to
3 be practical.

4 And I think unless one can imagine these
5 things, the days of research are probably very
6 different from what they were. The fifties and
7 sixties was a great expansion. Everybody saw the
8 great idea, biological research was wonderful.

9 Now I go to a university -- I was in
10 Lexington a couple of weeks ago giving a lecture,
11 and half the staff have no grants. I mean, they are
12 trying to work -- I mean, it's appalling. Every
13 university you go to, the people are totally without
14 funds.

15 They point at John, of course, but, I
16 mean, it's not John's fault. There are just not the
17 facilities around.

18 DR. CASSELL: Just to add something to
19 that, a couple of weeks ago I attended this
20 leadership exchange at OSTP. In fact, we were told
21 that over the next five years, the complete R&D
22 budgets to the universities is predicted to decrease
23 by 25 percent.

24 And I was not too disheartened until Neal
25 Lane got up at the end and said, "And we have no

1 reason to believe to believe that this won't occur."

2 DR. ASCHER: And that's not --

3 DR. CASSELL: And that's the last --

4 DR. ASCHER: That's not a version of moral
5 high ground. That is a national position of
6 weakness, vis-à-vis the other folks in this
7 discussion. How do they perceive that?

8 DR. RUSSELL: The big political decision
9 that is going to have to be made is the value of the
10 moral high ground commensurate with the technical
11 loss or the technical ability related to retaining -
12 -

13 DR. ASCHER: But the other guys say the
14 moral high ground is just because our whole
15 infrastructure for biomedical research is
16 collapsing, and we just folded, or we have another
17 strategy.

18 DR. HALVORSON: But the contact I have had
19 with Russia -- and I am sure everybody
20 else -- they are in a disaster situation with regard
21 to their science.

22 DR. ASCHER: Right. Theirs is collapsing
23 faster.

24 DR. HALVORSON: I mean, we think it's
25 terrible here. It is a calamity there.

1 DR. ASCHER: That's right.

2 DR. HALVORSON: So if they are going to
3 sustain a scientific community that is going to be
4 able to do things that will worry us, they are doing
5 it in the face of losing their people, of losing
6 their funding.

7 DR. HUGGINS: But, Harlyn, they may have
8 made the decision that BW warfare is sort of a cheap
9 way of establishing --

10 DR. HALVORSON: They are not putting money
11 into big missiles and atomic weapons anymore.

12 DR. ASCHER: That has always been the
13 case, John. It is the most cost effective
14 form --

15 DR. HALVORSON: They have a few nickels
16 left over for other --

17 DR. ASCHER: Absolutely.

18 DR. HALVORSON: It's a poor man's weapon,
19 and they are poor. So are the Iraqis.

20 DR. ASCHER: I hope Harlyn is right.

21 DR. HALVORSON: Well, in the long run,
22 they are going to have to be able to deal with
23 technical problems that involve even biological
24 warfare.

25 DR. ESPOSITO: The view of the most

1 important question is born in the article in Science
2 by Bill Gotlick (phonetic) and the subsequent
3 article by Roytzman Nadell (phonetic), which point
4 to the importance of determining the pathobiology
5 and the way the virus evolved to overcome the immune
6 system.

7 That's a key to future diagnostics, to
8 future public health benefits and the
9 advantages -- and that's what weighs in the
10 advantages and disadvantages of keeping the virus.
11 And on the other hand, you have the risk in that
12 equation.

13 So basically, in terms, then, of the
14 pathobiology, some things need to be learned. For
15 example, what we were doing with tumor necrosis
16 factor receptor, what the Novo-Sibirsk Laboratory is
17 doing with the interferon gamma receptor and other
18 poxviruses, what pox virologists are doing to look
19 at all these cytokine response modifiers.

20 That is right now one of the hottest areas
21 in poxvirology. The second area, which Dr. Moss has
22 an experiment going on, is to define the host range
23 specificity of poxviruses.

24 What are the factors involved in
25 determining the host range? So host range and

1 virulence always have been the key scientific
2 questions regarding poxviruses and virtually all
3 viruses, I think.

4 So that -- and from those, you develop
5 practical applications, such as learning how to
6 diagnose, look at what aspect of the immune system
7 we are going to do to diagnose this, look at what
8 aspects of virologic aspects can we look at to
9 diagnose this, and by understanding the biology of
10 the viruses where we lead into those practical
11 applications that lead to vaccine development, as
12 well as diagnostic development.

13 So that was the scientific argument for
14 having a need for the authentic gene products,
15 because what we can craft by biotechnology today may
16 have to have a little bit of tuneup by knowing how
17 these proteins interact with each other in terms of
18 even if it was kept, and once we reached that one
19 burning question that's going to be a great boon to
20 science, then maybe we would be able to ask that.

21 On the other hand, there is the risk
22 assessment of having it.

23 So those were the two issues that lead
24 into the scientific research that's going on.

25 DR. CASSELL: And if you had a --

1 DR. ESPOSITO: Or the research proposed is
2 the risk aspect.

3 DR. CASSELL: And if you had a suitable
4 animal model where you could actually address the
5 question of pathogenesis, what would be your
6 recommendation as far as proceeding with the
7 studies?

8 DR. ESPOSITO: Well, Professor Fenner
9 argues that ectromelia, which is probably -- and he
10 studied that virus much more than I have in terms of
11 its phenotype and what we are learning now about the
12 genome organization of ectromelia virus, that that
13 is a suitable, reasonable laboratory model for
14 looking at the biology of poxviruses in general,
15 particularly orthopox viruses.

16 We can make assumptions from all of this.
17 For example, antiviral drugs. I think if they are
18 focusing a DNA polymerase, which has 98 to 100
19 percent identity with smallpox virus DNA polymerase
20 and these antivirals then, for example, could
21 probably -- you are going to get -- in a mouse model
22 system, you are going to pretty much get an answer.

23 Of course, what you are not going to get
24 answer in those studies is the dosage that you have
25 to use in a human to have the same effect as in a

1 mouse.

2 So there are ramifications, which I am not
3 an antiviral person to know how you can translate
4 from one system to the next in that regard.

5 DR. ASCHER: One thing I have not heard
6 discussed is that Brian's presentation and you sort
7 of indicated that the work with the agent had really
8 slowed down and had sort of been phased out in a
9 clearly stated way.

10 And that's actually been more clear than
11 the plans for destruction, which have sort of
12 floated.

13 But if anyone wants to know what you have
14 actually done or been doing, it's clear. So one of
15 the questions is: Could we say that a moratorium on
16 research with the virulent organism be a strategy
17 for a period of time? In other words, make it clear
18 that we are not going to work with it. That has
19 never really been stated.

20 You have done it, because you have said
21 what you are doing and not doing. So everyone
22 knows, but it has never been stated as an outcome,
23 that we are not going to work with it, period.

24 And let's see if the other side will agree
25 with that, and then get that verified. And the next

1 step is you destroy it, but you destroy it then
2 after you decided that scientifically there is no
3 point in resurrecting it later to compare with
4 ectromelia or to do anything else at some point.

5 DR. ESPOSITO: Well, there is a scientific
6 community of pox virology which is out there, which
7 is, you know, 150 to 200 people that make their
8 livelihood working on and understanding poxviruses,
9 per se.

10 DR. ASCHER: But a moratorium on variola,
11 I'm saying, on working with it at all.

12 DR. ESPOSITO: But for a long time they
13 have looked at the virulent organism as -- what they
14 are asking in their systems is basically -- in the
15 back of a lot of that science is what is happening.

16
17 I mean, I would have a hard time thinking
18 that you are going to convince Dr. Sanderchev
19 (phonetic), who may be, for example, trying to
20 develop a biological company or something like that,
21 that you are going to be able to have a moratorium
22 on that.

23 DR. CASSELL: John?

24 DR. LAMONTAGNE: Well, I mean, I would add
25 to what Joe has said and maybe some of the comments

1 that I heard from Dr. Barmus (phonetic) the other
2 day when I talked to him about this meeting.

3 As many of you know, Dr. Barmus has
4 expressed the view that he is not in favor of the
5 destruction of the stocks.

6 And in the conversation with me, he argued
7 that it would be useful, again along the lines of
8 the argument that Bernie Moss and others have
9 written about, that with the sequencing information
10 that is now available, it is theoretically possible
11 to start thinking about constructing transgenic
12 models in mice, for example, that might be closer to
13 the human thinking as the more amenable to a certain
14 population.

15 DR. CASSELL: And using the skid hues
16 (phonetic) to ask the epidemiologic questions, and
17 that would be a very powerful combination.

18 DR. LAMONTAGNE: Exactly. And he believes
19 that this kind of information would be lost without
20 the ability to do that work.

21 DR. ASCHER: But on the other hand, it's
22 clear that that is not going to get funded and is
23 not going to be done under the current constraints.

24
25 So to justify continuation of keeping it

1 though research is not going to happen is not truly
2 clear as an outcome. We should not come out of this
3 meeting recommending research that we in our hearts
4 know is not going to be done because there is no
5 money or no space.

6 DR. CASSELL: But it could be done in the
7 intramural program, in terms of the transgenic mice
8 and containment and plastic dome isolators, I mean,
9 you have a much better chance of containing that
10 than a lot of other things one might choose to do.
11 So I would see those as being very feasible
12 experiments.

13 DR. LAMONTAGNE: I am not sure I
14 understand why it would not be done.

15 DR. ASCHER: We have no BL-4 space.

16 DR. CASSELL: But you don't need it for
17 this.

18 DR. ASCHER: For working with variola?

19 DR. CASSELL: In plastic dome isolators?

20 DR. ASCHER: Oh, you sure do.

21 DR. CASSELL: Or stainless steel
22 isolators? I mean, that's --

23 DR. ASCHER: What I'm trying -- is not
24 have it blow up in our face later on, where we are
25 talking about a research agenda, and it's just pie

1 in the sky because it isn't going to happen, because
2 then people come back and say that this baloney.

3 And that's is what I read in that one
4 article, to say it is great to justify, but you had
5 better put it in your funding line to get me to
6 believe it. And I don't think we heard today that
7 anyone is putting it in their funding line.

8 DR. RAUCH: Well, you know, people at
9 USAMRIID came up with a three-pronged research plan
10 at our request. Of course, whether that gets full
11 funding behind it is another question.

12 I mean, the department is going -- my
13 department is going down the road of addressing this
14 research plan. If we didn't have an attention of
15 funding it, we would not have asked for it. Okay?

16 Now, I can't sit here and tell you that I
17 am 100 percent sure that this plan will be fully
18 funded next year. I mean, I can't --

19 DR. ASCHER: I just would like to
20 associate the two so we don't necessarily justify
21 keeping it for the purpose of a research plan that
22 doesn't happen.

23 We can talk about what research agenda
24 remains, what key issues could be addressed in the
25 future. And we could say that prior to destruction

1 those things should be addressed, and then you can
2 go out for funding or not. And you make your
3 decision on whether it gets high enough priority.

4 The two are linked together, and we don't
5 end up keeping it three years while you don't fund
6 it. It sort of makes sense. And then people will
7 decide how serious they are about the issue.

8 I mean, it's put up or shut up. You
9 either do the research, or the thing is going to go
10 down the toilet. And that's not a bad a strategy.

11 DR. KRIKORIAN: I think for this
12 discussion, it would be better from a political
13 perspective if we tried to eliminate the concept of
14 funding and say the world -- it is an ideal world,
15 and if the research needs to be done, it would be
16 done. And let's prioritize it from there and go
17 forward, for the sake of the discussion.

18 DR. RAUCH: I mean, I don't want anybody
19 to walk away from this meeting thinking that DOD put
20 together a research plan without the intention of
21 fully funding it. That is not the case.

22 DR. ASCHER: Right. But there are two
23 levels of things. I guess what I am saying is that
24 Joe outlined very, very basic issues about the
25 biology of this virus that are worth knowing long

1 term.

2 I agree completely. And so in our
3 statement we would say the big picture issues is the
4 pathobiology of this prototypical human infectious
5 disease is a very interesting problem and is worthy
6 of further consideration.

7 It is also the short-term goal that our
8 study of antivirals is a goal, and you would have to
9 then just list them all. And depending on what
10 level of funding you could get, you could choose
11 from that laundry list.

12 Once you have satisfied everybody that you
13 have done everything that is appropriate, you stop.

14 And maybe you never get there.

15 DR. CASSELL: It seems to me that the
16 things that are readily apparent is that a strong
17 program in comparative pox virology is certainly
18 warranted, based on everything that we have heard
19 today. And what I have also heard is that those
20 programs have been declining with declining funds.

21 And along those lines, John, what would be
22 the status of programs in comparative virology
23 today? Do you know, as far as numbers of
24 investigators and having trained expertise in this
25 whole area of pox virology, what we are talking

1 about?

2 DR. LAMONTAGNE: That is a very difficult
3 question to answer, Gail. I can tell you that on
4 the perspective on the Microbiology and Infection
5 Disease Division that I am the director of, our
6 level of number of projects that we support is
7 steady state.

8 It's at about the same level now that that
9 it was last year, and that's about 1,455.

10 We do not foresee any dramatic growth in
11 that. There is a lot of interest in pathogenesis
12 and in comparative virologic problems. I think
13 within the intramural program, Dr. Moss, as Joe
14 pointed out, is interested in some of these
15 pathogenesis questions.

16 And it's quite plausible to me that
17 someone will come up, now that they have a lot of
18 sequence information, with some clones perhaps,
19 genes that might encode for the receptor for pox
20 viruses and might start trying to express that gene
21 in transgenic mice or in other model systems. And
22 suddenly, you would have developed the possibility
23 for evaluating for antivirals, for example, much
24 more rapidly than you had ever in the past.

25 So all of these things would affect at

1 that particular point in time the decision as to
2 whether or not resources should or should not go
3 into that particular project.

4 I don't know whether that answered your
5 question, Gail.

6 DR. CASSELL: But just guessing the
7 numbers of individuals actively working in the area
8 of comparative pox virology right now extramurally
9 would be rather small in comparison to that --

10 DR. LAMONTAGNE: I think it's relatively
11 small. I think that there are probably ten groups
12 in the U.S. outside the federal groups that are
13 working in pox virology today.

14 DR. ESPOSITO: We have an international
15 poxvirus meeting, and we get roughly 150 people. So
16 that is principal investigators and their main post
17 -- so I would say worldwide, we are talking about a
18 couple of dozen, maybe three dozen, laboratories
19 that are doing poxvirus research.

20 DR. CASSELL: Three dozen worldwide.

21 DR. ESPOSITO: Two or three dozen
22 worldwide.

23 DR. ASCHER: So this group could easily
24 make the statement that concern about support for
25 comparative pox virology is felt and that it should

1 be attempted to be maintained at some level.

2 DR. ESPOSITO: We have a meeting coming up
3 in 1996.

4 DR. RUSSELL: One of the things that
5 occurs to me in this is, is the promise of the
6 chemotherapy option sufficiently valuable?

7 I have the highest level of skepticism
8 about viral chemotherapy to start with, but we still
9 have to ask the question: Is it sufficiently
10 valuable to really fully exploit it to the extent
11 that we can before destruction?

12 DR. ASCHER: You kept hearing me say it
13 about what I think would happen. We even mentioned
14 at the break the possibility of proposing such a
15 study in collaboration with the folks in Russia as
16 sort of a key public health issue, independent of
17 threat or anything about that.

18 DR. RAUCH: Almost as a condition to fully
19 exploit whatever is in the inventory in
20 chemotherapy, to maximize any possible options and
21 produce a set of downstream leads.

22 DR. ASCHER: And, of course, if one of
23 those really panned out, like acyclovir was a
24 winner, it would really defuse a lot of the other
25 issues. In fact, it might completely defuse some of

1 them.

2 DR. RAUCH: It would sure make a lot of
3 people sleep better if you had a --

4 DR. ASCHER: It might be a good foot in
5 the door.

6 DR. RAUCH: -- good agent.

7 DR. ESPOSITO: Not only antivirals. I
8 would like to make one comment that one thing that
9 we have noticed with the tumor necrosis factor
10 receptor is that rabbit antibody that we made
11 against that bacterial-expressed protein well
12 neutralize poxviruses that produced that protein.

13 So it has potential for a post-exposure
14 prophylaxis.

15 DR. RAUCH: Is that a possible
16 immunotherapy, as it were?

17 DR. ESPOSITO: It has -- in addition to
18 looking at antivirals that target the DNA
19 polymerase, the potential for this as a post-
20 exposure therapy is real.

21 DR. ASCHER: I mean, that is hot in cancer
22 now, and that is hot in other infectious diseases.

23 DR. RUSSELL: The nature of that says you
24 have to test it against the variola gene in some in
25 vitro.

1 PARTICIPANT: At some time you would,
2 unless you made a vaccinia that re-stressed it,
3 right?

4 DR. ESPOSITO: Well, we don't know what
5 would happen to that vaccinia. We are suggesting
6 this protein is part of the receptor you are talking
7 about, so I don't know.

8 PARTICIPANT: Well, I think it is kind of
9 a catch-22 in some ways.

10 DR. ESPOSITO: Yes. I mean, the test
11 system for the TNF receptor is hands-down camelpox,
12 oddly as that sounds. There are only two amino
13 acids different in the protein, and it has
14 essentially the same activity as the smallpox one.

15 DR. CASSELL: And the gerbilpox.

16 DR. ESPOSITO: So theoretically -- no.
17 The gerbilpox is not.

18 DR. CASSELL: It's not? Because it was
19 close in everything else it looked like.

20 DR. ESPOSITO: Gerbilpox turns out to be
21 an unfortunate story, because what we are seeing now
22 with our HA and our TNF receptor sequencing is that
23 it looks like the earliest stocks of gerbilpox that
24 we can find are cross-contaminated with vaccinia.

25 And I think we are going to have to

1 eliminate that until -- I have called Professor
2 Dunbill (phonetic) in South Africa, looking for the
3 real mccooy.

4 DR. BENENSON: When you are responsible
5 for a ward full of patients with smallpox, or when I
6 was, the best thing I could do, the only thing I
7 could do, was assign a pretty nurse to the ward.

8 If I had any drugs that had a promise of
9 activity that was more acceptable to the patient
10 than Marberg, I would have had a happy day.

11 So that the need for a drug, if we
12 consider that there is a threat which was due, I
13 think, having a drug available makes a tremendous
14 difference.

15 DR. ASCHER: And it has the herpes gene
16 and the herpes product, and it's a DNA virus. I
17 can't imagine --

18 DR. BENENSON: It can cure lots of other
19 things at the same time.

20 DR. HALVORSON: But if you are going after
21 a very fundamental mechanism, as we heard earlier,
22 do you need the virulent strain to do the screening?

23 DR. ASCHER: No.

24 DR. RUSSELL: No, but you have some real
25 need for reality testing.

1 DR. HALVORSON: And then you are through.

2 DR. RUSSELL: And they you are through.

3 But at some point, you need to test reality. You
4 have this three-pronged heterology problem unless
5 you have some reality testing.

6 DR. ASCHER: Hopefully, if you had a
7 parallel development of your surrogates, your other
8 pox virus for your antivirals, and then you did a
9 one-time validation in the challenge model, aerosol
10 or otherwise, with variola, you might make a case.

11 At that point you no longer need it
12 because you have validated all the other models, the
13 surrogates for all of the further antiviral
14 development.

15 And that would be a judgment call, based
16 on how clear the results are. And if they are very
17 clear, it knocks it out in tissue culture of
18 monkeypox or --

19 DR. ESPOSITO: Yes. Without a
20 pathogenesis study in the model system, you don't
21 know that that's a valid model system. You are just
22 presuming that a monkey is going to be a valid model
23 system.

24 DR. ASCHER: Right. You have to do the
25 experiment.

1 PARTICIPANT: There is no such thing as a
2 one-time experiment.

3 DR. ASCHER: Well, that's the problem.
4 That's what I'm saying.

5 DR. ESPOSITO: You can't do that with a
6 one-time experiment to determine the pathogenesis of
7 the disease.

8 DR. ASCHER: So what was your answer,
9 Phil? You asked the question. Do you think it's
10 worth it, the chemotherapy? It's pretty attractive.

11 DR. RUSSELL: I am balancing enthusiasm
12 for an answer with my skepticism about viral
13 chemotherapy. I think on the balance you have to
14 say -- I still don't know.

15 PARTICIPANT: Acyclovir works pretty well
16 on herpes and encephalitis.

17 DR. RUSSELL: What?

18 PARTICIPANT: Acyclovir works pretty well
19 on herpes and encephalitis.

20 DR. RUSSELL: Yes. It is a lot slower
21 disease. You know, it's an experiment that really
22 has to be done. But it seems to me that there is a
23 compelling reason to do a set of experiments of
24 these drugs.

25 Now, whether you can jury rig the system

1 and do them without more than a very small amount of
2 work with the live agents, you are not -- you always
3 get down to the final reality test.

4 You always get down to the issue of -- you
5 don't want to test a drug after you have a ward full
6 of patients. You really want to have a lot more
7 confidence.

8 You are talking about stockpiles. You are
9 talking about other kinds of issues here.

10 DR. ESPOSITO: Well, no pharmaceutical
11 company is going to take the risk of producing, of
12 manufacturing the product.

13 DR. RUSSELL: If they get paid for it,
14 they will manufacture it. But you really -- you
15 have to have a really valid scientific basis for
16 stockpiling an agent against a contingency.

17 And to do that without a test against a
18 live agent at least at some point in the development
19 process is very problematic.

20 DR. ASCHER: I guess back to my earlier
21 comment, the issue of declaring a moratorium on work
22 versus destroying the virus, a statement that came
23 out with clearly stated priorities for possible
24 continued research would then tell everybody what
25 may or may not happen.

1 And anyone could then look at that list
2 and find out what is or isn't going on at any point
3 in time.

4 And then there is no question about
5 playing games, you know. If they call up and say:
6 Okay, you talked about basic pathobiology of
7 poxviruses. Are you working with variola now? You
8 say: No, I'm not.

9 That could be made public. But it is
10 still a worthwhile, long-term reason to keep it, one
11 of many. There are also a number of reasons to get
12 rid of it. So we just line them all, and people can
13 decide based on adding the factors together.

14 DR. ESPOSITO: Well, those two science
15 articles basically did that.

16 DR. ASCHER: Yes, except there are
17 mistakes in there that we need to get straightened
18 out, like a million will die if it escapes from your
19 lab. We just have to get some of it clarified.

20 DR. LAMONTAGNE: Can I just ask a good
21 question? Joe, if you look at the existing systems,
22 I mean the ones that Dr. Fenner talked about, for
23 example, like the ectromelia in micepox and monkeys
24 and camelpox that you mentioned, how faithful are
25 those as surrogates for variola in humans?

1 And could one learn, as Dr. Fenner argues,
2 from those experiments rather than using variola as
3 the test system?

4 DR. ESPOSITO: His argument and --

5 DR. LAMONTAGNE: How translatable are
6 they, in other words?

7 DR. ESPOSITO: I am trying to think of an
8 experiment that I know of that was done and
9 published where it wasn't translatable, and I can't
10 think of any. Maybe --

11 PARTICIPANT: The virology is
12 translatable, but that doesn't meet the regulatory
13 problems that you are going to face.

14 DR. ASCHER: What, getting acyclovir
15 approved? It is approved.

16 PARTICIPANT: Well, because the strategy
17 they are talking about, Phil, is --

18 DR. RUSSELL: Is it approved for use
19 in --

20 DR. CASSELL: Mousepox?

21 DR. ASCHER: There would be no
22 restriction. If the company is going to sell it for
23 that purpose, they would have to qualify it. But at
24 this point --

25 DR. RUSSELL: You just answered my

1 question. Can the Defense Department stockpile it?

2 No, because the company can't sell it to them for
3 that purpose.

4 DR. ASCHER: Well, that is a true --

5 DR. RUSSELL: I am here to tell you there
6 are regulatory problems.

7 DR. ASCHER: That is a key point.

8 DR. RUSSELL: Big time regulatory
9 problems. And we have been in that big do-do, and we
10 need to recognize that we are going to be in it
11 again.

12 DR. ASCHER: And that's one of the reasons
13 to find out. That's one of the reasons to find out
14 the answer to that question.

15 Very important, because if we assume it
16 happens and assume that there is going to be enough
17 of it hanging around the local pharmacies, forget
18 it.

19 DR. RUSSELL: Yes. If you are talking
20 about a chemotherapy option to meet the contingency
21 requirements for terrorists or what have you, you
22 are talking about having some validated approval for
23 that product for that purpose. Otherwise you get
24 into trouble.

25 Now, how you are going to get validated

1 approval, I don't know. There is a question: Can
2 you do it on the basis of mousepox? You would be
3 setting one hell of a precedence. I will tell you
4 that.

5 DR. ASCHER: Can you think -- we have all
6 taken the pretest, I think, of these questions. I
7 have the answers, and I only missed one. And it was
8 the most important one, so that's a problem.

9 But we have back from CDC -- I think
10 everyone has a copy -- and I have from Peter
11 Jahrling some draft responses. Phil Russell has
12 also typed out responses, which he is going to be
13 listening and will be the starting point for our
14 written response.

15 So he has an electronic version. It's
16 better because then we are not giving back the same
17 answers that we got from our people.

18 We need to make however many of those, 10,
19 12. And we can still start because the first one is
20 fairly easy. Then we will bring them in as they go
21 along.

22 There are short answers and there are long
23 answers. We are starting on key questions, I.1.,
24 Re-emergence. Is three a risk of that in addition
25 to the possibility of covert or undiscovered

1 laboratory stocks. Viable virus might exist in
2 natural reservoir.

3 The answer is yes, and they concur in the
4 theoretical possibility that preserved corpses from
5 cold storage or other storage, it's
6 possible -- they both reflect to date that this has
7 not been done successfully.

8 And the military reflects concern that
9 this is a possible line of investigation that might
10 get confused with other work in other parts of the
11 world.

12 DR. CASSELL: Can I ask a question of Joe?

13 DR. ASCHER: Yes.

14 DR. CASSELL: It may be naive, but using
15 your new, most sensitive techniques, like your Eliza
16 or also PCR, have you screened various populations
17 around the world? Are you using these re-agents?

18 DR. ESPOSITO: No. These are manuscripts
19 that are just being accepted for publication. We
20 haven't had real world experience.

21 Well, we had some bones from a Monangahela
22 Indian preserve that was in the Carnegie Museum.
23 And an archeologist asked us to test these, which
24 turned out negative. But
25 that --

1 DR. CASSELL: So in terms of the database
2 as far as negatives in which you would have been
3 looking at specificity of your test, how extensively
4 has that been evaluated using actual clinical
5 specimens?

6 DR. ESPOSITO: Well, we have done clinical
7 specimens that are in the repository, all that are
8 available. Most of the stuff is tissue culture
9 grown in virus. There a couple of dozen clinical
10 specimens in there, and the test worked very fine on
11 that.

12 As well, Dr. Shchelkunov has the
13 technology do that, and I presume that he would go
14 back to that material from the permafrost that was
15 antigen positive and try to PCR from that.

16 When I was there a few years ago, I saw
17 the videotape, also. And the idea was that they had
18 seen antigen but were not able to grow virus. Now
19 he should have that technology to look for virus
20 DNA, but apparently there is no virus in that
21 material.

22 DR. CASSELL: So if there were --

23 DR. ESPOSITO: The finding of DNA doesn't
24 mean there is live virus there.

25 DR. CASSELL: But if there were an

1 avirulent strain, completely avirulent, but out
2 there, we wouldn't have looked for it using your new
3 technology.

4 DR. ASCHER: Are your scabs culture
5 positive?

6 DR. ESPOSITO: Oh, yes.

7 DR. ASCHER: Now, 1995.

8 DR. ESPOSITO: We didn't grow the scab
9 material.

10 DR. ASCHER: But it is fairly routinely
11 felt that they are.

12 DR. ESPOSITO: Usually scabs are loaded
13 with virus material.

14 DR. ASCHER: Is that, then, another
15 possible source in nature --

16 DR. ESPOSITO: Scab material?

17 DR. ASCHER: -- in addition to corpses? I
18 mean, somebody who just put some scabs in the
19 freezer.

20 DR. ESPOSITO: Well, there have been like
21 what Brian says here, this middle field crips
22 (phonetic) probably had corpses that were in there.

23

24 There would be dried out material.
25 Whenever that's been looked for, it has always been

1 negative, whether it's been dust, bones or
2 permafrost material.

3 DR. HENDERSON: As a practical matter,
4 what we endeavored to do when we saw a case in a
5 country with, let's say in a new area of a country,
6 was to try to trace the source of that. And we were
7 almost invariably successful in so doing.

8 If indeed scabs or various other bits of
9 material were a problem, we should have seen what
10 appeared to be spontaneous cases. We just did not
11 see those. We did not see those.

12 DR. ASCHER: Okay. Part B. Given that
13 the virus has been sequenced, could the whole virus
14 be reconstituted into viable infective and
15 pathogenetic agent at some time in the future?

16 The flavor of the responses are
17 theoretically -- it is theoretically possible.
18 Period.

19 DR. LAMONTAGNE: Well, there has only been
20 one virus where it would have sort of a chemical
21 synthesis.

22 DR. ASCHER: In the molecular --

23 DR. RUSSELL: We are not talking about
24 cold chemical synthesis. We are talking about how
25 there have been -- to my knowledge --

1 DR. ASCHER: SIV, the molecular clone of
2 SIV is infectious.

3 DR. LAMONTAGNE: Well, no. I am talking
4 about actually chemically synthesizing an infected
5 virus. It has been done with polio. But I
6 think -- has there ever really been an example of a
7 reconstituted class in virology? I don't know.

8 DR. RUSSELL: No. But I discussed this
9 extensively with Bernie Moss and with Enzo Piretti
10 and with Joe here, and I talked to Josh about it.
11 There is a consensus that it is not only
12 theoretically possible, but as a practical matter
13 could be done in a year or two.

14 DR. LAMONTAGNE: Somebody will do it.

15 DR. RUSSELL: Well --

16 DR. LAMONTAGNE: With some system, it will
17 be done.

18 DR. RUSSELL: Yes. These guys are getting
19 so incredibly sophisticated in shuffling genes in
20 and out. They have all the genes, it's just a
21 matter of using the right strategy.

22 DR. ASCHER: And the public
23 perception --

24 DR. RUSSELL: All it takes is -- you have
25 the information. We have the technology. All you

1 need is the determination. I think we have to make
2 that assumption that it's going to happen.

3 Now, if you really need it, it would
4 probably take you six years.

5 DR. ASCHER: And it's smaller than a
6 dinosaur. And the public's perception is they can
7 make dinosaurs this way.

8 DR. RUSSELL: I don't think there is any
9 other determination we can make from a policy point
10 of view that is doable.

11 DR. ESPOSITO: It was testable with
12 vaccinia clones to see if you could stitch back the
13 genome together.

14 I think Dr. Moss has tried that
15 experiment, but the person that was doing it wasn't
16 very well experienced in those matters. But he had
17 actually at one time tried.

18 DR. ASCHER: But there is a hierarchy of
19 risk of reconstituting the viable product from the
20 standpoint of clones, PCR product, PCR prep, or
21 typed out sequences in terms of order of magnitudes
22 at this point.

23 And so what you would say is your
24 confidence of that risk would be related to whether
25 you are starting from clones or you are starting

1 from typewritten material.

2 And I think we would say that
3 reconstitution at this point from a pure sequence
4 would be extremely difficult and take a great deal
5 of time and effort, but it is theoretically
6 possible.

7 DR. ESPOSITO: Well, with vaccinia you
8 have 151 genes that are virtually identical. So you
9 only have to go the rest of the way to the 188.
10 That's not -- that is a simple experiment in today's
11 --

12 DR. ASCHER: Right, but the clones are a
13 lot easier.

14 DR. ESPOSITO: Clones are a lot easier.
15 But you could have a machine and make --

16 DR. ASCHER: Even that is arguable,
17 whether it is easier.

18 DR. LAMONTAGNE: What you are saying,
19 Phil, is you could modify vaccinia by introducing
20 the right gene.

21 DR. RUSSELL: Just one after another until
22 you have 100 percent.

23 DR. LAMONTAGNE: For ectromelia or
24 monkeypox, which --

25 DR. RUSSELL: Or camelpox. That was one

1 that keeps shuffling genes in and out until you wind
2 up with something else. And somewhere -- now, the
3 issue is how you really validate what you have.

4 The intimation is that if you are
5 determined to do it for nefarious purposes, you
6 might blow the whole roof.

7 DR. ESPOSITO: The article in Nature that
8 you received earlier suggests that that is actually
9 a doable thing. That was part of the discussion at
10 that table.

11 DR. BENENSON: If all the DNA was
12 destroyed, could you do it?

13 DR. ASCHER: Yes.

14 DR. RUSSELL: Well, you start with another
15 virus that's related.

16 DR. ESPOSITO: Yes. You could start with
17 vaccinia, and you only have to put that little bit
18 on the ends.

19 DR. BENENSON: But those differences are
20 critical.

21 DR. ASCHER: You have the paper sequence,
22 though. You know the written out sequence.

23 DR. BENENSON: All right.

24 DR. ASCHER: You just type it in to
25 your -- only four letters.

1 DR. LAMONTAGNE: Well, I think what you do
2 have is you have all these sequences in the clones
3 that have been used for sequencing information.

4 Those clones exist somewhere, and they are
5 probably pretty -- I don't know how tightly
6 controlled they are.

7 DR. RUSSELL: Six laboratories. If two
8 people have the knowledge, it's not a secret
9 anymore. Lord knows where those clones are.

10 DR. ESPOSITO: We are developing --
11 through WHO orthopox committee recommendations, they
12 asked us to develop a repository of the clone
13 material, which my technician is presently doing,
14 going through genome by genome and developing clone
15 material.

16 And that was -- eventually, we were going
17 to exchange that material with Novo-Sibirsk, and
18 they would provide us the India clones. And we
19 would have these two repositories as the clone
20 material. So that was the recommendation of the
21 orthopox --

22 DR. LAMONTAGNE: I think you have your
23 answer to number two.

24 PARTICIPANT: How will you know when you
25 have arrived with that? I mean, you are assuming

1 that you have an animal model to test the
2 pathogenesis. The infectivity of the newly
3 constituted or reconstituted agent?

4 PARTICIPANT: I think Peter used the word
5 for -- evaluation or something like that. That is
6 the same thing.

7 DR. CHIN: Can I get some clarification?
8 This particular question, re-emergence, depending on
9 the answer, is that a good argument for or against
10 retaining the virus?

11 DR. RUSSELL: It comes out both ways,
12 doesn't it?

13 DR. CHIN: I don't know what the relevance
14 of this question is.

15 DR. ASCHER: That's what I was trying
16 to --

17 DR. RUSSELL: It comes out in both
18 directions.

19 DR. ASCHER: That's right.

20 DR. CASSELL: But wait a second. With
21 regards to b, if in fact it can be readily done like
22 we have just heard, then doesn't the destruction
23 become a moot point?

24 DR. LAMONTAGNE: Well, the minute you do
25 it, you have to destroy it.

1 DR. CASSELL: Pardon?

2 DR. RUSSELL: The minute you do it, you
3 have to destroy it. If you succeed, you have to
4 self-destruct.

5 DR. LAMONTAGNE: I think that is at the
6 heart of some of the arguments against destruction.

7 DR. CASSELL: That's right.

8 DR. LAMONTAGNE: You are doing it
9 for -- by destroying it, you are not really doing
10 anything other than something symbolic. I think
11 that was the question. I don't know.

12 DR. HENDERSON: I think this was raised in
13 the committee that considered this. The feeling was
14 that even though this is possible, and I think the
15 committee recognizes as well that this is a very
16 feasible thing, the point is you are putting a major
17 barrier in there in terms of somebody else sort of
18 using this, that at least there is a barrier of
19 significance.

20 DR. HALVORSON: I would like that barrier
21 to be dropped even, or raised even, higher in the
22 sense that historically we ended up with clones
23 before we had PCR, before we had a lot of
24 sequencing.

25 I would like to get rid of those clones in

1 the sense of increasing my confidence on this thing
2 being reconstituted. And we could also talk about
3 getting rid of all DNA in the sense of the true
4 chemical or getting rid of all PCR product.

5 But at some level, I am not happy with
6 just killing the infectious material. I would also
7 like to include the clones, just as a proposal.

8 DR. ESPOSITO: But if you get a published
9 paper, you can't kill that.

10 DR. ASCHER: What?

11 DR. ESPOSITO: There is a published paper
12 that spells out the sequence.

13 DR. ASCHER: No. Kill the clones. Kill
14 the cloned material. Pull in all the cloned
15 material and destroy it along with the viable virus
16 as part of that proposal, not let the pieces out
17 anymore.

18 DR. ESPOSITO: Maybe you want to explain
19 the reason why the clones were separated out as the
20 material to retain as part of the archive, in
21 addition to the sequence.

22 DR. HENDERSON: I am not quite sure I
23 know.

24 DR. ASCHER: It was done because that was
25 the current technology in terms of what you could do

1 with genetic engineering or molecular biology,
2 because cloning was the way to go. Now you could do
3 the same thing from PCR from scabs.

4 DR. HENDERSON: No, but there was an
5 initial recommendation that clones be destroyed.

6 DR. ASCHER: Yes.

7 DR. HENDERSON: Then that was reversed at
8 the 1994 meeting, and it was suggested they not be
9 destroyed.

10 DR. ASCHER: But I am saying I would think
11 that in terms of the ease -- and if we
12 don't --

13 DR. HENDERSON: And what you would say is
14 that the committee ought to return to the previous
15 posture of destroying the clones if they are going
16 to destroy the virus.

17 DR. ASCHER: To raise the bar on making it
18 again.

19 DR. CASSELL: But with the sequence
20 published and with the homology with the vaccinia or
21 the camelpox, it still is a moot point almost. I
22 mean, really.

23 DR. ESPOSITO: There are about a dozen
24 different countries with the clones.

25 DR. RUSSELL: How vas can you synthesize

1 the gene?

2 DR. CASSELL: It is getting easier and
3 easier.

4 DR. RUSSELL: Pretty fast.

5 DR. CASSELL: Absolutely. And Parkin
6 Elmer (phonetic) has a new machine that is not even
7 on the market yet.

8 DR. RUSSELL: These beautiful machines
9 that synthesize --

10 DR. ASCHER: I'm serious.

11 DR. RUSSELL: Yes, I know. You could type
12 out the bloody gene. What good are your -- what is
13 the value, the relative value, of your clones? I
14 think that is a moot issue, too.

15 DR. CASSELL: So you would almost have to
16 go back to where you started in terms of the
17 moratorium on research with the virus or anything
18 that resembles the virus.

19 So in addition to destroying the stocks,
20 then you would have to also make the recommendation
21 that in fact it would be illegal to do research on
22 virus.

23 DR. RUSSELL: To have a clone or
24 synthesize one, because if you find somebody with a
25 clone, well, you may go out and -- I made the

1 sucker.

2 DR. ASCHER: That's exactly where we are
3 headed, back to store the original rack concept,
4 that you don't do that.

5 DR. CASSELL: And then try to police that.

6 DR. ASCHER: Well, again, it is the issue
7 that D.A. raised last night, which is if it appears,
8 you know someone has gone against a published
9 recommendation. It's not something that just turned
10 up in their lap.

11 Jim, you wanted to show this coming up
12 again. What was your answer to your question of is
13 it a pro or is it a con? How did you take it away?

14 DR. HALVORSON: Well, I think it's both.
15 That's why I was --

16 DR. HENDERSON: I think certain of these
17 scientific questions that are raised here, they are
18 having very different views expressed about these
19 and the importance of it.

20 How important, for example, is it if there
21 are viruses in bodies for -- and there are those who
22 have said this is terribly important.

23 And since there is likely to be virus
24 there, this argues firmly against destruction of the
25 virus. Others have said that it makes no

1 difference.

2 So what if there is virus in bodies in the
3 sun? Who cares? You find them. Good. You destroy
4 them. You have identified it. Destroy it. So
5 where is the big issue?

6 But this is the difference. I think we
7 are coming to a point of understanding where we are
8 on this, and I sense a general agreement around the
9 table on this. But it is just -- to at least begin
10 from a common base would be useful.

11 DR. ASCHER: Okay. Harlyn, you said
12 something about number two. Is that --

13 DR. HALVORSON: No, no. I was referring
14 to 1b, the one we just finished.

15 DR. ASCHER: Oh, okay. Good.

16 We are probably going to want to say
17 something about two.

18 It says, "Are present laboratory methods
19 adequate for rapid diagnosis? Will authentic
20 strains of infectious virus be useful to validate
21 the tests? Comprehensive analytic system in the
22 clinical or field samples."

23 I think the answer -- Joe said that they
24 have working procedures. Peter said he would like
25 to get them a little further along in terms of

1 practicality. Joe said that was a good idea.

2 So we reference that at some level, that
3 the diagnostic procedures are very clearly working
4 well, but they should be into a practical package
5 for national use.

6 Now, then, the stickler, which people have
7 to discuss is whether the viable virus is needed to
8 validate them further. And I think my conclusion
9 was no.

10 DR. CASSELL: Going back to a, would you
11 not want to stipulate there that in terms of having
12 rigorously evaluated specificity of these tests on
13 negative specimens, clinical specimens, that really
14 hasn't been done yet?

15 DR. ESPOSITO: We don't get clinical
16 specimens.

17 DR. CASSELL: No, negative, negative,
18 negative. I mean, in other words, sure, you can
19 show that you can specifically differentiate between
20 the poxviruses on using the cell cultures that you
21 have used.

22 But you have not gone to different patient
23 populations around the world, clinically
24 asymptomatic, as you would with any diagnostic test.

25 DR. ASCHER: A thousand chickenpox.

1 DR. CASSELL: Exactly. To show true
2 specificity.

3 DR. ESPOSITO: The primers have been used
4 to search the whole gene bank, and they do not match
5 up very well with anything else in there but
6 poxvirus. So the primers --

7 DR. RUSSELL: What about the human gene?

8 DR. ESPOSITO: Well, that is not sequenced
9 totally yet. But whatever is in the gene bank --

10 DR. RUSSELL: No. I am talking about if
11 you are using a primer from the tumor necrosis
12 factor, you are using something that is not in the
13 human --

14 DR. ESPOSITO: Forty percent -- right.
15 It's diverged. The amino acid sequence is where the
16 homology is, not the nucleotide sequence.

17 DR. CASSELL: And what about --

18 DR. RUSSELL: Clinical testing would be of
19 use.

20 DR. ESPOSITO: We took all the primers and
21 put them against the whole gene bank as it is today,
22 a recent gene bank release, and they don't hit on
23 anything but poxvirus.

24 DR. CASSELL: And the Eliza?

25 DR. ESPOSITO: The Eliza is -- you just

1 saw the first experiment. So we are still in its
2 infancy there.

3 DR. LAMONTAGNE: I think, Gail, what you
4 are suggesting is we test this on a validated 1,000
5 measles cases.

6 DR. CASSELL: Right.

7 DR. ASCHER: That would be what part of
8 the field transfer would be for Peter to put it out
9 and really show that it works.

10 DR. CASSELL: Because until you do that,
11 do you really know that they are not some avirulent
12 forms that might be closely related but yet
13 completely undetected at the present time by present
14 methods?

15 DR. LAMONTAGNE: Or cases of -- I guess,
16 D.A., there are still cases of monkeypox that are
17 currently used --

18 DR. HENDERSON: They are very hard to
19 find. Avirulent forms you wouldn't be looking at.
20 You might be looking at other orthopox viruses
21 isolated in some other way, I suppose.

22 There aren't that many turning up, though.
23 It is not going to be easy to validate this.

24 DR. ASCHER: Alan didn't get to speak this
25 morning, and maybe you would like to add

1 here --

2 PARTICIPANT: I was just going to ask to
3 clarify -- I think you would agree that PCR bands
4 would just be a presumptive positive or it would
5 have to be validated by sequences.

6 So even if you had the bad luck to get a
7 band of the same size and even had the bad luck to
8 have a restriction applied in exactly the same
9 distance from the two ends, you would still have to
10 sequence the -- with the level of uncertainty that
11 there is really a smallpox out there.

12 I am sure, Joe, you would not want to
13 sequence it before you told people that it was
14 really smallpox.

15 DR. ESPOSITO: We want to sequence a lot
16 more than one gene, I'm sure.

17 PARTICIPANT: Right. I mean, different
18 (inaudible) from different places.

19 DR. ESPOSITO: The test systems that are
20 out there, there is -- what's called cowpox is
21 occurring in Europe. It's a disease transmitted
22 from felines to people. The reservoir for that is
23 not clear. Not many cases, but we do see that.

24 We are trying to establish a coloration in
25 the future, once we get the serologic test to sero-

1 survey. In addition to working, say, with our Hanta
2 virus group, there will be lots of rodent sera
3 available there.

4 DR. RUSSELL: Let me ask you a question,
5 Joe. If you had a clinical specimen that yielded a
6 PCR product that had the right sequence for two PCR
7 products, one out of the hemagglutinin and one out
8 of the other gene, would you call that smallpox, or
9 would you also try to isolate the virus and do a
10 neutralization test?

11 DR. ESPOSITO: I would go into the BL-4
12 laboratory and take a look at it.

13 DR. RUSSELL: And then if you did isolate
14 the virus, would you want to compare it to the -- I
15 tell you -- what is your level of confidence in
16 calling it smallpox before you go into the BL-4
17 laboratory?

18 DR. ASCHER: Look under the M. Look in
19 the book.

20 DR. ESPOSITO: Well, if it is a poxvirus
21 and it has a hemagglutinin gene --

22 DR. RUSSELL: I didn't want to put you on
23 the spot.

24 DR. ESPOSITO: Yes. I mean, we have
25 looked at a couple dozen of them. That's all I can

1 say.

2 You saw what we have looked at so far. We
3 have not looked at every poxvirus in everybody's
4 freezer yet to be able to say that with the level of
5 confidence that you are asking for.

6 We have done some experiments. We have a
7 reasonable degree of certainty. That phylogenetic
8 tree is not lying to us. So we have a fairly high
9 degree of certainty.

10 But, you know, without smallpox being out
11 there already, you know, still out there, we are not
12 going to get the clinical specimens to do what you
13 are asking.

14 DR. HENDERSON: Phil, I think you may be
15 looking at the whole question of diagnosis. If you
16 turned up something on that, and it is from a
17 patient, you are going to see a rash, then right
18 away you are going to know a lot.

19 DR. ASCHER: Exactly.

20 DR. CASSELL: But the point is, what if
21 you have a positive, and you don't see a rash? How
22 do you interpret the results?

23 DR. ASCHER: You wouldn't do the test.

24 DR. HENDERSON: I think with much more
25 caution.

1 DR. RUSSELL: With great caution.

2 DR. ASCHER: It is an issue of prior
3 probability.

4 DR. RUSSELL: Well, you would never do it.

5 DR. ASCHER: Why would you do a test on
6 people with chronic fatigue or Gelfour (phonetic)
7 syndrome -- you see, there you go.

8 DR. HENDERSON: I think that would be a
9 problem.

10 DR. HALVORSON: Let me ask a related
11 question here. I assume that we will end up having
12 two places for diagnosis, one here and the one we
13 have at CDC. Is that the intent?

14 DR. RUSSELL: In a perfect world, at least
15 two.

16 DR. ASCHER: They would have to work that
17 out, but yes, hopefully they would back each other
18 up and keep your PCR labs clean.

19 DR. HALVORSON: So if you have to go back
20 to the verification, you have to solve the problem
21 of samples then getting back to CDC to use their
22 facilities.

23 DR. ASCHER: Keep PCR product off the
24 shuttle.

25 DR. RUSSELL: To put another spin on it,

1 though, you can say that the molecular technology
2 will give you all the information you need to make
3 very, very good political public health medical
4 judgments.

5 DR. LAMONTAGNE: I would say, Phil, if you
6 are looking back to the 1960s on this, you have an
7 electron microscope, and you put the specimen under
8 there and you saw the typical bricks.

9 Then you would know from looking at that
10 patient that you have smallpox or that he has
11 vaccinia. But you have it right there. That is the
12 diagnosis.

13 DR. ASCHER: That's what I said. That's
14 why I would go in the BL-4 once I have it.

15 DR. LAMONTAGNE: And the rest of it
16 doesn't matter.

17 DR. ASCHER: Don't do DFA, right?

18 Okay. And, Peter, you are okay with that
19 one, because your proposal did reference the use of
20 live virus, at least at this preliminary validation
21 step. But then you can live without it?

22 DR. JAHRLING: Yes. I think that --

23 DR. ASCHER: Okay. Now we are -- are
24 present laboratory methods sufficiently sensitive?
25 We just basically included the CDC and the Army

1 response concur.

2 Yes, and then there is a little more
3 detail in Peter, where he says, "It depends on the
4 urgency and level of subtlety" and what Alan said
5 about full sequencing and all of that.

6 DR. LAMONTAGNE: That is only true if it
7 is maintained. It is so technical, so person-
8 dependent. Unless you have the ongoing RD, that
9 will never hold up.

10 DR. ASCHER: Yes. It's not a box you put
11 away and --

12 DR. LAMONTAGNE: It's not a box you put
13 away. It's something that's a living, breathing,
14 person-dependent system. And it has to be
15 maintained with an R&D program. If you put it in a
16 box, it will die.

17 DR. ASCHER: Then one of our high level
18 bullets has to be a diagnostic capability with
19 continued training proficiency and maintenance of
20 reagents and all of the quality control on various
21 specificity questions.

22 DR. ESPOSITO: The simpler you can make
23 the diagnostic, the easier it's going to be to keep
24 that technology alive in the future.

25 If you could get it down to a dipstick,

1 you have a test that is not going to require a
2 pocket PCR machine.

3 DR. ASCHER: Is it not true that one of
4 the egg on faces in the last sort of before my time
5 was a smallpox mis-call based on DFA, or is that a
6 rumor that was even before your time?

7 DR. ESPOSITO: I don't know. Before me.

8 DR. ASCHER: There was some suspect
9 smallpox that came through, and it was read as false
10 positive in retrospect by DFA.

11 DR. LAMONTAGNE: Yes. It was in
12 Washington, D.C., in 1964, I think it was. And the
13 call was made -- no, 1963. It was made at CDC.

14 DR. ASCHER: Yes. And it cast a pall over
15 immuno-fluorescents for the next 30 years, which we
16 finally have removed. But it meant, though, with an
17 untrained, first time I've ever done it
18 technologist, this is what you get. I just wanted
19 to put it on the record. It's absolutely clear.

20 DR. LAMONTAGNE: We had a couple hundred
21 people under surveillance. I mean, God knows it was
22 a great to-do for about three, four days until they
23 got it straightened out and determined that it was a
24 case of --

25 DR. HENDERSON: Can I just ask a question

1 for information? Joe, how long does it take you to
2 make the call now, I mean, if you get a specimen for
3 somewhere else?

4 DR. ESPOSITO: I think in a couple of
5 hours we could make a presumptive call on the PCR
6 and electron microscopy.

7 If we had a large enough specimen, we
8 would do electron microscopy, PCR, and make a
9 presumptive call. And I think from there, we would
10 have to go into tissue culture to get something.

11 DR. ASCHER: If you look at Peter's
12 fielding proposal, you have, what, two stages, the
13 three hour and the twenty-four hour?

14 DR. JAHRLING: Yes.

15 DR. ASCHER: It's the same number, that
16 presumptive in three hours and twenty-four for the
17 second step. Pretty good.

18 DR. HENDERSON: So they are pretty good
19 right now.

20 DR. ASCHER: Yes. Yes?

21 PARTICIPANT: I would just like to ask a
22 question. How competent are the exposures to four
23 or five months of (inaudible) in a BW scenario would
24 manifest symptoms similar to what you would expect
25 to see in a potential outbreak?

1 Would you expect to see lesions, surface
2 lesions, skin lesions in that situation?

3 PARTICIPANT: In what virus?

4 DR. RUSSELL: You mean if a pure aerosol
5 root of infection, would you get the same -- I think
6 the answer to that is yes.

7 DR. CASSELL: How do you know?

8 DR. ASCHER: We are familiar with
9 the --

10 PARTICIPANT: Would it be a visceral
11 relief hemorrhagic syndrome versus -- no?

12 DR. ASCHER: We are familiar with the
13 Rocky Mountain spotted fever aerosol infection at
14 CDC with no rash, which scared the hell out of
15 everybody in terms of this issue. The question is:
16 Would you get rash?

17 DR. BENENSON: It's a good guess.

18 DR. LAMONTAGNE: In a very severe
19 smallpox, which was a hemorrhagic force, in which
20 there was capillary bleeding and bleeding
21 intestinally and so forth, and this was fatal within
22 a matter of a few days.

23 But what you found in every outbreak, and
24 I suspect would be here as well, suppose that that
25 was the manifestation, you are going to have

1 exposures on some sort of curve.

2 And you are going to find most of your
3 cases, I suspect, are going to be perfectly typical
4 cases. Even if you have a few abnormal ones, you
5 are not going to see all of them --

6 DR. RUSSELL: if you read that big book
7 carefully, you will find that there are some
8 descriptions of some respiratory transmissions. And
9 the pathology was mainly peripheral. Although the
10 first round of infection clearly was in the lung,
11 the pathology --

12 DR. CASSELL: What about if you have it in
13 VEE, so that you get death before you get
14 manifestational skin lesions?

15 DR. RUSSELL: You are arguing about only
16 high dose cases, and that will never occur. You may
17 have a worst case analysis, somebody blows an
18 aerosol, those in the middle may be very high dose.

19 Those around the edge are going to be low dose. So
20 they will be --

21 DR. ASCHER: Typical smallpox.

22 PARTICIPANT: Unless it is a building
23 scenario or something, other scenario --

24 DR. BENENSON: Clinical smallpox has a
25 viremia at one time. But you can shorten the

1 incubation period by giving it intravenously.

2 DR. RUSSELL: I think there is ectromelia
3 data. There is also ectromelia data that say same
4 thing. Even with high doses, that's where most of
5 the data was. With high dose aerosol in the mouth,
6 you have peripheral lesions.

7 DR. ASCHER: Okay. Now we get into one of
8 the questionable ones that I didn't necessarily
9 agree. Well, actually, no. I got the same answer.

10
11 Is there adequate characterization of the
12 variola strains available in existing libraries to
13 conduct epidemiologic assessments to determine the
14 origin of a variola virus which might appear in the
15 future?

16 And CDC provided new information that Joe
17 had gone into detail in terms of their library. I
18 sort of said probably not. Peter said probably not.

19 Based on the fact we have a lot less than with
20 other viruses, but there's also a lot less
21 variation.

22 So we conclude -- we got a fairly good
23 start, and you are moving right along. So it is
24 certainly not --

25 DR. RUSSELL: The collection will not

1 allow those kind of conclusions.

2 DR. ASCHER: Right.

3 DR. RUSSELL: Whatever is done, the
4 collection is totally limiting. So the answer still
5 has to be better, no matter what the technology.

6 DR. ASCHER: You have done just about
7 everything you can with it, and it's collection
8 limited, as Phil said.

9 DR. HENDERSON: I think we ought to be
10 clear on the collection. This was sort of a grab
11 sample right here at the end.

12 DR. RUSSELL: Right.

13 DR. HENDERSON: And one of the most
14 important epidemics that you might think about here
15 is the one that hit Iran in 1972 at 10,000 cases.
16 It spilled over into Iraq and Syria, coming from
17 Afghanistan.

18 We have no specimens whatsoever from that
19 whole bit, and none from Afghanistan, preceding
20 this. So we -- this would be an important one, if
21 you wanted to identify it, but we don't even have
22 specimens from that collection.

23 DR. BENENSON: Do you think it is
24 different from Bangladesh?

25 DR. HENDERSON: What?

1 DR. BENENSON: Do you think it is a
2 different virus from Bangladesh?

3 DR. HENDERSON: How do you know?

4 DR. BENENSON: If you know --
5 geographically, they are not too far apart.

6 DR. HENDERSON: No, but if we are really
7 going to change it to a point, it's not like the
8 Pole one, I don't think. But we don't -- and we
9 can't determine that.

10 DR. RUSSELL: One of the things that has
11 been a truism of molecular epidemiology and virology
12 in viruses, they have all produced surprises. I
13 mean, really, it happened in every instance where
14 they begin to molecular identification to strains.

15 And you say, "Holy Christ, we didn't know
16 that. We thought they came from someplace else."

17 So I think we are stuck with "We don't
18 know."

19 DR. CASSELL: So if you admit that, then
20 how can you say with absolute certainty that the
21 diagnostic tests are as good as they need to be?

22 DR. RUSSELL: I think by the definition of
23 -- well, I think if I go back to what is conserved
24 and what is variant.

25 DR. CASSELL: But how many total strains

1 have you looked at?

2 DR. ASCHER: Well, they list eight here.

3 DR. RUSSELL: You get into what defines
4 the species.

5 DR. CASSELL: Just asking.

6 DR. RUSSELL: I don't want to argue that
7 one. There are important gaps in the collections.

8 DR. CASSELL: We should probably
9 acknowledge right, right, so we don't get held
10 accountable later.

11 DR. RUSSELL: If it is a virulent
12 gene -- well, it would be virulent once you looked
13 at it when it comes along.

14 DR. ASCHER: Right.

15 DR. CASSELL: And very few things only
16 have one virulence gene, right?

17 DR. RUSSELL: Right.

18 DR. ASCHER: And if and when we decide
19 what is important in terms of having this
20 information, as I asked earlier, you could run
21 through them very quickly with PCR system or put
22 them away in such a form that they would be suitable
23 for that in the future even though they are now
24 destroyed. But that is all possible.

25 Part d, can laboratory technicians be

1 trained in variola diagnosis without having the
2 whole virus? Absolutely correct. Absolutely yes.
3 We have concurrence on that all around. CDC is
4 willing to train technicians.

5 Peter also says that plasmid reference
6 material would be sufficient to demonstrate the
7 exact result that live virus would give.

8 DR. JAHRLING: And you need a research
9 program to sustain it.

10 DR. ASCHER: Right. But you cannot train
11 them 15 years from now by opening up something and
12 taking the dust off of it and saying: here, do this
13 test. That isn't going to work.

14 Mutation. Is it conceivable that one or
15 more naturally occurring orthopox could mutate or be
16 deliberately manipulated in such a manner as to
17 acquire characteristics of transmissibility? The
18 answer is yes.

19 It is more likely to occur from
20 recombination between two viruses than by mutation
21 of one. Genetic engineering is also a possibility.

22 And the reference we made earlier to putting
23 material into vaccinia is clearly the case.

24 CDC said that the camelpox/monkeypox
25 points, as I mentioned before, are closer. A little

1 less concerned -- and there is no animal model to
2 test the mutated virus, even if they could be
3 prepared. So it would be hard to determine the
4 effects of the mutations.

5 But I guess the point of the question is
6 that if this was mutated into a human virulent
7 thing, is that possible? And the answer is yes.

8 DR. CASSELL: I would like to go on record
9 as saying that I am not convinced that we have
10 enough data to say that there is no suitable animal
11 model, because at the time the animal models were
12 evaluated, I think -- at least I trust you that it's
13 in the books, but I had somebody tell me that they
14 looked fairly extensively at this, and they wouldn't
15 concur with that statement.

16 After having heard what we heard today
17 with respect to some animal species, it seems like
18 theoretically there isn't suitable animal model. So
19 how can we sign our names to something that says
20 that there is no valid animal model, if in fact it
21 hasn't really been tested?

22 DR. LAMONTAGNE: I know the Indians use
23 monkeys. They demonstrated like a pregnant human.
24 A pregnant monkey that was given the smallpox would
25 die. Remember? I think that was something that

1 Iral (phonetic) was involved with.

2 DR. RUSSELL: Indian rhesus or iris or
3 sinos (phonetic), you know?

4 DR. LAMONTAGNE: Just monkey that's got
5 two arms and two legs. I don't know any of the
6 particulars. But they are -- the objective was to
7 see whether they could replicate these human
8 problems of the 18-year-old pregnant that got
9 vaccinated in infancy and proceeded to die with
10 smallpox. That was --

11 DR. ASCHER: I agree with Gail. We can
12 remove the reference to animal. It is a little
13 skeptical. It is not key to this.

14 DR. RUSSELL: Or qualify it that there is
15 no verifiable model at the present time.

16 DR. ASCHER: It is not really on the
17 point, so we can sort of leave it out and talk about
18 it later.

19 Alan?

20 PARTICIPANT: In the realm of kind of
21 genetic surprises and the things, I think Joe's work
22 has shown that it may be during the smallpox
23 eradication campaign, there was an intensive effort
24 on looking at those species where you might be most
25 likely to find the closest genetic presence of

1 smallpox, like gerbils and camels.

2 Those surely weren't the object of intense
3 scrutiny during the campaign and not by PCR or other
4 -- not a lot of virus. We only have one gerbilpox,
5 one thing that is called
6 gerbilpox --

7 DR. ESPOSITO: The fact that there was no
8 animal reservoir for the virus I think argues the
9 point that there is no animal model for the virus.
10 We would have had an animal reservoir, if there was
11 an animal model.

12 DR. CASSELL: But we develop animal models
13 every day with human pathogens, in which there is no
14 known animal reservoir for that particular pathogen.

15
16 PARTICIPANT: No. I am not saying there
17 is smallpox itself anywhere. Unambiguous, there
18 could be something very smallpox-like endemic in an
19 animal population somewhere.

20 DR. HENDERSON: Or you might have -- you
21 might be able to infect simians, certain simians,
22 with smallpox with transmissibility. That is a
23 different issue.

24 It is an animal model for a simian. I
25 think the other animals have been pretty well looked

1 at, and there isn't any. I do know we have recorded
2 a case or two cases in orangutan and chimpanzees in
3 zoos.

4 It is quite possible that you have
5 to -- what Bud is referring to his studies down in
6 Madras, but now, I do recall, I think it did infect
7 monkeys, or he tried to infect monkeys. And I don't
8 remember how that worked out.

9 DR. RUSSELL: But this question could
10 result in a one-way experiment. If you engineered a
11 virus, tested it in monkeys and it up-regulated the
12 virulence for monkeys, and you had left all the
13 known human virulent genes in there, you don't need
14 to do a whole hell of a lot more to see up-regulated
15 virus.

16 I think the feasibility of testing that in
17 monkeys and getting an operationally valid answer,
18 if not a totally scientific -- a negative experiment
19 doesn't help you in that regard. But a positive one
20 tells you that it goes up.

21 And if you didn't mess with the known
22 human virulence genes, the presumption of having an
23 up-regulated virus would be high, high enough for
24 operational decisions.

25 DR. ASCHER: B, is it conceivable that a

1 mutant variola virus could arise or be created which
2 would invade the immune response? The relative
3 answers to that are consistent. Very improbable,
4 unlikely, and virtually impossible are the three
5 choices of words.

6 DR. RUSSELL: All of them assume different
7 mechanisms, though.

8 DR. ASCHER: Right, but they also all
9 agree that if you had such a virus causing disease,
10 you would use the new virus as the starting point
11 for a program.

12 And the old virus is fairly much
13 irrelevant. And that was concurred. Don't need the
14 old virus. Don't need soul, if you've got the new
15 one.

16 DR. BENENSON: From a practical approach,
17 from a research approach, you would probably want to
18 compare the old and the new.

19 DR. ASCHER: Right, but it would not be
20 necessary.

21 DR. BENENSON: Not necessary for managing
22 the output.

23 DR. ASCHER: Correct, because you would
24 probably then go for a challenge model with your new
25 strain and evaluate your vaccine just like you would

1 whatever is current at the time.

2 DR. RUSSELL: Then you would deter it.

3 DR. ASCHER: Exactly. 4a, what are the
4 prospects for developing a less reactogenic vaccine?

5 We have good, excellent and there are several
6 already available.

7 Peter and folks didn't tell us about our
8 program in a lot of detail, but the subculture
9 product is moving along. Phase one?

10 DR. JAHRLING: There is one b. What are
11 you up to?

12 DR. ASCHER: And NIVAC is --

13 DR. LAMONTAGNE: I don't think anybody
14 seriously believes NIVAC has enough immunizing
15 potential to be useful against the poxvirus itself,
16 do they? Are there any data on that at all? No.

17 Well, you can compare it against
18 ectromelian mice, for example, or you can -- because
19 if it fails in all those systems, which I think it
20 would --

21 DR. ASCHER: Yes. I think --

22 DR. LAMONTAGNE: I gather it is a one-way
23 experiment.

24 DR. HENDERSON: I think there is a
25 question with regard to a, which is a bit of a

1 quandary. We thought or hoped we would be able to
2 develop a more attenuated -- see a more attenuated
3 smallpox back in the sixties, into the seventies.
4 And there were several candidates. You worked on
5 one, Bud.

6 The difficulty was when we did not get at
7 least serologic responses comparable to what we saw
8 when we had the New York Board of Health strain.
9 And what did we have, a failure rate of maybe 20
10 percent or what have you in the groups that
11 receiving this?

12 And then there were problems. Those not
13 responding serologically, when given the New York
14 Board of Health strain, did not respond well. It
15 was a serologic response.

16 We didn't know what this meant. We
17 finally came to the conclusion with that and a
18 German strain that we really could not risk trying
19 this out in a smallpox endemic area to test whether
20 it was effective or not. And we finally had to
21 abandon the whole effort.

22 The real issue is: How do you test
23 efficacy without the disease? That is the problem.
24 You can do it with maybe an experimental animal in
25 limited numbers if it is monkeys, but it still

1 leaves you with a lot of questions.

2 DR. ASCHER: The two approaches here, one
3 is to derive the material from a different cell
4 source, using the same starting product to make it
5 more state-of-the-art in terms of exogenous
6 material. The other is to delete things from it to
7 make it less immunogenic, as well as reactogenic.

8 And I think our response to the former is
9 that there are tissue culture procedures that may
10 make the same virus product more acceptable as a
11 human vaccine.

12 We have concerns about deletions at this
13 point, given the concerns about immunogenicity, any
14 modification.

15 DR. HENDERSON: Now, a tissue culture
16 vaccine was developed in Holland by the Wrights
17 Institute back in the early seventies. It was
18 tested in Indonesia and found fully effective and
19 very stable.

20 So it is a rabbit kidney cell tissue
21 culture vaccine. That has been done.

22 The question when -- as you say, I don't
23 think that is a problem. You would rather have
24 state-of-the-art rather than the damn cow hides that
25 we have been using, I would agree.

1 But it is a question of how you make a
2 less reactogenic smallpox vaccine when
3 reactogenicity, I think, is not the medium in which
4 it is grown, but the nature of the virus itself.
5 That's the problem.

6 DR. BENENSON: Our study compared four
7 different vaccines, and we had the attenuated CD-1
8 in there. We hoped that that would prove to be less
9 reactogenic and sufficiently antigenic.

10 It turned out that we had the New York
11 City Board of Health -- they had very few adverse
12 reactions among or high temperatures among the
13 children which had been tested; that the CD-1 had
14 some high fevers that we had not hoped to see.

15 But more important, after we had to take
16 the CD-1 on the schedule challenge with drivacs
17 (phonetic), a year later many of the children who
18 had had a vesicle (phonetic) were not protected
19 against primary looking infection on the re-
20 challenge whereas with that, they were -- so it's
21 not just does it replicate, does it produce
22 antibodies. Do those antibodies persist long enough
23 to be protective?

24 DR. RUSSELL: Let me make three points.
25 One is that past failures don't mean you stop

1 trying.

2 The second point is that the current
3 vaccination method by scarification is unacceptable
4 as a broad-based defense against the threat, partly
5 because of the -- the real problems were seen with
6 primary vaccination by the old method in totally
7 non-immune 18, 20-year-old recruits.

8 So if the military is facing a threat, it
9 has to be a better product. Whether this one is
10 going to succeed or not, and Lord only knows, I
11 don't.

12 The third point I would like to make is
13 that I believe it is possible to look at the immune
14 response to conventional vaccinations. Quantify it
15 in terms of humoral response; semi-quantify it in
16 terms of cellular response.

17 And develop a new product that will do the
18 same thing, that can be also evaluated in
19 heterologous systems where vaccinia also works. You
20 cannot test it against variola.

21 But I don't believe that we can rely on
22 either the current vaccine stocks, because I
23 don't -- I don't have D.A.'s confidence in the
24 stability of those stocks. And I do believe that we
25 need the capability of manufacturing a replacement

1 stock for the next generation.

2 DR. BENENSON: There is no argument
3 against that.

4 DR. RUSSELL: That has to be a new
5 technology.

6 DR. BENENSON: No. I'm all for it. The
7 only thing is that we have one vaccine which has
8 been field tested and been shown to be beautifully
9 protected. So we don't need clinical cases of
10 smallpox any longer to evaluate the vaccine.

11 DR. RUSSELL: No. We can surrogate
12 immunology.

13 DR. BENENSON: The important thing is, as
14 you said, do they develop an antibody, a
15 neutralizing antibody? And I am saying let's make
16 sure they neutralize the antibody. Persist rather
17 than just being a transient --

18 DR. HENDERSON: I am not saying it cannot
19 be done, Phil. What I am saying is I don't think it
20 is all that easy.

21 DR. RUSSELL: I don't think it is either.
22 If it was easy, we would have done it a long time
23 ago.

24 DR. HENDERSON: This is a fairly
25 complicated and fairly sophisticated sort of

1 approach. I think there is going to have to be a
2 lot of judgment, surrogate markers and a variety of
3 other things employed to identify when you have got
4 a product. And it is going to still be guessing.

5 DR. RUSSELL: And it is going to take some
6 money, too.

7 DR. HENDERSON: But I agree it should be
8 done, but it isn't going to be easy.

9 DR. RUSSELL: I think we can limit the
10 level of guessing, but unless there is assurance
11 that there is no threat, then we have to do it.

12 DR. BENENSON: Well, it is in phase one
13 testing now. I think we are pushing time.

14 DR. HALVORSON: Well, we could make a
15 comment on priorities, though.

16 DR. RUSSELL: I am not sure that this is
17 not going to require a modification and then more
18 phase one testing and so on. So I would not assume
19 that we are going to go from phase one to phase two
20 to --

21 PARTICIPANT: What is the parent strain?

22 DR. BENENSON: The original strain.

23 PARTICIPANT: The New York Board of Health
24 strain.

25 DR. ASCHER: It is the -- it is totally

1 the same. The nuance is --

2 DR. ESPOSITO: I think I can make a
3 comment about the New York Board of Health strain
4 from what I have heard from other pox virologists.
5 Some have looked at in mouse systems and testing
6 nude mice and that sort of thing -- have gotten the
7 strain from Wyatt, have gotten the strain from the
8 American type culture collection and have gotten
9 other strains called the New York Board of Health
10 strain.

11 It is clear now that they all have
12 differences, basically because they are all passaged
13 differently.

14 DR. RUSSELL: This one came from Wyatt, I
15 believe.

16 PARTICIPANT: It came from Konon
17 (phonetic). I can't remember all the details, but
18 basically, it was brought from Konon.

19 But in animal testing, it was not more
20 virulent but also not less virulent. It has the
21 same restriction profile as other -- it has the same
22 both biological and genetic markings, but of course
23 not in that sequence. So there are similar things,
24 indistinguishable from --

25 DR. CASSELL: Isn't this one area where if

1 you did have a valid animal model, that you could
2 certainly facilitate development of a vaccine?

3 DR. ASCHER: Yes, and --

4 DR. ESPOSITO: And test the efficacy
5 against an aerosolized strain, and you would be
6 right there.

7 DR. CASSELL: So --

8 DR. ASCHER: It is one of the scientific
9 things that we would give some priority to.

10 DR. HENDERSON: Valuable but not
11 essential, not critical.

12 DR. CASSELL: I understand what you are
13 saying, but in fact, if you have all -- well, we are
14 not supposed to talk about the destruction.

15 DR. ASCHER: Yes, Alan?

16 PARTICIPANT: Well, in your summary of
17 vaccine feasibility, you never address something
18 that is basically caught up by Joe and the TND
19 receptor analog, but you could construct sub-unit
20 augmentation things that would actually be variola-
21 specific genes targeted to -- not just the TNF
22 receptor analog, but another one like that that were
23 not even listed by the conventional vaccines.

24 So those are completely unacceptable
25 without animal model and variola. That is a long

1 leap away from (inaudible).

2 DR. ASCHER: You mean you don't want to
3 make a GP120 right away?

4 DR. CASSELL: So if you destroy the virus,
5 what would keep you from coming back, taking your
6 vaccinia, modifying that vaccinia, and then
7 developing an animal model and using it then to
8 evaluate your vaccine?

9 PARTICIPANT: As with almost everything we
10 are talking about it, would be a matter of how much
11 uncertainty you would want to live with.

12 DR. ASCHER: 4b, would present variola
13 stocks be required for the improvement or reduction
14 in reactogenicity of a vaccine? And the answer was
15 perhaps not necessary or not required for the
16 reasons we just stated, that you would use
17 surrogates at this point.

18 Unless you really had an animal model that
19 we believed in, we would not need the virus. And
20 failing the one, you cannot make a justification for
21 the other.

22 Okay. is the existing vaccine protective
23 against an aerosolized dose of variola virus across
24 a range of exposures that might be reasonably
25 expected in a military or a terrorist scenario? And

1 I got that one right.

2 I said, "Beats the hell out of me."

3 (Laughter.)

4 And the word is unknown. Exposure, of
5 course, is less, as we have all known. CDC agrees
6 it is unknown. It is something that down on the
7 list of research questions would certainly be worth
8 listing.

9 I am not sure we want to give it any high
10 priority, and it would probably be third so far in
11 our list. It is interesting they come in this
12 order.

13 Sort of animal models for antiviral,
14 animal model for vaccine, and now animal model for
15 aerosol. If you saw it the other way around, I
16 think you would be in trouble.

17 It could also tell you something about
18 whether the disease is atypical across the dose
19 range, the issue of high dose, really hemorrhagic
20 fever syndrome. You know, you have TNF. That is
21 nasty stuff.

22 And you get it loose in your system, and
23 you could very easily go out with some crazy
24 syndrome before you had a chance to put anything in
25 your skin. I don't know. Speculation.

1 Okay. D, is exposure to primates to
2 aerosolized variola virus or monkeypox virus a
3 reasonable model for evaluating the efficacy of
4 existing vaccine? Could such a model be used to
5 assess the efficacy of subsequent generations of
6 vaccine?

7 Well, I didn't have all the information,
8 so I said I didn't think so. CDC gave the same
9 response that we heard, which is smallpox virus does
10 not induce a model disease in monkeys that is
11 comparable to human disease.

12 We also heard early this morning that
13 there is some information about potentially some
14 other animal models that might be worth pursuing.
15 So the answer is: We don't know, possibly, we might
16 like to know that.

17 Any such model would of course be very
18 suitable for evaluating vaccines in the future. And
19 that is back to Gail's comment about a model in
20 general.

21 DR. ASCHER: We have still have a ways to
22 go, so moving right along, as they say, we are back
23 to 5a. I am just making sure that I agree with
24 everything we have.

25 Okay. 5a, how difficult would it be to

1 fully elucidate the interaction between -- and I
2 said hard, because I am an immunologist. We have
3 very difficult, and we have extremely difficult.

4 DR. RUSSELL: And virtually impossible.

5 DR. ASCHER: Virtually impossible. But,
6 you know, one of the things that I did not hear
7 clearly stated -- and maybe, Phil, if you have
8 notes, or Gail or somebody -- the one thing that
9 this represents is the prototypical resistance to
10 one virus induced by exposure to a variant. And we
11 have not really talked about the nature of the
12 vaccinia immune response.

13 DR. CASSELL: That's right.

14 DR. ASCHER: And that's independent of the
15 strains. So if you had a surrogate system where you
16 could show that you knew everything about the
17 vaccinia immune response and you could mimic that
18 with a subunit, you might be pretty happy.

19 DR. CASSELL: Well, that is kind of what I
20 was talking about with regard -- that if you do have
21 vaccine, and you can manipulate like you do, what is
22 to keep you then from developing a relevant animal
23 model and going on to further elucidate the immune
24 responses from the other questions?

25 DR. ASCHER: Right. So I would say that

1 to modify the very difficult or bordering on the
2 impossible comment here is that a lot could be
3 learned about the biology of this process by
4 studying the immunology of vaccinia independent of
5 the live variola.

6 DR. CASSELL: And could we not tack onto
7 that the fact that since vaccinia is being explored
8 as a recombinant vaccine for other diseases and
9 naripox (phonetic) and other things that are useful,
10 this could actually lead to a lot of useful
11 information that might be broadly applicable?

12 DR. ASCHER: Right.

13 DR. LAMONTAGNE: You are asking me? I
14 would say yes, but, I mean, I think that I would
15 make is that you have to remember that the vaccinia
16 infection is generally asymptomatic or mildly
17 symptomatic in humans.

18 In order to look at ways of intervening
19 therapeutically or immunologically in an infection
20 caused by something like variola, you might want to
21 study something like monkeypox or camelpox.

22 DR. ASCHER: Right.

23 DR. CASSELL: But you could look at it
24 both ways.

25 DR. LAMONTAGNE: Sure.

1 DR. ASCHER: But we don't even know about
2 the lymphocyte response, cellular immunity, which we
3 all believe is dominant. It is sort of -- a lot of
4 other diseases have been beat to death, but variola
5 has not been exploited. Ectromelia is a fabulous
6 example.

7 DR. LAMONTAGNE: Well, I think thanks to
8 Dr. Henderson's efforts, we wouldn't have our
9 chances to say that.

10 DR. ASCHER: Exactly. Right. Unless we
11 could get some samples from those volunteers,
12 wherever they are.

13 5b, would such studies require stocks of
14 Pole variola? Obviously, if you are trying to study
15 that, yes, you would. But other surrogates using,
16 you know, other poxviruses would be fully
17 appropriate.

18 But if you want to study variola and the
19 immune system, you are going to need variola.
20 That's fairly obvious.

21 What might be learned from other orthopox?

22 And the point is a lot. And the other answer is:
23 Most of what is desired to be known could be learned
24 from other orthopox viruses.

25 Without variola, a knowledge gap would

1 remain, and reasonable people would disagree about
2 the importance of that gap. So that -- and the
3 other response is: A great deal could be learned
4 about things like ectromelia, repeating ourselves.

5 How will the future development of
6 transgenic systems, cells and animals, change the
7 ability to access and exploit the immunopathogenic
8 mechanisms?

9 I tend to like that one, and that was the
10 only one I got wrong. We have: It seems unlikely
11 that a transgenic system would be superior to a good
12 primate model, and I think that is correct. I defer
13 to that. And it would be expensive, as noted.

14 The CDC says it is wishful thinking to
15 believe that altering genes of mice would make them
16 suitable substitutes. I think it is pretty
17 farfetched. But I have Skid Hughes running for HIV,
18 so I believe in anything.

19 DR. CASSELL: I mean, you know, it may be
20 realistic thinking to think that they would
21 identical to human, but one should hasten to point
22 out that a lot of useful information could probably
23 be generating from using such animals.

24 DR. ASCHER: Absolutely, and that is
25 this --

1 DR. LAMONTAGNE: If the questions are
2 framed tightly, they are useful, but they
3 don't -- they aren't models of anything.

4 DR. CASSELL: But you cannot discount
5 their utility completely.

6 DR. ASCHER: But put the skid system we
7 saw with some acyclovir, and if all of a sudden, you
8 know, you already did it with your other compounds,
9 and that seemed to be a reasonable system. But
10 that's not transgenic. Those are just manipulated
11 animals.

12 So I think the transgenic we will
13 broadened into including immuno-deficient mice or
14 odd mice. It doesn't have to be curing some odd
15 human receptor or maybe some strange humanized
16 animals.

17 DR. LAMONTAGNE: I think the whole field
18 of genetically manipulating mice or other species,
19 but particularly mice, is really exploding fairly
20 rapidly, and it is hard to know if five years from
21 now you might not have a mouse that --

22 DR. ASCHER: Well, I liked it. But as I
23 said, nobody else did.

24 DR. RUSSELL: I think there is a consensus
25 that so far both skid mice and transgenic mice have

1 been very disappointing in the productivity of the
2 information.

3 DR. CASSELL: But it really depends on
4 what you are studying, and they really have not been
5 exploited that much with infectious agents.

6 DR. RUSSELL: There has been an immense
7 amount of work done in HIV --

8 DR. CASSELL: Well --

9 DR. RUSSELL: -- and that has been
10 incredibly disappointing.

11 DR. ASCHER: The rate of change is high.
12 The level is low.

13 DR. CASSELL: I think the potential
14 combined with the fact that you can rear these
15 animals in stainless steel isolators --

16 DR. ASCHER: If you get permission from
17 your --

18 DR. CASSELL: -- in containment
19 facilities, it does make, could make, a pretty
20 useful model.

21 DR. ASCHER: If you can get permission
22 from your animal use committee.

23 DR. CASSELL: Well, I think you could if
24 in fact you were rearing them in stainless steel
25 isolators. The Lovine (phonetic) laboratory, I

1 mean, that is --

2 DR. ASCHER: Yes.

3 DR. LAMONTAGNE: Well, I still think that
4 if you are talking about variola challenges, you are
5 going to have real hard problems doing that even in
6 that kind of a situation.

7 DR. HUGGINS: Certainly aerosol challenges
8 -- the logistics of doing an aerosol challenge and
9 containing it almost require the (inaudible).

10 DR. LAMONTAGNE: I mean, I think you will
11 still find -- I mean, my only reasons for thinking
12 that it might be more helpful are they are going to
13 be a lot cheaper --

14 DR. RUSSELL: They are smaller than
15 monkeys.

16 DR. LAMONTAGNE: Than monkeys, and larger
17 experiments for -- I think that mice can be quite
18 instructive. I mean, I think they have been helpful
19 in understanding (inaudible) for example
20 (inaudible.)

21 PARTICIPANT: Influenza in mice has been a
22 good model for understanding immunology, very, very
23 good.

24 DR. RUSSELL: But bad for science -- but
25 polio in the transgenic mice tells us a lot about

1 transgenic mice.

2 What I have learned about transgenic mice
3 hasn't been very progressive, nothing about polio,
4 except that you still need monkeys to know where
5 there is -- I should believe the molecular
6 biologists.

7 DR. ASCHER: Okay. Now --

8 DR. RUSSELL: And that is always a
9 question.

10 DR. BENENSON: You have to remember the VI
11 antigen problem.

12 DR. RUSSELL: Wake up, Joe.

13 DR. BENENSON: The mice -- Morris Landing
14 (phonetic) made VI antigen, very protective in the
15 mouse, no effect at all on man. Now we have another
16 type of preparing VI antigen, which is very
17 effective in man.

18 So the very minor modification in the
19 formula made the difference in whether it worked for
20 man. But both worked in mouse.

21 So it's the preliminary introductory
22 studies of these things that have to be validated by
23 an all conflict system.

24 DR. ASCHER: Okay. Now we have a
25 procedural problem in that Brian did not

1 present -- or Brian did not have question six. And
2 Joe has some sort of -- he has some things written
3 out or some ideas he can contribute maybe.

4 But these are general questions, and we do
5 have some specific responses from DOD. We are going
6 to see -- Jim and I have been talking at the break
7 to see if we can maybe figure out what
8 the -- let's try to focus the discussion a little
9 bit.

10 And if public health means the negative
11 impact of variola disease in a population, then to
12 my mind, and I guess Jim would agree and he can
13 elaborate, whether you have the virus stock or not
14 does not necessarily help me. I don't see that it
15 does one thing or -- does anything either way.

16 If a terrorist decides tomorrow to release
17 it, they know full well from our discussion and can
18 figure out themselves that we would take the strain
19 that results from that and begin investigation in a
20 big way.

21 So is that misrepresenting what you said,
22 Jim? It doesn't help you one way or the other?

23 DR. CHIN: I think we need to discuss b, I
24 think, a little more in terms of retention of the
25 virus, implications, because I think one of the

1 concerns would be a sort of worst case scenario that
2 gets out of the laboratory.

3 You know, that science article has one
4 million cases could occur from that, I think, has to
5 be addressed.

6 And I think the discussions -- most of us
7 would agree that even under the worst case scenario,
8 it could be contained fairly rapidly with resources
9 that are available.

10 DR. ASCHER: I think that is the
11 conclusion. We just keep it simple.

12 DR. RUSSELL: I think that's true of any
13 scenario, that the first cases that you are stuck
14 with, unless you have chemotherapy. And then if you
15 have vaccine stocks and a responsive system, you can
16 contain the outbreak.

17 DR. CHIN: Yes, but there was that science
18 article of one million.

19 DR. ASCHER: But, also, there was other
20 press that said that they considered the likelihood
21 of escape fairly high.

22 And I think our statement -- and you have
23 probably done it already, Phil -- to say that we
24 considered the likelihood of a virus escaping from
25 its current containment to be very low, intentional

1 or otherwise.

2 And in the event of such a release, we
3 consider the public health implications to be
4 minimal with rapid control, with rapid recognition
5 and control very likely.

6 DR. RUSSELL: You want to make the
7 statement that an accidental release escape from a
8 repository probably would result in a few tens of
9 cases and could be contained, tens or hundreds of
10 cases and could be contained.

11 DR. HENDERSON: A limited number.

12 DR. RUSSELL: Yes. What you are really
13 talking about.

14 DR. HENDERSON: And the same would pertain
15 to the risk of, let's say, turning out virus in
16 people in permafrost bodies in permafrost.

17 It really is of no great consequence. If
18 you turn it up, you turn it up, but it is not going
19 to spread and escape.

20 Likewise, I think we also have the feeling
21 that if you had a mutant monkeypox virus that seemed
22 to have a better transmissibility than the present
23 strains have, that that likewise is not of great
24 consequence, because, again, you could -- if it
25 behaves as variola and it spreads, it is not going

1 to spread very rapidly.

2 And we do have a vaccine and control is
3 possible. For any one of these different factors
4 where you might see emergence, you don't see this as
5 really a public health threat that could not be
6 readily controlled. I think that would be the way
7 we word that.

8 DR. ASCHER: And I don't -- on the other
9 side, I don't think any of us see retention as any
10 form of deterrent. It is smoke, at worst.

11 DR. CASSELL: P.K., how did you answer
12 that question?

13 DR. RUSSELL: How did I -- the question on
14 6a?

15 DR. CASSELL: No, 6b.

16 DR. RUSSELL: For retention of variola
17 virus.

18 DR. CASSELL: Do you want to read it out
19 loud?

20 DR. RUSSELL: Yes. The retention of
21 variola virus could, if appropriate R&D were
22 conducted, improve the national ability to respond
23 to an intentional release.

24 And the reason for that is that I believe
25 it relates to the vaccine scenario, because I am

1 concerned about our current vaccine stocks, the
2 problem of using standard vaccination procedures in
3 the modern era in a totally unvaccinated population.
4

5 Not insurmountable, but if we had a better
6 vaccine that was less reactogenic and equally or
7 more effective, and I think that is possible, then
8 we would have a better capability of responding.

9 So if you assume an appropriate R&D
10 program of vaccine development, then retention gives
11 you a better defensive capability downstream. If
12 you don't have an R&D program, it's irrelevant.

13 DR. CASSELL: So is there anybody that
14 would object to what P.K. has said, because it
15 really is a pretty strong statement?

16 DR. ASCHER: Well, we did say this
17 clearly, that if you are going to wait for it and do
18 nothing and destroy the virus, you have it when it
19 comes up. You have your strategy and you proceed.

20 If you want to do something with it in the
21 meantime, you have to do something with it. There
22 is no point in keeping it if you are not going to do
23 something.

24 So it is one or the other, and this
25 basically says that.

1 DR. ESPOSITO: Is there any further
2 implication from the fact that if both samples of
3 the virus, the Russian samples and the U.S. samples,
4 were reduced in mass or number, to one strain each
5 in a simple vial, does that have implication or
6 reduced implication of keeping the stocks but
7 keeping less?

8 DR. RAUCH: That is just ceremonial. I
9 mean, is it not? I mean, really.

10 DR. ESPOSITO: Well, then you know the
11 ones that are at least admitted to. You have
12 narrowed it down to one, the India strain, the
13 Bangladesh strain, for example. And those sequences
14 are known.

15 DR. ASCHER: Right. It would simplify the
16 recordkeeping. It would simplify the verification,
17 all of that.

18 DR. LAMONTAGNE: All the threats, the
19 threats of it getting out or somebody stealing it,
20 also.

21 DR. ESPOSITO: It reduces the hazard. It
22 reduces public health implications.

23 DR. CASSELL: Except if the one vial were
24 stolen, then you really would be in trouble.

25 DR. ASCHER: So you are asking whether a

1 statement in there that an intermediate step on the
2 way to this of reducing non-essential
3 samples --

4 DR. ESPOSITO: Right.

5 DR. ASCHER: -- to make the eventual
6 process simpler would be supported. I think I would
7 support that.

8 DR. HALVORSON: But aren't we getting into
9 the political decision making now? The same
10 question comes up about whether moral persuasion is
11 part of the argument.

12 It is not something we should be dealing
13 with, but it is something that will rise at another
14 level of discussion.

15 DR. ASCHER: I think if Joe wants to say
16 would we object to him going down and looking
17 through his freezer and picking the 30 best samples
18 and using his judgment and throwing everything else
19 away to make his life easier, I would say I have no
20 problem with that. In fact, he probably could
21 recommend that. That is not political.

22 DR. ESPOSITO: Carrying it down to one
23 sample.

24 DR. HALVORSON: Yes, but it is not a
25 scientific question.

1 DR. ASCHER: No. That's an operational
2 thing. You would not have any problem with that.
3 And that is not going to influence the other side,
4 just as he said.

5 DR. HENDERSON: Well, except you are
6 raising the question: What are you retaining the
7 stocks for?

8 And you are retaining them to have a
9 variety of different types of agents in terms of
10 testing for a vaccine. I think it is destroy or
11 don't destroy. I think it is pretty hard to see
12 anything in between.

13 DR. ASCHER: Well, I am assuming retention
14 of PCR amplifiable stuff.

15 DR. HENDERSON: Retention of --

16 DR. ASCHER: Retention of PCR preps in
17 that comment, that you are going to destroy but
18 retain some genetic material for library purposes.
19 Maybe the technology is moving too fast. D.A. is
20 the one to ask. By destroyed, do you mean down the
21 toilet, down the toilet, or phenol in the tubes? It
22 is a different result.

23 DR. HENDERSON: I think what we are
24 looking at is at least the status of the
25 recommendation that Ben made, do we -- if we are

1 wanting to deviate from that, this is fine. If it
2 raises a whole -- there is a whole series of
3 different possible scenarios out there.

4 Once you say, well, we could destroy some
5 of it, we could be it in a third country, we could
6 put it in a bank vault, and there are a lot of other
7 things, I think it is probably best to stay away
8 from that and just say are we going to recommend its
9 destruction or retention and leave it at that.

10 DR. ASCHER: But does inactivation beyond
11 a shadow of a doubt equate with destruction to your
12 mind? If we take all of the existing viable stocks
13 down to the level of DNA preps, not amplified,
14 nothing more than just samples suitable for library
15 purposes in the future for either sequencing or PCR
16 --

17 DR. HENDERSON: Is this going to be
18 satisfactory in terms of testing against -- for a
19 vaccine or for an antiviral substance?

20 DR. ASCHER: No, absolutely not. It would
21 only give you phylogenetic capability.

22 DR. BENENSON: Right. That's right.
23 Which would you save, East Africa or Alaska
24 or --

25 DR. ASCHER: We could keep them all.

1 DR. BENENSON: You have three different
2 types to start with.

3 DR. ASCHER: I understand. But you could
4 keep all samples if you really inactivated them
5 beyond a shadow of a doubt. But would that be
6 politically equated with destroying it?

7 DR. ESPOSITO: If you had intact genome
8 DNA, you could very simply put that DNA in with
9 fowlpox that doesn't grow in mammalian tissue and
10 replicate the variola DNA.

11 DR. ASCHER: Right.

12 DR. ESPOSITO: That's the marker rescue
13 experiment that was done in the sixties.

14 DR. ASCHER: So I am asking the question
15 to get the answer, and the answer is we are talking
16 about really down the toilet, no more, except for
17 the clones.

18 DR. HENDERSON: I don't think this would
19 sell.

20 DR. CASSELL: It is still a moot point.

21 DR. ESPOSITO: The question of the clones
22 is can you stitch it together. Can you get back to
23 intact genome DNA?

24 DR. TAKAFUJI: If you think you know the
25 organism, then --

1 DR. HENDERSON: Both of those are
2 possible.

3 DR. ESPOSITO: Both of those are possible,
4 yes.

5 DR. RUSSELL: I am not sure we ought to
6 try to get too sophisticated in shades of
7 possibilities here.

8 I think the generic issue of can you
9 reconstruct the virus from sequence is enough of a
10 variable to make the rest of them almost -- let the
11 politicians argue about it.

12 DR. ASCHER: Okay. Part c.

13 DR. RUSSELL: We didn't get to a
14 discussion on part a. We jumped to b.

15 DR. ASCHER: Oh, I'm sorry. You
16 transitioned.

17 DR. HENDERSON: Have we -- in dealing with
18 b, for clarification, the implications we are
19 looking at for public health, we are looking at
20 different implications of different types of things
21 above they are referring to. One is a terrorist
22 attack, as opposed to an incidental emergence of
23 this from a permafrost.

24 If we are looking at -- if we consider
25 that there is no risk of a terrorist attack, you

1 would not be pursuing the issue, I think, of new
2 vaccines or chemotherapeutic practice.

3 But I think in qualifying the risk in
4 public health, we are making the case that there now
5 is perceived to be a very real risk of a terrorist
6 use or other and that, therefore, it is incumbent
7 upon us at this time to develop a better vaccine.
8 And it would be desirable if we had a
9 chemotherapeutic agent.

10 And, therefore, we are making the
11 recommendation that these stocks be retained because
12 we need those if we are going to develop a better
13 vaccine or chemotherapy. I am just trying to
14 clarify that that is what we are saying. Is that
15 correct?

16 DR. ASCHER: And I just modified that to
17 say until we have had at least a preliminary look at
18 those two issues in a clearly descending slope to
19 the end.

20 DR. HENDERSON: Because I think this is
21 what is going to have to be said to people around
22 the world, not just to our little of people looking
23 at policy. This has to be said to countries around
24 the world, and this has not been said so far.

25 DR. ASCHER: So this is the sound bite,

1 like we said at the break.

2 DR. RUSSELL: 6b we are talking about.

3 DR. ASCHER: No, no. What D.A. is saying
4 is the sound bite. If you reverse your position,
5 this has to be the sound bite.

6 DR. RUSSELL: The value of retention is
7 based on --

8 DR. ASCHER: The threat of use.

9 DR. RUSSELL: -- the threat of a terrorist
10 use, and its value revolves around chemotherapy and
11 --

12 DR. LAMONTAGNE: Isn't there another
13 element, though, that you can't really and
14 truthfully destruct?

15 DR. CASSELL: That's absolutely -- I would
16 argue that.

17 DR. LAMONTAGNE: That is a known, isn't
18 it? You can't assure --

19 DR. ASCHER: Sound bites are not that
20 long. You see, that's the problem. You have to say
21 what you want to put first.

22 DR. CASSELL: But that is an important
23 part.

24 DR. ASCHER: I understand.

25 DR. LAMONTAGNE: I mean, I think that is

1 what you were trying to get at earlier when you were
2 arguing whether down the toilet or just, you know --

3 DR. RAUCH: Well, don't they go hand in
4 hand, though?

5 DR. ASCHER: Yes.

6 DR. RAUCH: I mean, quantifying the risk
7 of terrorist use versus verification and compliance
8 or non-verification and noncompliance of destruction
9 --

10 DR. HENDERSON: I am concerned if you get
11 involved in verification, simply from the fact that
12 we know very well that all virologists are squirrels
13 and all squirrels put away these little tidbits of
14 isolates in the bottom of the freezer.

15 And I am sure there is a whole bunch of
16 squirrely virus isolates in a lot of different
17 places.

18 I think what one is looking at is the
19 question of destruction and -- let's say whatever
20 one does is laid out in an expert committee
21 report -- confirmation of destruction by independent
22 groups of known available stocks.

23 And I don't know how you can go into non-
24 known stocks and say, you know, we have to verify
25 that, too.

1 So I don't know how you are ever going to
2 determine that.

3 DR. LAMONTAGNE: But, D.A., even if you
4 could do that, if you have a system in place that
5 told you that you have destroyed everything that you
6 knew was there, you still have the clones floating
7 around, and you still have --

8 DR. CASSELL: You have the sequence, if it
9 is published.

10 DR. HENDERSON: And I think the question
11 we would ask is why would you want to keep your
12 stocks of variola for testing? And suppose that you
13 destroy yours, what difference does it make whether
14 they destroy theirs, really?

15 What you lose is your ability to zap them
16 after they have zapped you with smallpox. And I
17 think we basically felt that that probably was not
18 an acceptable zapper.

19 DR. ASCHER: Do you want to work on it a
20 little bit, see if we can finish what --

21 DR. CHIN: No. I think a -- I think the
22 Army has already responded.

23 DR. ASCHER: If you have not read it, go
24 ahead and look at it. The word there "uncertainty,
25 instability," whatever you want to say, is a concern

1 to all of us, I think. We said at the break that
2 maybe we should put in a -- because one of the high
3 level concerns is international instability.

4 And one of the criteria for us being more
5 comfortable with its destruction is resolution of
6 some of the international instability issues. That
7 can be specific or nonspecific.

8 I don't know if that is important, but it
9 is unclear. The Soviet Union. I mean, Russia is
10 such an unstable situation with an election coming
11 up. I can't say what is going to happen.

12 DR. WOLFE: Well, you can't just emphasize
13 Russia. You have to make an assumption that there
14 are other terrorist groups out there who very well
15 might have it or can get it.

16 DR. ASCHER: Absolutely.

17 DR. WOLFE: So, I mean, we can't just talk
18 about Russia here.

19 DR. ASCHER: No. I understand that. But
20 Russia is -- Russia is the weaponized question at
21 this point.

22 DR. CASSELL: But you are no longer just
23 talking about one country versus another country
24 like you may have been five years ago.

25 It is a potential threat from individuals,

1 though, using it. This may be even a greater issue,
2 and maybe a more convincing argument that going
3 through the ceremonial act between the countries
4 really doesn't matter anymore.

5 DR. ASCHER: It could be separatists or
6 Canadians or who knows.

7 DR. CASSELL: Or Americans.

8 DR. RAUCH: We just have to remember that
9 when we talk in terms of a specific country, we are
10 talking about a military threat, which really isn't
11 a terrorist threat. Although there is a
12 proliferation factor that might lend to a terrorist
13 incident.

14 DR. WOLFE: Well, the implications are the
15 same. And if we can all agree that we can make a
16 fair assumption that it is possible, if not likely,
17 that organizations or countries have the potential
18 to use this virus, then we need some defense against
19 it.

20 And the question comes down, we agree we
21 need a defense. Do we need the live virus to do
22 this? That, to me, is the crux of the whole thing.

23 DR. ASCHER: Right. We definitely state
24 what you just said, which is that we recognize the
25 potential for introduction of an intentional nature

1 from a variety of sources, either with some
2 difficulty or fairly easily.

3 And it is our assessment that retention of
4 the live virus at this time provides -- is neutral
5 regarding the probability of that happening.

6 It really is. It is not a deterrent. It
7 is neutral.

8 DR. WOLFE: But why do you say "neutral"?
9 I mean, the Army makes the point that they feel
10 that the live virus is useful. To continue to hold
11 the virus is useful to counter the threat.

12 DR. ASCHER: But Phil said unless you have
13 organized ongoing research to improve our position
14 with that live virus, holding it is
15 not --

16 DR. RUSSELL: The virus without an R&D
17 program is absolutely useless.

18 DR. ASCHER: Correct. We are beginning to
19 say this a little more clearly.

20 DR. RUSSELL: It's a political liability.
21 With an R&D program, it could materially enhance
22 the defensive posture. But the two are absolutely
23 linked, because the political liability of keeping
24 it is very, very, very substantial.

25 DR. ASCHER: That is what I was trying to

1 say earlier. We have to have them linked in our
2 statement. If we want to propose one, we have to
3 propose the other.

4 DR. RAUCH: Yes. I mean, I feel
5 comfortable with the linking. I mean, we have
6 presented and R&D plan. I mean, we weren't kidding
7 when we presented it.

8 DR. ASCHER: And what that would -- how
9 that would read in the context of sort of the
10 general overview I proposed is that you would say
11 something like short term or mid term prior to this
12 point in time which you have projected, we would
13 suggest the following questions be addressed in the
14 following priority.

15 Evaluation of chemotherapeutic is
16 currently available, and then we could vote on the
17 rest, vaccines.

18 DR. RUSSELL: I would be happier if
19 someone from the comptroller's office made that
20 statement, Terry.

21 DR. RAUCH: There is no new money, but
22 there is re-prioritization, right, of existing
23 resources?

24 DR. ASCHER: But then the point is,
25 failing the execution of that work as a decision

1 then that as a criterion for retaining it goes away.

2 And you don't say: Okay. We'll just hold it until
3 we decide to do that.

4 Once you decide to do that, you don't hold
5 it. That is the linkage we are talking about, and
6 it has to be clear. You almost say that, that in
7 the event that such a program is not considered
8 necessary or viable at this time, then the virus
9 should be destroyed. Period.

10 DR. CASSELL: It seems me that we keep
11 dancing around the issue. We were told to ignore
12 the politics, stick to the science, and what I have
13 heard the science say is that there is scientific
14 merit in further understanding pathogenesis, and
15 that because we have a published sequence and a high
16 degree of homology with other related viruses, that
17 destruction is really a moot point from a scientific
18 point of view.

19 It seems to me that that is the bottom
20 line of the science, if you get the politics like we
21 were told to do.

22 DR. ASCHER: But then that is not the
23 justification for keeping it. You are keeping it
24 because there is no point in getting rid of it.

25 DR. CASSELL: That's right.

1 DR. ASCHER: But that is not --

2 DR. CASSELL: But we were told not to
3 consider the politics or even address the question
4 of whether it should be destroyed or not but to
5 rather answer the questions that we have based on
6 the science.

7 DR. CHIN: The public health implications,
8 unless you are calling that policy, politics, the
9 public health implications are that if you have this
10 threat, you need -- you should be countering the
11 threat.

12 DR. HALVORSON: But in contrast to the
13 previous five questions, these are not scientific.

14 DR. CHIN: That's right. These are public
15 health implications.

16 DR. HALVORSON: These are implication
17 questions, and they are fundamental policy
18 questions.

19 DR. ASCHER: And this is the second
20 generation of questions after we were told not to
21 talk anything about policy. Very early discussions
22 in setting up this meeting --

23 DR. CHIN: No, not policy. When you talk
24 --

25 DR. ASCHER: Politics.

1 DR. HALVORSON: You are talking about the
2 scientific implications of these questions.

3 DR. ASCHER: Right. So this is the next
4 generation of questions, and I think we are able to
5 discuss some of this at some level.

6 Okay. Anything more on a, Jim?

7 DR. CHIN: Well, I think a could be worded
8 a little more gently.

9 DR. ASCHER: Right. Well, we will have to
10 work on the total content of the responses, but I
11 think we have a lot of potential words.

12 And then we wrap up with the sequence, in
13 light of the possibility of natural reservoir hidden
14 stocks, what could a determined opponent do to
15 develop an offensive BW threat using naturally
16 occurring variola or deliberately modifying?

17 Our assessment is that that is very likely
18 to work in the sense of the technology, both for the
19 production and delivery, is well known and not well
20 held.

21 So our view is that -- and the Army says
22 that re-emergent variola would be an effective
23 biological weapon, particularly when population
24 immunization has been discontinued. So the
25 potential for that is high.

1 DR. ESPOSITO: Does your proposed research
2 have any offensive overtones, rather than taking a
3 defensive posture on the proposed research?

4 DR. RUSSELL: Well, you are always accused
5 of that, even if you are making vaccines in
6 chemotherapy. I think that is an irrelevant
7 question.

8 DR. ESPOSITO: Well, it is not an
9 irrelevant question, but, I mean --

10 DR. RUSSELL: You can be accused of
11 anything, and you will be. That is a political
12 liability.

13 DR. ASCHER: What could a determined
14 opponent to make a threat? Just grow it and shoot
15 it off. I mean, it is not that difficult. Bud has
16 volunteered that he could show us how to do it very
17 quickly, right?

18 DR. BENENSON: That's only on the New York
19 subway. There is no ultraviolet light on the
20 subway.

21 DR. RUSSELL: John Lamontagne just made an
22 interesting point.

23 DR. ASCHER: Okay.

24 DR. RUSSELL: You don't need to hold that
25 variola stock to potentially up engineer an orthopox

1 virus. You could start with vaccinia and come out
2 with a -- shuffling the right genes in and out, come
3 up with just as bad an agent.

4 And if any group is out there up
5 engineering variola in one way or another by putting
6 immuno-suppressive genes or something else in it,
7 they could do the same damn thing with vaccinia.

8 Vaccinia has what, a number of genes that
9 are homologous, half of them?

10 DR. CASSELL: One hundred fifty-five out
11 of one hundred eighty-eight.

12 DR. RUSSELL: And these guys are getting
13 so smart about what the virulence restrictions are
14 that --

15 DR. ESPOSITO: You don't have to put
16 smallpox genes in vaccinia to make it virulent. I
17 mean, you can put poisons.

18 DR. RUSSELL: There are other ways of
19 doing it.

20 DR. ESPOSITO: The fact is you could think
21 of a scenario where you make a poisonous vaccinia,
22 rison (phonetic) or something like that, and
23 actually, because vaccinia doesn't spread as well as
24 variola, it is a much more targetable type of a
25 virulent.

1 DR. RUSSELL: Doing experiments to do
2 threat assessment in that arena, though, is
3 political suicide.

4 DR. ASCHER: Yes.

5 DR. CASSELL: So this has not been spelled
6 out in black and white by many of these responses,
7 and that is what I was actually getting at early
8 when I said it seems like we are dancing around the
9 science of it all. It really is a moot point.

10 DR. RUSSELL: Maybe we ought to stick in a
11 paragraph about the total potential of orthopox
12 virology to produce some God-awful critters.

13 DR. ESPOSITO: Well, it is the potential
14 virology in general. We don't have to --

15 DR. RUSSELL: Yes. You guys are worse
16 than us.

17 DR. ASCHER: I guess what Gail is trying
18 to say is our destruction has no effect on the
19 ability of someone else to get it going.

20 DR. CASSELL: I mean, five years ago,
21 things were certainly a lot different.

22 DR. RUSSELL: I had a totally different
23 view three years ago.

24 DR. CASSELL: And the debate about
25 destruction was certainly warranted. But now, it

1 does really seem to be a very moot point, given all
2 the advances in the past five years and the current
3 political situation.

4 DR. LAMONTAGNE: Well, it seems to be the
5 only one -- I'm not even sure how useful this would
6 be, I guess, as part of the discussion today.

7 But if one could be assured that by
8 destroying the variola stocks that existed in these
9 fragile political environments like Russia, if that
10 would reduce appreciably the risk of a terrorist or
11 other threat, that, I think, is the most powerful
12 argument for destruction.

13 DR. RAUCH: Yes. The terrorists are only
14 going to get derivatives of the stuff. They aren't
15 going to get --

16 DR. ASCHER: Is the cat out of the bag,
17 though?

18 DR. RAUCH: They are always way behind the
19 technology.

20 DR. HENDERSON: I don't know. I didn't
21 get a sense from this morning to what extent the cat
22 is out of the bag.

23 DR. LAMONTAGNE: Well, we mentioned three
24 combinations.

25 DR. ASCHER: Natural or intentional.

1 DR. LAMONTAGNE: I think the cat has left
2 the bag.

3 DR. CASSELL: Yes.

4 DR. RUSSELL: I think it is way out of the
5 bag.

6 DR. CASSELL: It is very much so, and big
7 bucks are being paid for all this technology and the
8 expertise. A lot of scientists out of work
9 everywhere.

10 DR. ASCHER: Yes.

11 DR. RUSSELL: Very good orthopox
12 virologists.

13 DR. HENDERSON: But I think the issue is
14 that you do have a lot of terrorist groups that are
15 far less sophisticated, that are not in a position
16 that we have seen to utilize high technology in a
17 lot of circumstances.

18 I think the committee, in discussing this,
19 felt that this destruction is no guarantee it won't
20 be used.

21 But it would serve to deter X number of
22 groups from getting access, that this would be an
23 aid in that sense, minimize the risk, not obliterate
24 it.

25 DR. ASCHER: Our destruction or global

1 destruction?

2 DR. HENDERSON: Global destruction.

3 DR. CASSELL: But, D.A., if you take that,
4 what you said, realizing that you are only
5 minimizing the risk within a certain group of
6 terrorists and weigh that against P.K.'s argument
7 about the virus vaccines, having an impact virus
8 vaccine development, having the impact virus and
9 pathogenesis studies that we have heard about,
10 coupled with the chemotherapy potential that we have
11 heard about --

12 DR. HENDERSON: But this is what we are
13 weighing. There is no question. Absolutely. There
14 are arguments on both sides of it. No, no, not to
15 negate it at all.

16 What we are saying and what is different
17 from what has been said, what we are asserting, is
18 that we see a very real risk at this point, a new
19 risk, a new appreciation that this is a serious
20 matter and that we really have to develop a vaccine,
21 a better vaccine, better chemotherapeutic agents.

22 And this applies for all countries around
23 the world. This is not just a U.S. problem. It is
24 a global problem, and that is why we need the virus.

25 DR. RUSSELL: If you add all these up, my

1 appreciation of the nature of the problem and the
2 solutions has changed drastically over a couple of a
3 very few months because of the impressive capability
4 that the orthopox virologists have.

5 DR. ASCHER: If we clearly spell out some
6 of these criteria, and in response to that, Russia
7 as a side issue looks at that list and says: Oh, we
8 can answer that or we can tell you that, that then
9 might be a chance to revisit the issue. And it also
10 might be some guidance to make that happen.

11 But I don't know. I mean, if you say you
12 would like to know about chemotherapy, you would
13 like to know about aerosol challenge, and they say:
14 Guys, we want to get rid of it. Here's our data,
15 you can --

16 DR. RUSSELL: I think that one way of
17 approaching this from a conceptual point of view,
18 D.A., is to say that the focus of the national
19 policy debate on the destruction of the variola is
20 the wrong focus.

21 What we need to do is look at the
22 potential of orthopox viruses in general as a threat
23 either to public health or a terrorist threat or a
24 threat from the a hostile power, and evaluate it in
25 that regard, putting the -- and then the issue of

1 variola virus is in the context of the total threat
2 and how much political leverage and how much
3 political value it has with regard to the total.

4 It may come out a stronger argument.
5 Destruction may wind up to be a stronger argument if
6 you look at it as a threat of the total, including,
7 you know, John's scenario.

8 DR. HALVORSON: Eventually, when you get
9 to this, you are going to be talking about these
10 issues to an audience that already has some level of
11 appreciation. And it is going to be sound bites.
12 You are not going to get a very elaborate
13 presentation.

14 God knows it has been hard enough, even in
15 an inter-agency working group, to get science
16 introduced. I mean, there are so many people that
17 don't really understand what is going on.

18 And they originally objected to destroying
19 the virus because we would be destroying against the
20 protection against a disease.

21 And we said, "No, no. These are two
22 different viruses."

23 You know, this is the problem, where we
24 have an agreement at least on the science and move
25 from there. But it has to be a fairly simple

1 explanation of science, I think, to some of these
2 people without a terribly complex argument.

3 DR. HALVORSON: Instead of responding to 6
4 in the way of a through g, wouldn't it be better to
5 put a paragraph describing what one can do with the
6 biology of the system at the present time? That
7 would, I think, be easier.

8 DR. ASCHER: D.A., what is the third world
9 view of the terrorist community and all of that?

10 DR. HENDERSON: I don't know that I could
11 speak on that.

12 DR. ASCHER: Well, I mean, is it --

13 DR. HENDERSON: My guess is not -- they
14 really are more concerned primarily with their own
15 problems and what have you. I don't think this is
16 regarded by most third world countries as a big
17 issue.

18 DR. HALVORSON: Except for those who have
19 internal --

20 DR. HENDERSON: Except those may be Kuwait
21 or the Saudis or others that might be susceptible
22 because of wealth or other reasons to being attacked
23 by that sort of a group.

24 DR. LAMONTAGNE: Or Russia.

25 DR. HENDERSON: Yes.

1 DR. LAMONTAGNE: I mean, I wonder if the
2 decision to remove from Novo-Sibirsk would be made
3 because of the internal security considerations in
4 Russia.

5 DR. ASCHER: We just use this term third
6 world for D.A.'s reference to the fact that at the
7 international level, there is a cadre of folks that
8 are behind this as an idea.

9 It would only take a Hutu/Tutsi release
10 to, I think, change a lot of that. But at this
11 point, they have knives and guns and cholera and a
12 few other things.

13 DR. LAMONTAGNE: Well, when you are up to
14 your knees in alligators or maybe it is a little
15 higher than that, you don't worry about some other
16 things.

17 DR. ASCHER: So your sound bite doesn't
18 talk much about that. It leads with -- like we
19 said.

20 Okay. D is easy because we have had a lot
21 of discussion thus far on all of these issues of
22 what existing stocks could do to improve detection,
23 protect against, prove vaccines. I think that just
24 has to be extracted from somebody's hearing of the
25 discussion so far.

1 They are all positive aspects of keeping
2 it. They would -- keeping it would obviously help
3 with all of that. No downside to that at all.

4 In addition, Peter mentions the geographic
5 molecular forensics as possibility of keeping the
6 phylogenetic stuff going.

7 DR. CHIN: I thought the discussion
8 downplayed that.

9 DR. ASCHER: Which?

10 DR. CHIN: The geographic value.

11 DR. ASCHER: Well, within the limit of the
12 collection, right.

13 DR. CHIN: Nobody is recommending that
14 that be done.

15 DR. LAMONTAGNE: That is very, very
16 ground.

17 DR. ASCHER: Okay. So detect and identify
18 the origin is what I am saying. That is not
19 considered necessarily to be particularly
20 interesting.

21 DR. CASSELL: Except that -- I mean,
22 detect the origin, if you had more information on
23 the variability, in other words the sequence from a
24 great number of strains, I mean --

25 DR. ASCHER: But if it shows up in the New

1 York subway, are you going to care whether it is
2 India 1967 or whatever in terms of then finding
3 where it came from? I don't think it really helps
4 you.

5 DR. LAMONTAGNE: It is not going to be
6 helpful.

7 DR. ASCHER: If it has another virus
8 running around inside of it, then you are really
9 going to be interested.

10 DR. WOLFE: Well, didn't we say before
11 that the stocks that are held at CDC are certain
12 strains, and the stocks that the Russians have are
13 certain strains, and they are not mutually
14 compatible?

15 DR. ASCHER: Right.

16 DR. WOLFE: So if the India strain is in
17 Russia, for instance, and we wanted to use forensics
18 --

19 DR. ESPOSITO: We have an India strain
20 which we have not looked at all. We presume it
21 is --

22 DR. WOLFE: Oh, you do have it.

23 DR. ESPOSITO: Yes. We have an India
24 strains.

25 PARTICIPANT: But the Russians have

1 strains that we don't have.

2 DR. ESPOSITO: Oh, yes. Like D.A.
3 mentioned, it was a grab at the end to just get
4 these things.

5 DR. WOLFE: I see the forensics as being
6 potentially useful. If a terrorist group gets it
7 from the Russians and it is a type you don't have in
8 your library, I see that as being helpful.

9 DR. CASSELL: You are not talking about a
10 lot of effort to get additional sequence data today
11 given the technology.

12 DR. RUSSELL: It should not take long to
13 do that.

14 DR. HENDERSON: Well, just what I was
15 saying, Phil. What we have are basically very
16 recent strains, I mean for the end of the program,
17 from a limited number of areas. One of the biggest
18 areas which I think we would be concerned about was
19 the Iran/Iraq/Syria strain --

20 DR. RUSSELL: You don't have that.

21 DR. HENDERSON: -- which we don't have.
22 We don't have, let's say, very much earlier strains.

23 The India 1967 is an unusual one, and we don't have
24 very many from 1967, even at CDC.

25 I think most all of them are 1970 and

1 beyond. And some of the earlier ones that, let's
2 say, might be extricated from a deep freeze and the
3 1950s and 1960s, nobody has them.

4 And the library was never constructed to
5 answer the questions that we have had to answer with
6 measles and polio for a very simple reason, that you
7 did not need to -- you weren't worried.

8 When you say a patient with smallpox, you
9 knew he had been in contact with another patient two
10 weeks before. And you could pretty well find out
11 where that was. You didn't need a molecular
12 virology to tell you where it was coming from.

13 So it is not a help. This is just
14 not -- we don't have the native stock at this time
15 to create maps such as we have for measles and
16 polio.

17 DR. LAMONTAGNE: But, D.A., I thought
18 Marty's point was that if you have the sequences of,
19 let's say, all the hemagglutinin from all
20 the --

21 DR. HENDERSON: From the ones we have.

22 DR. LAMONTAGNE: Then you could use that
23 as a fingerprint, and it might help in policing
24 whether or not these are being --

25 DR. HENDERSON: Where they came from.

1 DR. LAMONTAGNE: Where they came from. So
2 it may be an aid in implementing the final
3 destruction.

4 DR. HENDERSON: I don't know how you can
5 do it, really.

6 DR. LAMONTAGNE: If you had those
7 sequences, you would not need the live virus.

8 DR. HENDERSON: Which I gather -- was that
9 what you were trying to saying, Marty?

10 DR. WOLFE: What, the sequences versus the
11 live virus?

12 DR. HENDERSON: That if you had the
13 sequences with the fingerprints essentially of all
14 the strains, then you could more or less know where
15 they came from.

16 DR. WOLFE: Exactly.

17 DR. HENDERSON: Since they could only come
18 from Atlanta or other places.

19 DR. WOLFE: Or an Iraqi freezer.

20 DR. HENDERSON: The Iranians. They were
21 both isolating viruses.

22 DR. WOLFE: Were.

23 DR. ASCHER: In 1972? And why didn't we
24 get it?

25 DR. HENDERSON: Well, the strains that we

1 got were sent to Geneva for confirmation. In other
2 words, toward the end of the occurrence of smallpox
3 in a country, we began collecting specimens for
4 final verification.

5 And then they would be split. One week
6 they would go to Moscow and the other week to
7 Atlanta. This is really kind of a work which nobody
8 really wanted to do.

9 And so consequently, you wound up with
10 both places having a collection of strains, which
11 are probably from the same epidemics, a lot of them.

12
13 But the Iranians and Iraqis were doing
14 their own diagnosis and were trying both to cover up
15 the epidemics frantically and were suppressing all
16 information about it. So they didn't want to
17 specimens. That was for damn sure.

18 DR. ASCHER: So with the caveat for the
19 geographic issue, we will say d is generally
20 positive.

21 In light of the above, how can existing
22 stocks of variola virus assist efforts -- no. Where
23 are we?

24 Oh, the same question but ending "to
25 diagnose and treat deliberately modified or

1 manipulated strains of variola."

2 I don't think it is any different. Same
3 answer, because you have a sequence, and you are
4 still comparing back to back. The same issue of
5 picking up some other virus inside.

6 Anything different there, Peter? Let's
7 see. Same answer.

8 What are the probabilities of future
9 research questions arising, which we cannot now
10 frame, which would require all variola virus for
11 resolution?

12 That is mainly the issue of pathobiology
13 that Joe mentioned and just the general statement
14 from Peter that the virus is more than a sum of its
15 parts and having -- there is an overriding statement
16 that something in the future would happen.

17 But we will live with that, I mean, in the
18 sense that we don't see that as overriding. But we
19 cannot lie about it. It's very possible that
20 something could come along.

21 DR. CASSELL: So in fact what you are
22 doing is kind of taking issue with what Phil's
23 response was, saying that there was low probability
24 that future research questions would arise in which
25 having the intact virus would be useful.

1 DR. ASCHER: Right.

2 DR. CASSELL: Got that, Phil?

3 DR. RUSSELL: What?

4 DR. CASSELL: Did you get that?

5 DR. RUSSELL: No, but I will.

6 DR. ASCHER: No. I said there are
7 possibilities, but we have to limit the --

8 DR. CASSELL: No, no, no. I know, but
9 basically he was saying that they were very
10 relevant. Most questions could be answered with
11 other --

12 DR. ASCHER: Oh, okay. Yes. You are
13 talking about other poxviruses.

14 DR. CASSELL: Yes.

15 DR. ASCHER: Okay. 6g, in furtherance
16 advancement of knowledge -- that's always
17 good -- what priorities should be accorded to
18 possible experimental studies with stocks of variola
19 virus in contrast to potential
20 associated -- I don't think we can answer that one
21 very well.

22 We have to just speak to it as an
23 independent problem and that the prioritization is
24 really beyond us at this point.

25 We have previously acknowledged that there

1 is an identified threat, that our defenses are not
2 optimal. We have some, and there are a couple of
3 key questions that could be addressed by further
4 studies.

5 How you prioritize that depends on how
6 many new hemorrhagic fevers you have coming in the
7 door. Brian described it very well. I don't know.
8 It is certainly on the list.

9 What do you have there, Peter? It is more
10 of a general statement about -- and the last, the
11 precedent, to what extent would the destruction of
12 the variola virus set a precedent for destruction of
13 other viruses, such as the polio and measles virus,
14 should the disease become eradicated?

15 DR. ESPOSITO: You might want to look
16 through Walt Dowdell's (phonetic) statement about
17 that.

18 DR. ASCHER: I think it is -- I don't
19 think that has anything to do with it. Yes. Let's
20 see what Walt -- do you think that Walt said it?

21 DR. ESPOSITO: I think in the back of that
22 paper I gave you there is a statement of that
23 nature.

24 DR. ASCHER: Yes.

25 DR. ESPOSITO: I am not sure. It might

1 get you started in discussion anyway.

2 DR. ASCHER: I don't quite see that it
3 is --

4 DR. RUSSELL: Page seven.

5 DR. ASCHER: I think they are all
6 different.

7 DR. RUSSELL: It just says that he looks
8 eagerly to the debates. That's all.

9 DR. ESPOSITO: So I would imply from that
10 it is not setting a precedent.

11 DR. ASCHER: I think not at all.

12 DR. ESPOSITO: That these are all
13 independent issues. One is a virus from Serge and
14 one -- they are all different categories of
15 questions and answers.

16 DR. RUSSELL: You could make an argument
17 that because of the nature of the polio virus and
18 measles that post-eradication release would be much
19 more complex and difficult to deal with than the
20 post-eradication release of the smallpox virus.

21 PARTICIPANT: Is that right, D.A.?

22 DR. HENDERSON: Yes. That sure --

23 DR. RUSSELL: That measles and polio could
24 be very widespread and out of control before you
25 tumbled to it and figured out the extent of the

1 problem.

2 Smallpox, that's not going to happen in a
3 susceptible population. The first cases are going
4 to be identified. The second cases are going to be
5 identified. The vaccination program will be in
6 place. You will deal with it.

7 If you eradicate polio and you eradicate
8 measles and then stop vaccinating and those suckers
9 get out of the laboratory, polio can
10 be -- you can have hundreds of infections and
11 transmissions all over the bloody world before you
12 tumbled to it.

13 So that the problem of laboratory strains
14 of measles and polio is going to be, I think, very,
15 very important to the downstream issue.

16 And then -- I think it is a two-way
17 argument here, but the precedent then becomes kind
18 of very important, you know. We are really going to
19 be beating on an awful lot of people to destroy
20 polio stocks in a few years.

21 I mean, we are going to beating up on the
22 whole virology community to get all those strains of
23 polio out of their freezers and clean it up and so
24 forth.

25 We do have the precedent of that H1N1

1 fluke. Okay? It escaped from -- it punitively
2 escaped from a freezer and caused a worldwide
3 pandemic.

4 And we don't want that to happen. So
5 there is a precedent issue here and a downstream
6 bigger public health danger from those two than from
7 smallpox.

8 DR. CASSELL: So you have an awfully lot
9 of work that is going on with a polio replicons that
10 look like -- that would be very beneficial in trying
11 to then make an argument that you have all that,
12 that would not be very wise.

13 DR. RUSSELL: Then the polio guys are
14 going to come and say: What the hell? You guys
15 didn't even destroy smallpox virus. Why are you
16 beating up on us? This thing doesn't --

17 DR. ASCHER: Well, that is why the answer
18 has to be stated both sides.

19 DR. RUSSELL: That is why it is --

20 DR. ASCHER: It is a two-tailed test.

21 DR. RUSSELL: The precedent issue is more
22 than an exercise, an intellectual exercise. I think
23 the downstream issues with the other two viruses are
24 big-time issues.

25 DR. ASCHER: But the failure to destroy

1 also does not set a precedent, which is what you are
2 saying. In other words, it is not an automatic
3 reprieve for everybody else.

4 I mean, you can look at the enterovirus
5 collection in our lab and say that we should be
6 destroying half of those strains because they have
7 not occurred within my lifetime. And what is the
8 point of keeping them for reference?

9 And the answer is you keep them.

10 DR. RUSSELL: Having spent millions on
11 polio and billions on measles, and those
12 enteroviruses were not the killer that measles is.
13 They didn't have the implications of polio.

14 DR. HENDERSON: Phil, I take it another
15 way. It is going to be a few years yet before we
16 get to the point of having to ask the question on
17 polio. I think it is at least ten years before we
18 are going to have to ask the question.

19 And for measles, I think it is going to be
20 a lot longer than that. By that time, we are going
21 to have a lot more knowledge of basic virology and a
22 lot of other things. And it may be irrelevant
23 anyway, simply because it would be so easy to create
24 and construct the virus itself.

25 So, you know, I would just as soon -- I

1 would be fine to just leave this one alone and say
2 that we don't foresee this as having any precedent
3 setting problem --

4 DR. ASCHER: No. One way or the other.

5 DR. HENDERSON: -- one way or the other.

6 DR. LAMONTAGNE: But doesn't part of this
7 question have to do with the possibility of using
8 polio or measles as a BW agent?

9 DR. ESPOSITO: I don't think so.

10 DR. ASCHER: Polio or measles as a BW
11 agent. What is the score? Quick, Ernie, off the
12 top of your head, calculate it.

13 DR. TAKAFUJI: Well, we know that measles
14 in a very susceptible population (inaudible), for
15 instance, several centuries ago (inaudible). Polio
16 may not be as valuable a weapon.

17 I mean, you need to look in terms of the
18 potential for the (inaudible). So I think maybe
19 those kinds of things are going to come into this.
20 We will probably have other agents who --

21 DR. RUSSELL: They will never make the
22 upper end of the list.

23 DR. TAKAFUJI: I agree with you. I think
24 that the issues are totally irrelevant here in terms
25 of (inaudible) smallpox. Smallpox is a BW issue.

1 We are not foreseeing measles and polio as
2 BW agents in these kinds of procedures.

3 DR. LAMONTAGNE: Smallpox has, after all,
4 been used that way.

5 DR. RUSSELL: Not a precedent.

6 DR. ASCHER: Neither way.

7 DR. RUSSELL: It makes our life a lot more
8 simpler. We are running out of questions.

9 DR. RAUCH: We are running out of answers.

10 DR. ASCHER: Is that what the red line
11 means? Whatever it is, it didn't come through my
12 fax machine. That's it.

13 Now, Gail, you are going to have to help
14 here. What is your suggestion here? Because we are
15 going to need one or two people to sort of take what
16 Phil has and what Gail has and put some reasonable
17 approximation together and then talk about it.

18 Do you set a responses to the questions, a
19 crisp set, for Terry in the sense of having
20 something to take back on the questions themselves
21 and an overall statement of the nature I suggested,
22 sort of providing introductions --

23 DR. CASSELL: Well, I think it will take a
24 lot of hard work tonight to capture everything that
25 we just said in the last two hours, which is not so

1 easily said and is not already said.

2 And I am not sure how we want to try to
3 accomplish that, whether it is with a smaller group
4 and then come back to the bigger group in the
5 morning with it, or if we all come back and try to
6 go through and develop a written response.

7 DR. ASCHER: One suggestion is that Phil
8 polish his starting in the context of this
9 discussion.

10 DR. RUSSELL: Do I get to vote on this?

11 DR. CASSELL: While we all go to dinner,
12 and then we can come back and --

13 DR. ASCHER: No.

14 DR. RUSSELL: Yes. You guys go out and
15 drink a lot.

16 (Laughter.)

17 DR. ASCHER: And you and I have some quiet
18 time to independently do a little beginning on the
19 overall format.

20 And then after some time aside, pick a
21 time, 8:00 or something, to get together, and then
22 in little groups around computers sort of keep
23 moving with volunteers just sort of bouncing around
24 the room.

25 Phil's document being the response to the

1 questions, maybe you the background and overview,
2 and I will try and sort of fill in some of the
3 blanks.

4 DR. LAMONTAGNE: One area I feel a little
5 bit uncomfortable with is the answer to number six.

6 I think we need to look at those words.

7 DR. ASCHER: Yes.

8 DR. CASSELL: Very carefully.

9 DR. RUSSELL: Well, I think I would
10 suggest that I print this out, have people take a
11 look at it, and then I will -- I don't know.

12 DR. ASCHER: Bring it to the 8:00, having
13 read it. Bring it to when we meet with you later,
14 having already read it. Print it, take it along and
15 read it now.

16 DR. CASSELL: Have you altered it
17 substantially?

18 DR. RUSSELL: Well, there are a fair
19 amount of changes.

20 DR. ASCHER: Do you have an IBM --

21 DR. RUSSELL: It is 180 degrees on the
22 question number two, for example.

23 (Laughter.)

24 DR. CASSELL: So, Phil, give us an
25 executive summary, based on this afternoon's

1 270
discussion.

2 DR. ASCHER: If you consider 180
3 degrees --

4 DR. CASSELL: What would be your executive
5 summary?

6 DR. ASCHER: You can go off the record, I
7 would think, at this point. I told you 5:00. It is
8 6:00.

9 (Thereupon, at 6:00 o'clock, p.m.,
10 the hearing in the above-entitled
11 matter was concluded.)

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CERTIFICATE OF REPORTER

I, James E. Moore, being a court reporter, do hereby certify that I was authorized to and did report the above and foregoing proceedings, and that thereafter it was reduced to typewriting, under my supervision, and I further certify the pages numbered 3 through 278, inclusive, contain a full, true and correct transcription.

James E. Moore, Court Reporter