

1 infections that are produced by the model. The mean
2 is .01 estimated infections per year and here's the
3 distribution, so this might be skewed a little bit.
4 So if we look at the median here of 50th percentile,
5 it's like on the order of .001 infections per year.
6 Even the 95th percentile distribution is well below
7 one infection per year.

8 Now, again, you remember I mentioned that
9 we're only taking into account the prevalence of
10 asymptomatic sporadic CJD in the population. So if we
11 also wanted to account for a background theoretical
12 risk of asymptomatic variant CJD in the population, we
13 could take that into account and these numbers would
14 change accordingly. We just don't have data on or
15 even empirical data to make estimates on what the
16 background prevalence would be.

17 So in summary, based on the assumptions
18 used in the risk assessment and I really want to
19 emphasize that first part of the statement, that the
20 estimate iatrogenic CJD infection risk in the US from
21 the use of reprocessed neurosurgical instruments is
22 probably less than one per year. These estimates were

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1 derived using two approaches, the deterministic
2 approach and probablistic approach. Both give us
3 relatively the same answer which increases our
4 confidence that it's a robust assessment. Using these
5 approaches, we can examine risk under the different
6 model assumptions.

7 Again, I want to reiterate and underscore
8 the uncertainty associated with these parameter
9 estimates and then that carries over into the final
10 risk estimates. Nevertheless, this is a useful
11 exercise for allowing the regulators to determine the
12 magnitude of the background risk, what's the public
13 health impact as it stands now and what's the possible
14 effectiveness of running risk reduction measures that
15 might be proposed. Thank you.

16 CHAIRMAN EDMISTON: Thank you, Mr. Brown.
17 I want to thank our FDA colleagues for trying to
18 bring some clarity to a complex issue. I'd like to
19 open it to the panel again. We're going to go about
20 15 minutes and before we start, Dr. Gordon, I cut you
21 off earlier. Do you have a question you want to bring
22 forward?

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1 DR. GORDON: I do. I really was
2 interested in the background prevalence of CJD and I
3 guess there are some questions that are going to be
4 answered in a later discussion about the British
5 experience. But I was concerned about what percentage
6 of patients, of humans that get CJD may not to on to
7 develop clinical disease nor is there any evidence
8 that there's a pool of asymptomatic maybe a variant or
9 traditional CJD that could potentially be infectious
10 but may never go and develop clinical disease so they
11 could become apparent to us.

12 DR. MURPHY: That's a difficult question
13 to answer but I think what we have to do is look at
14 the surveillance data that has now been accumulated
15 over a period of several decades. Obviously, the end
16 point that we would see would be patients who are
17 recognized as having symptomatic disease. However,
18 patients who have autopsies for other reasons and are
19 found to have disease would therefore, also be
20 reported and be picked up and hopefully reported to
21 the Centers for Disease Control and Prevention.

22 We should mention that, of course, the

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1 percent of autopsies done in the United States has
2 dramatically fallen over the last two decades. So
3 this is no longer a terribly fruitful source for
4 recognizing disease. On the other hand, this is a
5 disease entity which has been recognized, was first
6 described in the 1920s. I think a great deal more
7 attention has been paid to it since the "60s and the
8 "70s and particularly since the "70s and the "80s when
9 iatrogenic transmission was first recognized.
10 Throughout that period, there has been no recognized
11 increase in the apparent prevalence of disease in this
12 country or worldwide for sporadic disease or for
13 genetic disease.

14 The rare instances of iatrogenic
15 transmission primarily related to infected dura mater
16 grafts and grown hormone and gonadotropin have
17 increased over time and it's again worth pointing out
18 for those figures that surveillance for those entities
19 is increasing. Most of the exposures occurred in the
20 1970s and the 1980s. We are still seeing the tail end
21 of patients finally developing disease many years
22 after exposure. What we know of the natural history

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1 of human TSEs is that there is apparently a long
2 incubation period. There appears to be some
3 variability depending on the allo type of the normal
4 prion protein that one is carrying. In the studies
5 that were done in kuru in, you know, patients who
6 developed disease in the "50s and "60s and those who
7 have been followed afterwards as well as in the
8 patient study for exposure to possible iatrogenic
9 transmission, there appears to be increased
10 susceptibility to developing disease and perhaps with
11 a shorter incubation period.

12 If you happen to be homozygous for
13 methionine methionine, at the point of the protein
14 which is encoded by Codon 129. And being heterozygous
15 or homozygous for valine valine appears to give a
16 relative degree of protection but it's also clear from
17 the iatrogenic cases that that protection is relative.

18 It is not absolute. That apparently if you acquire
19 enough of an inoculate, you will get disease if you
20 live for a long enough period of time but that's
21 basically what we know about it at the present time.
22 CDC has been very interested in continuing to look for

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1 cases of CJD in hopes of detecting should it occur the
2 presence of variant CJD due to TSE transmission in the
3 United States. So far there has been no evidence of
4 that in this country at this time.

5 CHAIRMAN EDMISTON: Dr. Butcher, you had a
6 comment or question.

7 DR. BUTCHER: Yes, a question. First of
8 all, I think the staff did give an excellent
9 presentation and I know that the scope of today's
10 discussion is on the TSE and parameters, but the brief
11 question that I would like to ask is there any level
12 of doing things so that -- or can we be sure that if
13 we say that we develop a level that we will not detect
14 CJD, TSE and that type of a thing? Are there other
15 things that the process will escape? You know, are
16 there other things that we have to worry about? In
17 other words, is there a certain level where we can say
18 this is the way we're going to process all of the
19 instrumentation and we know that no other things that
20 we have to worry about although I know today we're
21 just focusing on this area.

22 DR. MURPHY: Well, the problem with

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1 respect to TSE transmission is that at the present
2 time we don't know the lower limit of detection for
3 any of the assay methods that we have. As far as we
4 know, at the present time, the animal models are the
5 most sensitive. The immunoassays, it depends on the
6 exact assay and how it has been validated in terms of
7 detecting transmission and cell culture models are
8 really research models at the present time. So we
9 don't have a way of being certain that we have
10 detected everything and we're going to have to live at
11 the present time with that degree of uncertainty.

12 We don't know at the present time exactly
13 how reliably we would be able to estimate how much
14 material would be left on an instrument that have been
15 cleaned with all of the possible things that we could
16 do to clean an instrument. We were absolutely certain
17 that it was 100 percent clean. Can we measure that to
18 point minus 10? No, our assays are not that sensitive
19 at the present time. So we're working in a world with
20 uncertainty. We have uncertainty about the biological
21 disease. There are limitations to our ability to
22 measure our lower limit of detection and at the

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1 present time, and I'm basing this on what the TSEAC
2 panel said to us two years ago, we cannot say that a
3 given minimal level of the presence of the abnormal
4 isoform of the prion protein is safe. We don't know
5 that.

6 CHAIRMAN EDMISTON: Dr. --

7 DR. MURPHY: So, I'm afraid I'm answering
8 your questions with questions.

9 CHAIRMAN EDMISTON: Dr. Haines, are you
10 comfortable with the risk assessment that was
11 presented by the FDA?

12 DR. HAINES: Well, I had a couple of
13 questions and one with respect to that. In the
14 deterministic model calculations are made on the
15 sensitivity to the assumptions for each individual and
16 not to be an alarmist, but did you do the calculation
17 with each of the parameters at its worst estimate?

18 MR. BROWN: We did not. It's an easy
19 enough exercise to do, of course, but the probablistic
20 model, of course, has upper bounds that would be
21 representative of those upper bound values, so we did
22 not.

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1 DR. HAINES: A lot has been made about --
2 emphasis has been put on the fact that we haven't had
3 a report of iatrogenic transmission in the United
4 States since 1980 or so. But how -- do we have any
5 information on how confident we are that cases would
6 be reported? Since that time there's some very
7 powerful legal reasons that speculation about the
8 transmission of such a disease would discourage --
9 would be discouraged. And how confident are we that
10 the reporting is good?

11 MR. BROWN: I'm actually going to defer to
12 my colleagues who are experts in infectious disease to
13 answer that.

14 DR. MURPHY: To recognize iatrogenic
15 transmission of Creutzfeldt-Jakob disease, you would
16 have to take an excellent history on the patient,
17 looking for known exposure sources such as has the
18 patient received transfusions, has the patient
19 received dura mater in a prior surgical implantation,
20 has this patient received growth hormone. You might
21 ask about other surgeries. To definitely tie any of
22 those potential risk factors to CJD transmission, you

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1 would also then have to go back and look -- let's say
2 the patient had had a prior non-neurosurgical
3 procedure and then died and was found to have CJD.
4 The prior surgery was perhaps removal of a gall
5 bladder. All right, you're going to have to figure
6 out where that procedure was done and then you're
7 going to have to go to that other hospital and try to
8 learn whether or not in what time frame, we're not
9 sure, that hospital might have cared for and/or
10 performed surgery on a patient who might have been
11 known to have CJD. Had the patient performed surgery
12 on a patient who was asymptomatic and themselves
13 developed CJD five years later at another hospital
14 where the history of their prior surgery at this
15 intermediate hospital was not even elicited, there
16 would be no way to make the connection.

17 In fact, it's very difficult. The
18 epidemiologic studies that have been done looking for
19 the possibility that surgery of any type of
20 neurosurgery in particular is a risk factor for Jakob-
21 Creutzfeldt disease which is probably the only way to
22 really get at that have been flawed by being

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1 relatively small or having potential bias in terms of
2 the way they collect their patient populations and
3 their control populations. Those studies have not
4 consistently shown a relationship with surgery.
5 There's one study that did show a relationship and
6 another study that did not show a relationship.

7 The end result seems to be that we cannot
8 pin down any specific risk factor in the patients who
9 are recognized as having CJD that might relate to a
10 possible iatrogenic transmission. There have been
11 reported clusters in the literature but none of those
12 -- in none of those can we definitely pin down a
13 common iatrogenic risk. There was a publication, I
14 think, in the 1970s from England where two close
15 neighbors and -- three people from a small town all
16 shared a dentist, developed CJD but they could not
17 trace the dental records. There was no evidence that
18 in fact, those patients had received dental care
19 within close periods of time and those were the only
20 three patients.

21 There is a cluster of patients whose
22 common factor was alleged to be dining at a race

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1 course in New Jersey. I used to work in Philadelphia
2 so I'm rather aware of that. Again, these on further
3 investigation appeared to be not food borne cases of
4 CJD but in fact, sporadic cases over a period of time.

5 So, no, we don't know that answer.

6 CHAIRMAN EDMISTON: Yes, Dr. Coffey.

7 DR. COFFEY: Yeah, the situation maybe
8 even more problematic given the difficulty as Dr.
9 Haines well knows in any community of actually making
10 an accurate diagnosis of ordinary neurologic
11 disorders, you know, in the United States and
12 elsewhere in the developing world, you know, let alone
13 making the diagnosis of -- an accurate diagnosis of
14 CJD in an elderly person with a dementing illness or
15 given the recent history of falling autopsy rates,
16 most of which probably don't include the brain anyhow.

17 So even if a person is diagnosed with CJD
18 and let's call them, you know, the host, you know the
19 chances of tracing back let's say the vector or the
20 source, you know, could be, you know, as you said
21 vanishingly low. So there's probably more undiagnosed
22 cases or even undiagnosed human to human or

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1 interiatogenic transmission than diagnosed cases, you
2 know, apart from the specific, you know, dura mater
3 and growth hormone cases.

4 DR. MURPHY: The fact is that we do not
5 know. We are not seeing in the general population a
6 significant increase in dementia that could not be
7 accounted for on the basis of vascular dementia or
8 Alzheimer's disease. The clinical presentation of
9 Jakob-Creutzfeldt disease while it may be non-specific
10 in its early stages, becomes fairly apparent in its
11 later stages and the rapidity of its course and
12 rapidity of the deterioration which the patient
13 experiences. But recognizing patients who die with
14 but not of symptomatic disease, this is an open
15 question which we cannot answer at the present time.
16 However, we have no evidence that things have changed
17 over the years and in the last 20 years in particular,
18 a great deal of attention had been paid to this area.

19 CHAIRMAN EDMISTON: I think we'll stop and
20 this point and take a break. However --

21 DR. SCHONBERGER: Can I ask one?

22 CHAIRMAN EDMISTON: One brief question.

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1 DR. SCHONBERGER: Yeah, I was on the -- I
2 guess on Ron Brown's model, I detect some -- well,
3 let's put it this way, there's confusion at least in
4 my mind and maybe confusion in the way it's being
5 presented on the -- when we call it the patient,
6 whether we're talking about the patient as the source
7 or the patient as the recipient of the exposure. We
8 seem to jump back and forth and specifically that
9 issue about calculating the mass. You talk about 20
10 surgical equipments each with a certain mass and you
11 multiplied them, and you apply that to the recipient,
12 but isn't that really the 20 is really what you're
13 applying to the source. That you get 20 instruments
14 that are potentially contaminated. The recipient,
15 however, doesn't get all those 20 instruments worked
16 on the recipient unless we have to make the assumption
17 that these kits all stay together. Is that what
18 you're making the assumption about, that these same 20
19 instruments will be used from patient to patient.

20 Am I -- do you catch where I've --

21 MR. BROWN: Oh, absolutely, and because we
22 do use patient for both parameters, because we're

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1 talking about the patients as being both the source
2 and the recipient.

3 DR. SCHONBERGER: That's what confuses me.

4 MR. BROWN: Right, so we were not being
5 explicit that the devices were kept together and
6 sterilized together. It's just that you could have
7 any --

8 DR. SCHONBERGER: But doesn't that mess up
9 your mass calculation? You could have one -- this one
10 asymptomatic individual infects 20 instruments. Where
11 is that in the model, because now we have potential
12 for 20 different patients getting exposed and I didn't
13 see that in your model.

14 MR. BROWN: No. For example, we are
15 assuming that each of those 20 recipients could be
16 exposed to those 20 devices. So where we take into
17 account the potential for them to be exposed, is by
18 the prevalence of CJD in the population so that
19 there's a probability that those -- the recipient
20 patients would be exposed. So we don't always assume
21 that those 20 instruments would carry directly over.
22 It's just any 20 instruments. That's why I broke down

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1 the exposure into two parts. What's the probability
2 of exposure? Then if we think exposure does occur,
3 then how much of that material is transferred? So
4 we're only assuming that 20 is on the -- those 20
5 instruments are used on the recipient.

6 CHAIRMAN EDMISTON: Let me point out to
7 the panel that these speakers will not be sequestered.

8 They will be available to us for the rest of the day.

9 And I suspect with 100 percent certainty that we will
10 be drawing them back for further questions during the
11 deliberation, but we have a little bit of extra time
12 before lunch, so I will query that panel again if they
13 have any further questions. At this time, let's take
14 a 15-minute break and come back at 20 of 11:00 and
15 we'll have Mr. Hilderly's presentation. Thank you.

16 (Whereupon, the foregoing matter went off
17 the record at 10:25 a.m. and went back on the record
18 at 10:44 a.m.)

19 CHAIRMAN EDMISTON: I would like to call
20 this meeting back into order. We now will continue on
21 our agenda with a presentation from Mr. Allan
22 Hilderley who is a Senior Medical Device Specialist at

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1 the Medicines and Healthcare Products Regulatory
2 Agency, U.K.

3 Mr. Hidderley?

4 MR. HIDDERLEY: Good morning. My name is
5 Allan Hidderley. I'm from the Medicines and
6 Healthcare Products Regulatory Agency. I'm one of
7 their Senior Medical Device Specialists within the
8 Agency. I have lead responsibility for sterilization
9 technologies, decontamination, TSE issues both on
10 human and animal models, and I represent the devices
11 sector of the Agency.

12 Next slide please. What I would like to
13 talk to you is briefly who the NDHRHL, the risk of CJ
14 transmission, as an interim view as of this year and
15 also U.K.'s Departments of Health strategy, and
16 research and development on decontamination, and
17 possible requirements from a regulator's perspective.

18 And also forming my comments in summary.

19 Okay. The formation of the MHRH was
20 constituted in 2003 and was formerly two separate
21 agencies, one the Medical Devices Agencies, the one I
22 worked for, and the Medicines Control Agency. Both

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1 regulators, obviously one from the medical devices
2 sector, and one from the medicine sector, we conjoined
3 together to form the MHRA.

4 The MHRH is the regulatory agency. It's
5 an executive agency of the Department of Health which
6 is for the U.K. The MHRA's role is to protect and
7 promote public health and patient safety by ensuring
8 that medicines, healthcare products, and medical
9 equipment meet the appropriate standards of safety,
10 quality, performance, and effectiveness and are used
11 safely as well.

12 We also -- the devices sector is a
13 competent authority for European medical device
14 regulations with the U.K. I say the U.K., that also
15 includes England, Scotland, Ireland, and Wales.

16 So to talk about vCJD and the transmission
17 device surgery, prion to transmissible agents, as
18 we've talked about previously, cause vCJD and other
19 prion diseases and are known to resist conventional
20 sterilization procedures. This has been proven by
21 experiments and also within the healthcare sector
22 themselves with different sterilization procedures

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1 have been proven to be ineffective. For example,
2 formaldehyde treatment can fix the tissues. Steam
3 sterilization has known restrictions as well.

4 The unknown population prevalence of
5 asymptomatic vCJD has lead to concerns within the U.K.
6 and worldwide about transmission by a wide range of
7 surgical procedures. Obviously the most risk area is
8 from neurosurgery but we've looked at all areas of
9 surgery.

10 The Spongiform Encephalopathy Advisory
11 Committee, SEAC, in the U.K. advised in 2002, 2003
12 that the most important aspect of decontaminating a
13 surgical instrument is the cleaning part of the
14 process to remove prion proteins. I talk about them -
15 - we talk in the U.K. as decontamination being an all-
16 encompassing process. That includes the cleaning, the
17 disinfection, and all sterilization of any medical
18 device. So when I use decontamination, it is within
19 that perspective.

20 Next. New evidence is now available,
21 notably that the infectivity of various tissues in
22 those incubating vCJD may be changed. The amount of

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1 tissue liable to remain on surgical instruments after
2 cleaning has been changed. And the likely effects of
3 moist heat sterilization in reducing the infectivity
4 of prion particles has also been reviewed. And
5 possible mechanism of vCJD transmission has also been
6 updated.

7 Information on those areas has been made
8 available through research developments being
9 undertaken both with the Department of Health, who I
10 work for, and the government and the scientific
11 community.

12 The infectivity of various tissues and
13 those incubating vCJD are the potential infectivity of
14 key tissues, the current Department of Health's view,
15 and this was undertaken by the Department of Health
16 EOR branch, which will report in March of this year.

17 This has been alluded to in other
18 conversations as being the Department of Health's
19 perspective as of 2001. What I'm talking about now is
20 an updated view that's been reviewed and published
21 this year in June.

22 Previous assumptions of infectivity being

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1 widely distributed through the body prior to
2 exhibiting clinical symptoms still appear valid as was
3 originally purported into the review in 2001.

4 However current indications which are
5 awaiting publications, so this is hot off the press,
6 suggest that anterior eye tissues are less infected
7 than previously considered, spinal cord may be
8 significantly less infected than brain although the
9 levels are still high. And similarly, lymphoid
10 tissues appear to carry lower levels other than tonsil
11 or spleen.

12 These current indications, however, are
13 based on bioassay experiments on a variety of tissues
14 now nearing completion. However such results must be
15 treated with caution, particularly since it has only
16 been possible to test small numbers of tissue samples.

17 The amount of tissue liable to remain on
18 surgical instruments after cleaning, general overviews
19 of studies again awaiting publication or residues
20 remaining after standard decontamination procedures --
21 I say standard decontamination procedures, those that
22 are applicable in the U.K. For example, for moist

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1 heat sterilization, we use 134 degrees centigrade for
2 a plateau stage of three minutes.

3 Many cleaned instruments appear to have
4 greater than 2.2 milligrams of protein remaining after
5 going through that process. Now this has been taken
6 from instruments that were submitted after going
7 through the decontamination cycle in a hospital
8 environment to our research and development colleagues
9 at various universities to assess the actual burden
10 remaining.

11 And that cleaning procedures would still
12 remain highly variable. And protein appears to be
13 strongly hydrophobic and combined tightly to stainless
14 steel surfaces. This is an important issue of
15 consideration. Bind tightly to steel surface and
16 therefore prove very difficult to remove.

17 This is again a caveat. This observation
18 based on experiments that start with clean surfaces
19 rather than existing layers of tissues you would
20 normally get going through a standard decontamination
21 process in a hospital environment.

22 The material found experimentally

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1 comprises a total residue that may have built upon
2 previous uses and not removed. Only a small
3 proportion may have come from the most recent presumed
4 infected patient as was discussed earlier.

5 In reality, therefore, does this mean the
6 whole residue has come from the most recent patient?
7 Or infected material converting the normal protein in
8 the preexisting residue into its infected form,
9 therefore in situ prior to its reuse on the
10 instrument. These are areas that have been discussed
11 and do need consideration. And are being considered
12 in the U.K.

13 Prion resistance to conventional forms of
14 decontamination -- as has been stated, prions are
15 highly resistant to conventional forms of
16 decontamination procedures, notably steam
17 sterilization and moist heat sterilization.

18 And the degree of resistance varies
19 between different strains of prions with differences
20 in the relative protease resistance of the abnormal
21 form of prion protein and thermal activation of prion
22 infectivity. This was first discussed by Taylor in

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1 his paper in 2002.

2 Prior resistance to conventional forms of
3 decontamination, again heating of some of the TSC
4 strains have shown to produce infectious T cells quite
5 significantly but without reducing the level of
6 abnormal prion proteins remaining, which has been
7 quantifiable with the Western Blot technique. Western
8 Blot is the standard technique that is used for
9 detecting prions at a fairly medium level. And this
10 was first discussed by Somerville in 2002.

11 Decontamination methods that demonstrate
12 activity against the abnormal forms of prion protein
13 must therefore be verified by bioassay for infectivity
14 itself. This has been long thought of by ourselves in
15 the department and the scientific community but has
16 been published again by Collinge in 2005 of this year.

17 One of the likely effects of moist heat
18 sterilization, reducing the infectivity of prion
19 particles. As has been said, different TSCs show why
20 the different degrees of thermostability. That means
21 that depending on the strain, they may be effected by
22 lower or higher temperatures, longer or shorter times.

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1 Current experiments are showing that vCJD
2 may result in infectivity being reduced between two
3 and three logs using standard moist heat sterilization
4 processes. Not that very high.

5 And that second and subsequent cycles are
6 likely to be significantly less effective. Why we
7 went down that road originally -- the decision was
8 made that to use 134 degrees Centigrade for 18 minutes
9 for the moist heat sterilization or six consecutive
10 cycles at 134 for three minutes. As has been stated,
11 those second and subsequent cycles have been proven to
12 be ineffective.

13 What are other possible mechanisms of vCJD
14 transmission? The material remaining on an instrument
15 may become detached from the instrument and become a
16 route of infectivity. This has been long established
17 in 2002, 2001.

18 However, material on an instrument need
19 not to become detached from it to pose a risk. And
20 efficient route may be settled on its own remaining
21 bounded instrument surface But in contact with
22 acceptable protein. This was discussed by Weissman in

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1 2002.

2 Weissmann suggests that this may be by
3 material remaining bound to the instrument surface but
4 in contact with susceptible protein, setting off a
5 chain reaction, for want of a better word, of prion
6 conversion. Weissmann calls this a contact model.

7 Most recent evidence lends weight to this
8 actual contact model but provided that the contact is
9 prolonged. And as has been talked about previously,
10 how this is being done is by stainless steel wires
11 inserted into the animals themselves.

12 So whether it has been placed and removed
13 straight away or left in contact, evidence would
14 suggest that the longer the contact time, is the more
15 problem you've got. But the contact model itself does
16 not invalidate the model of detachment. But it may be
17 plausible that both mechanisms may occur, i.e., either
18 by contact or the material coming off the instrument
19 into the susceptible host.

20 Next slide please. Model overall
21 reduction in infectivity would be required from the
22 decontamination cycle of a highly contaminated used

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1 surgical instrument. Within SEAC we actually asked
2 this question. And the scientific community went back
3 to do some experimental studies.

4 And they came back and decided to stop the
5 infectivity being passed on after each use of the
6 instrument, it could be at a possible 6 log times 10
7 reduction in infectivity would be required. To stop
8 any transmission occurring would require a ten to the
9 seven, ten to the eight log reduction in infectivity.

10 However, at present, current data suggests
11 that the best case scenario for an overall
12 decontamination cycle is 5.5 to the 10 log reduction
13 in infectivity from the existing decontamination
14 cycles and the proposed cycles that are being
15 suggested.

16 The Department of Health undertook a
17 strategy review on the decontamination of prions from
18 surgical instruments and set up a research and
19 development program. And over the last five years,
20 we've actually submitted 26 research projects that
21 have cost -- I'll use -- say it in U.S., 11.7 million
22 dollars.

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1 And the strategy is based upon three
2 processes. That's estimating the current risk,
3 detecting contamination protein, and developing new
4 inactivation techniques.

5 Estimating the current risk, some of the
6 areas that are being looked at might involve
7 determining the thermal resistance of vCJD by more
8 research and development programs, determining the
9 current protein load on surgical instruments after
10 going through a standard decontamination cycle -- I
11 emphasize the word standard decontamination as has
12 come out of a hospital environment, and assessing the
13 risk of transmission by a disease or surgery.

14 Then we have determining the contaminating
15 protein itself. Detection -- the worry about
16 something going in this area is detection of prions
17 before processing to identify potential hazardous
18 instruments. Are some instruments more susceptible to
19 prions for a day or two and are therefore more
20 difficult to remove than others?

21 The screening of instruments for prions
22 and total prion load and protein load and the

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1 detection of very low levels on instruments and within
2 crevices of those instruments. Why are we looking at
3 very low levels? As has been discussed previously,
4 what is a lower level of infectivity? Because it is
5 still a huge unknown.

6 And then developing new activation
7 techniques. These are the areas that are being looked
8 at in this particular part of the scenario, assessing
9 the efficacy of current decontamination methods. Are
10 those methods that we use acceptable? Do we need to
11 modify them? Do they need changing? Or are they
12 completely ineffective?

13 Developing new technologies to inactivate
14 all prions. And I emphasize the word all again. And
15 developing new technologies to clean instruments. As
16 I say, SEAC's advice is that the most important stage
17 in the whole decontamination cycle is the cleaning of
18 the instruments.

19 Next, looking at it from my particular
20 perspective as a regulator, if new products were to
21 come along that say can deactivate prions, is there
22 information available that we can link into?

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1 And within Europe from the regulatory
2 perspective of medical devices, the expectations are
3 that reference be made to what we call harmonized
4 standard. Therefore if the manufacturer complies with
5 that particular standard, they are said to be in
6 compliance with that particular requirement of the
7 directive, the problem being there is no specific
8 reference to prion deactivation processes. So we
9 could be working in the dark on this one.

10 But if it is considered that it is a
11 terminal process, is it a sterilization process? Is
12 it a removal process? Are those processes one in the
13 same? If we assume that it may be a sterilization
14 process and a terminal process, then there is an
15 appropriate standard that's both published within
16 Europe and internationally. And the reference is
17 there which is BN ES ISO 14937 which was put together
18 originally to be the standard basic information for
19 how appropriate sterilization standards for medical
20 devices would be written.

21 And it talks about the actual
22 characterization of the sterilizing agent. And the

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1 development of validation processes.

2 Next slide please. So we assume that this
3 standard may be a useful tool to use. It was
4 developed as a template. That is to say for the way
5 in which all medical device sterilization standards
6 would be considered. Prion deactivation may be
7 considered to be sterilization. That's debatable.

8 But if it is, the process required may be
9 appropriate to use the standard and it is the way it
10 has been written as a way of guiding a manufacturer
11 through the process.

12 Next slide please. Some of the possible
13 requirements that are listed in this particular
14 standard. It starts off by talking about the
15 deactivating agent characterization being the key
16 focus. That is to define what the agent is itself.
17 I'm not talking about the agent in this context. I
18 mean the agent that does the process, the product, the
19 removal of, not the prion itself -- that the removal,
20 the inactivation, deactivation, whatever term you
21 wanted to use.

22 It also has to demonstrate the

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1 effectiveness in deactivating prior particles. There
2 is an uncertainty there. And if you came too late,
3 that has been alluded to previously.

4 Also to identify the factors which
5 influence the effectiveness of the agent. Assess the
6 effect of exposure to the agent by handling materials.

7 One of the recognized methods at the present time is
8 one mole is sodium hydroxide at 60 degrees centigrade.

9 The assumption is that this will help quiet the
10 adverse effect on sterilization and the actual
11 surgical instruments themselves.

12 Studies are being undertaken looking at
13 that particular aspect, intending to show that
14 stainless steel is not as readily effected as first
15 thought. How practical is using one mole of sodium
16 hydroxide at 60 degrees centigrade? And also to
17 identify the requirement as we are looking at all the
18 safety of personnel and the protection of the
19 environment as well. These are key areas that would
20 need to be discussed in a technical dossiers, a folio
21 from the manufacturer.

22 Next. And then we come actually to the

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1 validation. Again, an uncertainty. The validation is
2 to demonstrate that the deactivation process
3 established in process definition can be delivered
4 effectively and reproducibly to the product. And this
5 will improve the standard IQ, OQ, and PQ systems.

6 But what about control systems? Or
7 performance standards applicable to such a process.
8 And would this be able to assume that the product
9 would give a safe and effective process -- product at
10 the end.

11 Next please. Therefore, the validation
12 should show how effective decontamination is against
13 native VCG, abnormal prions as absorbed under
14 surgical steel surfaces rather than simply with tissue
15 homogenized.

16 This is a gain from a recent paper issued
17 by Collinge which talks about really, the standard
18 technologies that have been used so far is to use and
19 the instruments and needles are put into as
20 transferred as part of the animal

21 But how effective are those particular
22 animal prion models to the human form of vCJD? And at

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1 present, there does not appear to be a sensitive
2 indicator animal in which to assay vCJD infectivity on
3 stainless steel.

4 Next please. Examples of TSC models which
5 have been used so far appear to be based on animal
6 models from example brain extracted from hamsters and
7 infected with scrapie as discussed previously. This
8 scrapie 263K hamster model seems to be the way most
9 scientific areas are being looked at for the removal
10 of prions. But again I ask the question. How
11 appropriate is this particular model to the human form
12 of vCJD?

13 Next please. In 2001, Flechsig made the
14 statement that the use of stainless steel wires as a
15 model of surgical instruments is an essential element
16 of validating potential decontamination regimes. He
17 found the metal bound prions appear to have a higher
18 specific infectivity than those in tissues and may be
19 more resistant to degradation.

20 But again the same question. They're
21 looking at stainless steel. And as has been stated
22 previously, surgical instruments, although the

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1 majority are various types of surgical steel, they
2 may, in fact, not be stainless steel. There is a
3 whole host of instruments using ophthalmologic
4 neurosurgery made in titanium, pure titanium, nothing
5 to do with stainless steel. Has the same effect with
6 titanium as stainless steel? A question.

7 So some of my -- next slide please -- some
8 of my comments are from this areas and the areas that
9 have been discussed previously. Research is available
10 which suggests abnormal prion protein changes
11 conformation during some matters of sterilization.
12 This conformational change made make abnormal prion
13 proteins adhere better to surgical instruments, not
14 fully inactivate the sterilization process during this
15 infectivity of the protein.

16 Next please. New activation agents are
17 presented to the market where the models chosen may
18 not be substantive enough to ensure that the product
19 and process is fully validated. I say that because
20 again, the recent areas that have been looked at and
21 the Kauf Institute in Germany are also using the same
22 sorts of scenarios, again using the hamster scrapie

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1 263K model. Are those models appropriate?

2 And these are the questions within the
3 U.K. as a regulator we are asking in part. Fairly
4 recently we've gone back to SEAC to ask this very
5 question for they are the scientists and the community
6 to look at what is an appropriate model that may be
7 used that would give the representative form of human
8 form of prions.

9 Research has progressed at a rapid rate in
10 the U.K. in that last two years. And there are
11 systems now in place which are giving very sensitive
12 techniques to allow detection of protein but these are
13 not yet readily available to the market. Some of the
14 areas that are being looked at from
15 electronmicroscopy, certain types of it are actually
16 detecting prion protein at nano particles.

17 And how appropriate these particular
18 systems would be in practical terms is still to be
19 debated.

20 So in summary, understanding of prions and
21 their adherence onto surgical instruments is advancing
22 at a rapid pace. But what about other materials used

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1 in the manufacture of surgical instruments? I talk
2 titanium and various plastics. Neoprene, for example,
3 is a common plastic agent used in endoscopes. Does
4 the same scenario apply?

5 And there does not appear to be agreement
6 within the scientific community as the most
7 appropriate animal prion stray model that is
8 representative of the human form of vCJD for use in
9 research and product process development.

10 Abnormal prion protein is used as a
11 surrogate marker for prion infectivity. But in
12 certain circumstances, infectivity in prion protein
13 respond differently to treatment in the different
14 types of treatments that are made.

15 Finally, I apologize. I've raised more
16 questions than provided answers. And justification of
17 how we're actually doing this is that the current
18 state of research and understanding of prion
19 decontamination within the scientific community is
20 still evolving and evolving at a rapid rate I might
21 add.

22 But as yet, I don't believe there are

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1 definitive answers. However at this rapid rate of
2 understanding, there does appear to be a glimmer of
3 light at the end of the tunnel. Thank you.

4 CHAIRMAN EDMISTON: Thank you, Mr.
5 Hilderley. Let me open this up to the panel for a few
6 questions before we move on to the public session. Do
7 any of the members of the panel have a wish of asking
8 Mr. Hilderley a question based on his presentation?
9 Dr. Coffey?

10 DR. COFFEY: Yes. All right. Well,
11 you've probably seen the six questions that are being
12 put on to this panel by FDA. Does your agency at
13 present have answers to those six questions?

14 (Laughter.)

15 MR. HIDERLEY: I'm sure you know the
16 answer to that. No, we don't. And that's the reason
17 we have developed links we built to the scientific
18 community and other agencies as well to address these
19 very questions.

20 CHAIRMAN EDMISTON: Dr. Lurie?

21 MEMBER LURIE: Thank you. Thank you for
22 the presentation. Can you help us -- help me anyway

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1 or the group to understand what kind of standards are
2 used for other infectious agents beside TSE? Agents
3 such as HIV, therapeutic genes, or injected viruses
4 that we use in clinical practice so that we have some
5 idea of the level of protection that we would need,
6 you know, for TSE.

7 MR. HIDDENLEY: Okay. There are
8 international standards which may make it within the
9 U.S. It was a secretary form looking at the
10 sterilization standards for medical devices. And
11 they're based on one, the particular standard I talked
12 about from novel processes, and those processes are
13 not readily defined. And when we wrote this
14 particular standard, we were very much aware of the
15 potential for prion proteins. But for new
16 sterilization technologies coming along, gas bottles,
17 for example, but the main ones are based on
18 irradiation, steam, and ethylene oxide.

19 And those are the sterilization standards
20 that would be used not just by industry but hospital
21 environments as well for ensuring that all devices are
22 part of the sterilization process.

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1 Does that answer your question?

2 MEMBER LURIE: I'm sorry. I was asking
3 more about numbers of what log ratios one would expect
4 to get rid of, infectious particles.

5 MR. HIDDERLEY: Well, sterilization, we
6 talk about the sterility assurance level. That is a
7 10 to the minus 6 level. That means that there is, as
8 has been discussed previously, you would expect to
9 have one microbe remaining on one million products.
10 And that's the standard we use in the U.K. And within
11 the U.S. as well.

12 CHAIRMAN EDMISTON: Dr. Priola?

13 MEMBER PRIOLA: Just a quick question. On
14 one of your slides, you had mentioned that following
15 standard decontamination procedures, many cleaned
16 instruments appear to have greater than two milligrams
17 of protein remaining.

18 MR. HIDDERLEY: Yes.

19 MEMBER PRIOLA: Do you know how that was
20 determined?

21 MR. HIDDERLEY: Yes. We asked a number of
22 universities to take sets of instruments -- we chose

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1 sets of instruments purely at random after they had
2 gone through a complete decontamination cycle from a
3 number of hospital sites. And then sent them to the
4 particular universities to assess.

5 And the easiest way they did it was purely
6 and simply after a lot of heartache in looking at the
7 methods, just by washing off the instruments and
8 simply filtering the residue and measuring it from
9 that.

10 CHAIRMAN EDMISTON: Dr. Jarvis?

11 MEMBER JARVIS: A follow up to that
12 question. Could you describe -- I assume if they come
13 from different hospitals, that the standard
14 decontamination might be different in those hospitals.
15 Could you describe what was done?

16 MR. HIDDENLEY: Sure. Wherever possible
17 within the U.K., we try to use a standardized process.

18 When SEAC first made the recommendation about
19 cleaning being the most effective part of the
20 decontamination cycle, that set a whole program into
21 place in 2000.

22 And, in fact, some 200 million pounds has

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1 been spent updating hospital sterilization departments
2 and decontamination departments to a baseline
3 standard. So in theory -- and it is theory -- those
4 departments should be applying the same processes and
5 standards of how they process their instruments.

6 But as was seen from the various amount of
7 tissue that were remaining, there were problems.

8 MEMBER JARVIS: In terms of cleaning, do
9 they use a standardized enzymatic cleaner? What kind
10 of processes do they use for cleaning before
11 sterilization?

12 MR. HIDDENLEY: It's quite early to be
13 honest. There in the process, which we've been
14 waiting for with bated breath probably three years, a
15 standard in the process of being published
16 specifically for wash and disinfectors used in the
17 sterilization of medical devices at an international
18 level? And we're still waiting for that.

19 So because there is no agreed standard,
20 all of standards are laid down within their own
21 professional organizations within sterile services in
22 the U.K., there isn't one particular model that they

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1 have to use. They can vary that.

2 Although can I say -- sorry -- if they are
3 considered to be a manufacturer under the medical
4 devices directive, there are baseline standards which
5 they must comply with for regulatory reasons. But not
6 all hospitals have to comply with the directive.

7 CHAIRMAN EDMISTON: Dr. Hidderley -- Mr.
8 Hidderley, will you be able to stay the afternoon with
9 us?

10 MR. HIDDERLEY: I'm here all day.

11 CHAIRMAN EDMISTON: Perfect. Dr. Gordon,
12 you had a question?

13 MEMBER GORDON: I wanted to ask a little
14 about the validity of the animal models, to explore
15 that a little bit. And I was curious about how the
16 bird and animal models compared with what you might
17 see in clinical practice. If there is any way to
18 correlate what you'd see in these animals versus
19 humans?

20 The issue, I guess, is that we are seeing
21 ID50s quoted for the animal models but we don't know
22 what the ID50 is for people. And if the ID50 is at

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1 such a level that they are logs off from one another,
2 is there going to be any validity between what we even
3 find in the animal models and what's going to happen
4 in humans with regard to developing disease?

5 MR. HIDDENLEY: We asked the same scenario
6 from our scientific community probably two years ago.
7 And we're still waiting for the results of those
8 deliberations I'm afraid. Hopefully they said it
9 should be towards the end of this year. So I can't
10 offer you any clear cut information.

11 CHAIRMAN EDMISTON: One further question
12 from Ms. Howe.

13 MS. HOWE: You'd mentioned that there are
14 some procedures that are becoming available but
15 they're not marketable. Is your goal to have
16 something available that could be standardized at all
17 hospital facilities? Or are you looking at the option
18 of having super decontamination facilities?

19 MR. HIDDENLEY: Both. If you call them
20 super decontamination facilities, I hate the word, but
21 there are certain departments that are being combined
22 together to get very large departments. But the

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1 standard will still have to be, as with any other
2 process within the hospital, met. There was no
3 difference.

4 CHAIRMAN EDMISTON: Thank you very much.

5 At this time, we'll proceed on to the
6 first of our two open public hearing sessions to this
7 meeting. The second public hearing session will
8 follow the industry discussions this afternoon.

9 Some individuals have given advance notice
10 of wishing to address the panel. If there is anyone
11 now wishing to address the panel, please identify
12 yourself.

13 Before we move on to that, however, I need
14 -- just some homework to take care of. I'd like to
15 remind the public observers of this meeting that while
16 this portion of the meeting is open to the public,
17 public attendees may not participate except at the
18 specific request of the Chair.

19 I would ask at this time that persons
20 addressing the panel come forward to the microphone
21 and speak clearly as the transcriptionist is dependent
22 on this means for providing an accurate transcript of

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1 the presentation.

2 I would also request that if you have a
3 hard copy of your presentation, please give that to
4 the Secretary.

5 One more statement. This is to be read
6 verbatim at general matters meetings.

7 Both the Food and Drug Administration and
8 the public believe in a transparent process for
9 information gathering and decision-making to ensure
10 such transparency at the open public hearing session
11 of the Advisory Committee Meeting, the FDA believes it
12 is important to understand the context of the
13 individual's presentation.

14 For this reason, the FDA encourages you at
15 the open public hearing to begin your presentation, to
16 advise the Committee of any financial relationships
17 that you may have with any companies or groups that
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19 For example, the financial information may
20 be a company's CEO, group payment, travel, lodging or
21 any other expenses in connection with your
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1 Likewise, FDA encourages you at the
2 beginning of your statement to advise the Committee if
3 you do not have such financial relationships. And if
4 you do choose not to address this issue of financial
5 relation at the beginning of your statement, it will
6 not preclude you from speaking at this meeting.

7 We will now begin with the first speaker,
8 Dr. Conte. And I should remind the speakers during
9 the session, the presentations are limited to ten
10 minutes.

11 DR. CONTE: Thank you very much. I'd like
12 to thank the FDA and the panel for affording me the
13 opportunity to speak briefly this morning.

14 I am John Conte. I'm a Professor of
15 Medicine and Epidemiology and Microbiology at the
16 University of California in San Francisco. And for
17 more than 30 years have been either involved with or
18 the Director of Infection Control and Hospital
19 Epidemiology for the Medical Center in San Francisco.

20 The University of California in San
21 Francisco, the Medical Center is a center for research
22 regarding prion diseases and is also a center for the

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1 clinical care of patients with transmissible
2 spongiform encephalopathies.

3 That is my background. And I am going to
4 mainly focus on the impact of prion diseases and the
5 potential for transmission on the hospital. Even
6 though my slides say the public health, this is a
7 public health problem but specifically focused on what
8 the effect is on hospitals.

9 Before I understood the context of my
10 comments and how many slides would show the
11 transmissible encephalopathies, I put this list on the
12 board but we are talking about the same diseases that
13 have been previously mentioned, classic Creutzfeldt-
14 Jakob disease, the variant form of the disease in
15 humans, the iatrogenic transmission of the disease,
16 other TSEs such as Kuru and GSS Syndrome and the like,
17 mad cow disease itself and chronic wasting disease in
18 deer and elk and scrapie in sheep, these are the
19 diseases that have prions as their etiology and for
20 which the potential, at least, of transmission is
21 discussed or a problem.

22 Could I have the second slide, yes. As

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1 previously mentioned, transmission has been documented
2 iatrogenically involving -- and I will go back over
3 the details of this. It has been presented at length
4 in cornea graphs, growth hormone, stereotactic EEG
5 placements, neurosurgical equipment, dura matographs,
6 and more recently blood.

7 Next slide please. I want to emphasize
8 that this is a feared disease. The disease presents
9 with multifocal neurological abnormalities, dementia.
10 It is progressive. It is invariably fatal. There is
11 no prevention. And there is no treatment.

12 Additionally, the incubation period is
13 long and measured in many, many months to many, many
14 years. It is likely that, as has been mentioned, any
15 symptomatic carrier state does exist, in other words
16 preclinical infection of tissues where the potential
17 for transmission does exist. And there is probably a
18 period unknown at the present time of prionemia when
19 the blood is also infectious. And I think the
20 reference to transmission by blood transfusions
21 suggests this possibility.

22 When individuals are infected and

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1 ultimately die, prions as in animals can be found in
2 multiple tissues. There is a focus on the brain and
3 the so-called high risk tissues, spinal cord, cranial
4 nerves, eye, lymphoreticular tissue, and blood.

5 I would like to emphasize though that the
6 acid test of which tissues are infected or are not
7 infected has really not been applied in a very
8 systematic way. And by that I mean most of the
9 judgements about infectivity of tissues have been made
10 from pathological specimens, from immunohistochemistry
11 and the like, which although those stains and
12 procedures do serve a purpose, do not have the level
13 of sensitivity to make a judgment about ultimate
14 infectivity.

15 And so it is quite possible that more
16 tissues are involved than have been described.

17 Finally, the prions as has been
18 summarized, are extremely resistant to standard
19 methods, usual methods of disinfection, autoclaving,
20 glutaraldehyde, ionizing irradiation, and the like.
21 And are a very special type of I say infectious in
22 quotation marks because this is not a virus. It is

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1 not a bacterium. It is a protein but it behaves like
2 an infectious agent.

3 Now the disconnect that I'd like to
4 emphasize for you is the disconnect between what seems
5 to be a low transmission rate as has been adequately
6 documented -- iatrogenic transmissions, for example,
7 which have been enumerated and the impact on hospitals
8 because what has evolved in the recent years and the
9 time frame is perhaps five to ten years or so are the
10 CDC and the World Health Organization recommendations
11 for infection control.

12 And these are extensive. And burdensome I
13 might add. They revolve around -- these
14 recommendations revolve around risk assessment for
15 patients to try to identify those patients who are
16 likely to have a prion-related disease.

17 That once having identified those
18 patients, one carries out certain policies and
19 procedures.

20 There are some problems with that. We
21 have, for example, at the University of California
22 developed very elaborate protocols to try and identify

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1 those patients who might have a prion-related disease.

2 And we -- it is difficult to agree upon who those
3 patients are.

4 It is clear, for example, that somebody
5 has a diagnosed and classic CJV syndrome if they fall
6 into that category. But once you get past that and
7 you get into the less clear diagnostic categories, the
8 decisions become more and more difficult with regard
9 to instrument management and handling.

10 As a consequence, we have, like many other
11 major medical centers, introduced destruction of
12 instruments as our mainstay of prevention. And I
13 would like to at this point in time, and I apologize
14 for the delay in identification -- I just saw my own
15 note to remind myself that I -- besides my academic
16 hat, I have a financial interest in InPro which is a
17 biotechnology company and am a consultant for them. I
18 want to disclose that information.

19 But the mainstay of our approach has been
20 destruction of neurosurgical instruments and the use
21 of sodium hydroxide extensively throughout the
22 hospital. Sodium hydroxide usually in one normal

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1 concentration is four percent sodium hydroxide is
2 recommended throughout the World Health Organizations
3 recommendations for decontamination of surfaces and
4 the like. And it is recommended in our policies and
5 procedures.

6 It even goes as far as to say that if a
7 healthcare worker comes into contact with a
8 potentially contaminated tissue like cerebral spinal
9 fluid, that one consider apply sodium hydroxide to the
10 skin. But for a brief period of time because if it is
11 left on, it causes burning and itself is a toxic
12 agent.

13 Sodium hydroxide is not FDA approved for
14 any of these indications. The scientific basis for
15 making these recommendations is rather thin. And
16 these recommendations are not really evidence based by
17 current standards and are based on just guesstimates
18 and interpretation of the literature.

19 I would also like to add that there is a
20 problem in hospitals with all of the other instruments
21 that are used on patients who either have or who are
22 likely to have prion-related diseases.

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1 And they include, for example, fiberoptic
2 scopes. And it has been determined that the
3 lymphoreticular system, the appendix, and other cells
4 can manifest prions or be contaminated with or contain
5 prions.

6 So gastrosopes, colonoscopes,
7 laparoscopes, these instruments are heat sensitive.
8 They cannot be autoclaved. They generally cannot be
9 immersed for long period of time in sodium hydroxide.

10 They are expensive instruments. They run
11 25, 30, 35, 40,000 dollars. And it raises an issue
12 which to me was reminiscent of when the HIV epidemic
13 was emerging which is to say that I reviewed a
14 protocol where statements were made that if a patient
15 with CJD or possible CJD has let's say a
16 gastrointestinal bleed which might well occur,
17 requiring diagnostic evaluation with some form of
18 endoscope, that fiberoptic endoscopes not be used on
19 that patient.

20 That doesn't meet the standard of care
21 that should be applied to all patients. You can't
22 withhold diagnostic instrumentation from a patient

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1 because of a diagnosis that they might have. At least
2 not at the present state of the art and of our medical
3 legal system.

4 This also arose when we were considering
5 taking care of HIV patients. If you recall and you
6 were involved about whether or not to do certain
7 surgical procedures, whether or not they could go to
8 the operating room, all of which eventually, of
9 course, were disregarded.

10 And I have to go on. I see the red light
11 flashing. I'm sorry. So besides the scopes, optical
12 equipment, tenometers, dental procedures which come in
13 contact with the cranial nerves, the trigeminal nerve,
14 the cranial nerve, it also, you know, can contain
15 prions. And all of these pieces of equipment raise
16 the question of prion transmission. So it's not only
17 neurosurgical instruments.

18 I can conclude, if I might, can I have
19 another minute or two?

20 CHAIRMAN EDMISTON: Yes, of course.

21 DR. CONTE: That there is this disconnect
22 between the wonderful -- I'm pleased with the

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1 epidemiologic, an attempt at introducing science into
2 a very difficult subject but there is a disconnect
3 between the burden on hospitals and what we do.

4 There is no FDA approved disinfection
5 strategy or solution or technique for prion
6 elimination. So we're operating in a totally off
7 label area with all of our recommendations.

8 I would like to emphasize the safety
9 issues for healthcare workers in two respects. One is
10 sodium hydroxide is an unsafe chemical. One mole of
11 sodium hydroxide is four percent sodium hydroxide. It
12 has to be prepared from stock solutions that are ten
13 times that concentration.

14 And even keeping those stock solutions
15 around is itself a health hazard for individuals who
16 are in care of those stock solutions.

17 Secondly, there are no post-exposure
18 strategies, so-called PEP, as we have for HIV or for
19 hepatitis. There are no PEP strategies that have
20 really even emerged for prion exposure.

21 So this had led to the sort of on-the-fly
22 recommendation that sodium hydroxide be used. And

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1 that you immediately call the hotline number and tell
2 them what happened.

3 Of course the person on the end of the
4 hotline has no idea what to tell you when you tell
5 them that you have been exposed to prions. So there
6 is a healthcare worker safety issue with sodium
7 hydroxide with exposure. And the both of those events
8 create anxiety in our healthcare workers about taking
9 care of patients with CJD disease.

10 So in summary, we don't have a very good
11 situation on the hospital side. By that I mean we are
12 involved in enormous expense, commitment of resources,
13 destruction of instruments. It is not that easy to
14 identify all the patients who may or may not be
15 involved with this kind of disease.

16 We have inadequately decontaminated
17 fiberoptic scopes because there is no current
18 treatment to apply to a fiberoptic scope. And this
19 goes for all hospitals.

20 There is the problem of missed cases.
21 Don't forget if you happen to miss a case and the
22 instruments -- and this relates to also the model that

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1 was presented -- if we miss a case and the instruments
2 are used, those instruments are not only used once.
3 If they go back into the pool of instruments, they are
4 used repeatedly, over, and over, and over again.

5 And there is no evidence that repeated
6 exposure to the standard disinfection cleaning systems
7 removes the prions. It may reduce the burden. But
8 whether or not that reduces the infectivity is less
9 likely in my mind based on the information we have.

10 So that if one has repeated exposures and
11 the impossibility of trying to identify all of the
12 patients who have been exposed to repeated exposures
13 of instruments that were put back in the instrument
14 pool.

15 CHAIRMAN EDMISTON: Thank you, Dr. Conte.

16 DR. CONTE: And I am -- that is my final
17 point. So thank you.

18 CHAIRMAN EDMISTON: Thank you very much.
19 Do any members of the panel have questions for Dr.
20 Conte? Yes, Mr. Evans?

21 MEMBER EVANS: Dr. Conte, thank you for
22 you interest from the hospital perspective. You

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1 mentioned that your facility uses instrument
2 destruction as a primary source of managing these
3 instruments. Do you have an estimated cost for your
4 facility?

5 DR. CONTE: I don't know I'm sorry to say.

6 And we should have. But I don't.

7 And we also have not addressed -- we are
8 destroying neurosurgical instruments but -- and the
9 meetings I'm referring to are as recent as just last
10 week -- we -- what about laryngoscopes?

11 What about dental equipment? What about
12 instruments that come into contact with
13 lymphoreticular tissue? Should one destroy all of
14 those instruments, too? Or at least try and use
15 disposable instruments in all those incidents. And I
16 think those are unanswered questions. And it is a
17 tremendous cost but I don't know what the cost is.

18 CHAIRMAN EDMISTON: Dr. Lurie?

19 MEMBER LURIE: Thank you. Thank you for
20 that presentation. In the references that it was
21 suggested that we take a look at, one was from the
22 Journal of Virology, Dr. Jackson, who suggested there

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1 is an enzymatic detergent method for effective prior
2 decontamination of surgical steel.

3 Can you share with us, Dr. Conte, your
4 experience with that? And why you don't use that
5 method?

6 DR. CONTE: I didn't know the question was
7 directed at me. So the question was what? Why don't
8 we use enzymatic --

9 MEMBER LURIE: I'm sorry. Right. The
10 Jackson article suggest that the enzyme detergent
11 method is effective for prion decontamination. And
12 you've talked about sodium hydroxide Drano method.
13 And I'm wondering why this method wouldn't be more
14 effective.

15 DR. CONTE: Well, most hospitals use as a
16 pre -- the procedure in our hospital is similar to
17 most hospitals, which is to say that when instruments
18 come, they are placed in an enzymatic detergent and
19 they are either agitated or in some way cleaned using
20 a pre-sterilization step.

21 In our center, and I think this is shared
22 by many centers, certain instruments of certain

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1 configurations like drills, saws, and the like are
2 inspected for visual contamination. And are cleaned
3 manually before they are even put in the enzyme
4 detergent.

5 This is done by people in full protective
6 clothing and who have been trained to do that. From
7 the enzymatic detergent then the instruments are then
8 rinsed in a sterile -- in water basically and are then
9 prepared for routine sterilization which in our
10 institution is a high pressure, high temperature, 134
11 degrees for four minutes in a porous load autoclave.

12 So we do use an enzymatic step which most
13 hospitals do. I am aware of the paper and whether
14 that then results in elimination of prions is really
15 what this, you know, what the discussion has been
16 about it seems to me.

17 CHAIRMAN EDMISTON: Before we ask Dr.
18 Conte another question, is there anyone else in the
19 audience who wants to make a presentation in this
20 morning's session, public session?

21 (No response.)

22 CHAIRMAN EDMISTON: No? Dr. Schonberger?

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1 MEMBER SCHONBERGER: Yes. Dr. Conte,
2 isn't it true that most hospitals do not throw away
3 their equipment on a routine basis?

4 And I'm wondering given the World Health
5 Organizations recommendations to which you referred,
6 there are a number of grade or grade levels of
7 decontamination that were thought to be, you know,
8 reasonable although less effective as is throwing it
9 out clearly. And you point out the disconnect between
10 risk and benefits, so to speak.

11 Why in your hospital do you throw away the
12 equipment?

13 DR. CONTE: Yes, well thank you for asking
14 that question.

15 I don't have the data, the surveillance to
16 really say how this is handled at a community level, a
17 medium-size hospital level, and a medical center
18 level. I think it is probably fair to say -- I have
19 reasonable certainty of this statement that major
20 medical centers are attempting to identify patients
21 who have prion-related diseases and in those patients
22 who are suspect for prion-related disease, in those

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1 patients are discarding neurosurgical instruments, at
2 UC Stanford and others.

3 Now in hospitals in the community where
4 they might not see these patients for many, many, many
5 months, and there is a less sensitivity to this, they
6 are perhaps not doing it. I can't answer that
7 question.

8 And there is a disconnect because the
9 World Health Organization recommendations and the CDC
10 recommendations create this burden of identification
11 and then their primary choice is destruction of the
12 instruments.

13 But then the exact wording is -- after
14 that recommendation -- that if this is not practical
15 or feasible -- if this is not practical or feasible,
16 that you then use one of the methods in the annex,
17 okay, and the annex of the World Health Organization
18 recommendations to which the CDC refers contains three
19 strategies, all of which deal with sodium hydroxide
20 in, you know, various concentrations and hot sodium
21 hydroxide followed by autoclaving and the like.

22 Now most hospitals have chosen not to be

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1 involved in hot sodium hydroxide autoclaving that I'm
2 aware of. And we haven't. So we have taken the
3 strategy of discarding the instruments and not
4 becoming involved with the use of sodium hydroxide in
5 the sterile processing department.

6 CHAIRMAN EDMISTON: Dr. Jarvis?

7 MEMBER JARVIS: Just a quick question.
8 You mentioned on your slide about transmitted tissues.
9 One was blood. I know the intensive surveillance
10 studies done of patients who receive large volumes of
11 blood products have not identified any CJD
12 transmission.

13 And I wonder if you could elaborate on
14 either the case or cases that you were describing
15 there.

16 DR. CONTE: I can't elaborate further
17 other than that I meant to say that there are two
18 cases, as was presented, of blood related, you know,
19 CJD related to blood transfusion.

20 MEMBER JARVIS: He's talking about
21 variability, Judy.

22 CHAIRMAN EDMISTON: Okay. That's a

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1 different topic.

2 DR. CONTE: I mean apart from that, I have
3 no further data on it.

4 MEMBER ARDUINO: So even though the
5 recommendations say to quarantine instruments, you
6 don't bother to quarantine instruments until you kind
7 of find out? Or is it you just cut out the step?

8 DR. CONTE: Well, our group met and tried
9 to decide how one would quarantine instruments. When
10 the discussion came up about quarantining instruments,
11 it was very reminiscent of a discussion we had two
12 weeks ago which was how does one do this? What does
13 it mean?

14 You have to have some -- first of all, you
15 have to have some suspicion that the person that was
16 operated on requires quarantining the instruments. So
17 have to clearly define what that track is.

18 Secondly, what does quarantining mean? We
19 were sure where to keep the instruments. Under what
20 conditions? Are they hung dry? Are they put in
21 wraps? The issue of quarantining itself is not
22 clearly defined other than stated as a strategy.

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1 And so because we couldn't really come to
2 grips with what quarantining meant, and perhaps this
3 is just the way we do things at UC, we decided that we
4 would not have that category for all practical
5 purposes. We either identify the correct people,
6 destroy the instruments or we don't.

7 CHAIRMAN EDMISTON: Dr. Priola?

8 MEMBER PRIOLA: No, that's okay.

9 CHAIRMAN EDMISTON: Let me ask you a
10 question, all right? And actually we have a number of
11 infection control personnel on the committee and we
12 also have practitioners. Let me ask you this
13 question.

14 Let's suppose this panel was able to come
15 up with a suggestion -- recommendation to the FDA
16 which a manufacturer was able to fulfil, in other
17 words we could actually ascertain a threshold limit,
18 and in a diagnostic case where you had a positive CJD
19 patient in which all of the clinical parameters and
20 pathologic parameters are in place, and you had a
21 proprietary product available, would you still destroy
22 those instruments?

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1 DR. CONTE: I have two answers to the
2 question. One is remember that the World Health
3 Organization and the CDC both say that if destruction
4 of instruments is not practical, you can use any one
5 of these three strategies to decontaminate and
6 disinfect the instruments.

7 So they are without any evidence really
8 essentially no science behind the recommendations --
9 without any evidence, they are making the
10 recommendation that since sodium hydroxide has some
11 anti-prion effect that has been demonstrated, that
12 this would be an option. And that you could do this.

13 So I'd have to answer your question and
14 say that if I had a product which had science behind
15 it and it was clearly validated and showed whatever it
16 was decided to be below threshold levels, that this
17 product resulted in from its correct use, I would
18 accept that as a way of disinfecting instruments if I
19 was going to accept the fact that sodium hydroxide is
20 an alternative for which there was no science. I
21 think that the bar is quite high. I think the bar is
22 going to be quite high to make that claim.

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1 But I believe that such a bar can be
2 achieved. And the answer would be yes. I would do
3 that.

4 CHAIRMAN EDMISTON: Dr. Schonberger?

5 DR. CONTE: But also may I just pare my
6 answer by saying that such a product, I think that the
7 main use of the product would be the wider use where
8 in all of these other areas, where destruction of
9 instruments really isn't an option and the cleaning of
10 surfaces and the like where an effective anti-prion
11 disinfectant, which was validated, was available, that
12 this would be a very, very important addition to
13 hospitals at the present time.

14 MEMBER SCHONBERGER: The destruction of
15 instruments was a very controversial issue at the time
16 that the recommendations were decided upon.

17 DR. CONTE: Right.

18 MEMBER SCHONBERGER: And there were many
19 on the committee, including many at CDC that was not
20 in favor of destruction of equipment. And you are
21 right, the WHO recommendations say that's the most
22 effective.

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1 And so the statement that really comes
2 from CDC reads as follows: Destruction of heat
3 resistant surgical instruments that come in contact
4 with high infectivity tissues, albeit the safest and
5 most unambiguous method as described in the WHO
6 guidelines, may not be practical or cost effective.

7 That was a signal for people at the local
8 level like yourself to make a decision. Is this
9 really practical or cost effective? The idea was to
10 kind of give you a way out but nevertheless not to
11 contradict WHO which was saying look, the safest and
12 most unambiguous thing is throw the instruments out
13 which is also a valid approach.

14 So that's why I was asking whether in your
15 hospital you had any kind of committee go over this to
16 decide is this really the cost effective and practical
17 approach to take.

18 DR. CONTE: Well, the answer is absolutely
19 yes. We had multiple, multiple meetings. And you see
20 we have resident experts in prion diseases that we
21 draw on. And the problem has been that the
22 alternative, which was disinfection by using various

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1 sodium hydroxide strategies is not evidence based.

2 And so even though we don't like to -- you
3 know, we recognize the cost and the inconvenience, you
4 know, of destroying instruments, we didn't want to do
5 the alternative, which was a, you know, not validated
6 and scientifically based. So we destroy instruments.

7 CHAIRMAN EDMISTON: Let me bring things
8 back on track for a minute. Destroying instruments is
9 one component but that's more in the clinical practice
10 realm, I want to go back to this issue of a priority
11 component.

12 Mr. Hilderley, can you come up to the
13 podium and stand next to Dr. Conte? Let me ask you --
14 and I think you gave me -- that's a great picture, you
15 know?

16 (Laughter.)

17 CHAIRMAN EDMISTON: Hands across the sea.
18 I love that. All right. Let me pose that question
19 again because I think this is really the key.

20 The key is from the regulatory
21 perspective, if a claim is going to come forward that
22 I have a proprietary substance that can effectively

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1 reduce the viral burden so to speak, would the
2 population at risk -- and you're the population at
3 risk, too -- would you accept that in your practice?

4 What I'm sensing here is it's a twofold
5 issue. Whatever comes forward to the FDA is always
6 going to be adjunctive to what are the traditional or
7 accepted cleaning and disinfecting practices within
8 the institution, within the hospital. Is that
9 correct, Mr. Hidderley? Do you think that's a valid
10 comment to make?

11 That whatever comes forward is always
12 going to be front end adjunctive to what we tend to do
13 right now in our hospitals?

14 MR. HIDDERLEY: From the R&D side at
15 present --

16 CHAIRMAN EDMISTON: Can you speak into the
17 microphone?

18 MR. HIDDERLEY: Sure.

19 CHAIRMAN EDMISTON: Thank you.

20 MR. HIDDERLEY: From the R&D development
21 taking place at the moment, yes that would appear to
22 be the case.

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1 Whether it is something that comes up in
2 front of the process or takes over the whole process,
3 there are different products, for example there is a
4 product we talked about using, a gas plasma system
5 which literally strips the surface monolayer of the
6 instruments, which is an entire processing so we
7 might.

8 The argument is whether that's a total
9 process or part of the whole process. And these
10 debates are still going off even with the
11 manufacturers themselves.

12 CHAIRMAN EDMISTON: Because from a user's
13 perspective, I think it is going to be veery
14 difficult. The risk is never going to be zero. It's
15 going to be very difficult to get to, for some
16 individuals, an acceptable level of risk.

17 So I'm putting this to you again. If
18 there was in front of you a device or a proprietary
19 product, an enzyme, some other vehicle that could
20 reduce that viral burden to a percentage -- 75 percent
21 of what is acceptable, do you think that would be
22 embraced by the infection control and ID community in

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1 the U.S.?

2 DR. CONTE: Well, I do for all the reasons
3 that I said. Now the issue of instruments used -- I'm
4 sorry to get back to this but that seems to be the
5 core point. The issue of high risk instruments in
6 neurosurgical tissues used in patients with CJD is a
7 very special, worst case if you will, scenario.

8 But remember that the CDC and the World
9 Health Organization recommendations are not that you
10 will destroy instruments. It's that you have sort of
11 two options. You can destroy instruments. But if
12 that's not feasible or too costly, you can use the
13 sodium hydroxide method.

14 So I would have to again say that allowing
15 that disinfection which is not evidence based would be
16 okay for hospitals to do. I would have to say that if
17 there was an evidence-based disinfectant, then I would
18 have faith in that.

19 CHAIRMAN EDMISTON: Currently the burden
20 is placed upon the institution. And the perspective
21 of the institution in terms of what the risk may be.
22 Dr. Haines did you have --

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1 MEMBER HAINES: Well, I think we shouldn't
2 leave out there is an end user behavioral factor. I
3 don't know a neurosurgeon who would knowingly and
4 willing take an instrument that had been used to
5 obtain brain tissue from a patient with CJD and
6 deliberately use that on another patient no matter,
7 under current circumstances, what had been done to it.

8 So I think there would be a huge barrier
9 to get past in that special group of patients.

10 CHAIRMAN EDMISTON: That's a very good
11 point. In essence, there is really nothing out there
12 from your perspective that would give you such a
13 comfort level that you would be willing to use that
14 device again, especially if it was a critical device,
15 a biopsy needle or a stereotaxis -- how about a
16 stereotaxis device? Would you --

17 MEMBER HAINES: The part that entered the
18 brain, I can't imagine using again.

19 MEMBER LURIE: But is that different from
20 the way you felt in the 1980s when HIV was discovered?

21 MEMBER HAINES: Well, you know, we were
22 dealing -- you are dealing there with an infectious

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1 agent that you at least have some analogies to and a
2 great deal of comfort that it is possible to reduce
3 the burden to a level that can be fought.

4 MEMBER LURIE: I'm sorry, that's now. But
5 at the time that we started first operating on people,
6 we had no idea what HIV was. And so I remember having
7 parallel issues of people not wanting to operate on
8 patients, people not wanting to use their instruments,
9 not coming into rooms.

10 MEMBER HAINES: No, that's absolutely
11 correct.

12 MEMBER LURIE: And till there are people
13 in San Francisco who wear these spacesuits when they
14 operate on these patients.

15 So I'm wondering if this agent existed,
16 through time we would get used to the fact?

17 DR. CONTE: Oh certainly, yes.
18 Absolutely.

19 CHAIRMAN EDMISTON: I think what we'll
20 need to do right now, this is getting into a spirited
21 conversation, I want you to think about some of these
22 issues before we get to this afternoon. I think we'll

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1 be able to revisit some of these comments.

2 I want to thank both you gentlemen for
3 coming up a second time and addressing this. And at
4 this point, I think it would

5 CHAIRMAN EDMISTON: I would now like to
6 call the meeting back to order, and I would like to
7 remind the public observers of the meeting that while
8 this portion of the meeting is open to public
9 observation, public attendees may not participate
10 unless specifically requested to do so by the Chair.
11 We will now continue our presentations with industry
12 related to today's topic.

13 Is Dr. Burke in the audience? Dr. Burke,
14 could you identify your affiliation, please? As per
15 the public session, I'm not counting your time right
16 now. All right? But just in case there was some
17 concern, we're going to attempt to limit the dysentery
18 - I said dysentery - dissertation. Sorry, that's a
19 Freudian slip.

20 (Laughter.)

21 CHAIRMAN EDMISTON: We'll try and limit
22 the presentations for 10 minutes, please.

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1 DR. BURKE: Okay. Well, I'm Peter Burke,
2 Senior Vice President and Chief Technology Officer for
3 STERIS Corporation. STERIS Corporation is a publicly
4 traded company, \$1.1 billion, specialize in
5 sterilization, disinfection, and decontamination.
6 It's my pleasure to represent STERIS at this important
7 meeting on a difficult scientific and regulatory
8 matter. STERIS believes that it is crucial for the
9 healthcare community to have proven methodologies that
10 permit reuse of medical devices, exposes and TSEs. It
11 is our belief that the current World Health
12 Organization guidance inadequately addresses the needs
13 of healthcare professionals from both a device
14 compatibility, most importantly, and staff safety
15 perspective, while potentially not rendering the
16 incidents prion free following processing with some
17 methods in use today.

18 STERIS applauds CDRH's move to establish
19 appropriate test months and specific criteria for
20 regulation of prion decontamination claims. STERIS
21 believes that prion decontamination needs to be, as
22 you'll see in the slide now, efficacious against

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1 prions and remove and inactivate from surfaces;
2 therefore, test methods to conform the efficacy should
3 be surface-based, as currently required, for all other
4 antimicrobial divisions by CDRH; for instance, AOC
5 sporocidal test for sterilization claims.

6 Any test methodology should consider
7 compatibility. This is an example up here. This is a
8 real example, and what you're seeing is corrosion.
9 This is by courtesy of Windsor Hospital in Canada.
10 They ended up throwing \$8 million worth of equipment
11 because of the fact that they had a one-hour cycle in
12 one normal NaOH at 134 degrees temperature in the
13 autoclave. We know about this because they called us
14 to see if their warranty still on the autoclave was
15 appropriate. And, of course, we had to give them also
16 not good news on that, that they have violated their
17 warranty, so it presents us with a real problem from a
18 compatibility perspective.

19 Safety is another problem associated with
20 use of either bleach and/or one normal caustic. I
21 think the gentleman from UCSF spoke very eloquently
22 about the fact of the safety to the people handling

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1 the equipment. In this particular case, they had to
2 evacuate the floor once the autoclave was opened, so
3 it was a safety hazard, as well. And lastly, the
4 method should be practical, optimally fitting into
5 existing cleaning, disinfection, and sterilization
6 practices at either medical, dental, or other
7 facilities. Next slide, please.

8 In vitro methods today we believe are not
9 currently acceptable. There's wide variation and non-
10 correlation with in vivo data today. Variance in
11 published data is too contradictory to permit a prion
12 inactivation claim. Hence, an in vivo surface-based
13 test method we believe is recommended, and should be
14 based, as I said before, on the fact that normal
15 antimicrobial methods they had previously used.
16 Animal and prion test strains, the material should be
17 widely available, an ability to different --
18 formulation differences and different physical forms
19 of active agents, heat, liquid, and gas should be
20 considered, and you'll see why. I have some data that
21 you'll be interested in that shows the
22 differentiation. Next slide, please.

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1 STERIS has been working in this area for
2 about two to three years with the Commission of Atomic
3 Energy Prion Unit Laboratory outside of France, which
4 is equivalent to the CDC for that particular area in
5 Paris. And collaborated on a modification of method
6 first used by Dr. Weissmann, and I think has been
7 talked about already today. And this is a methodology
8 that consists, and I won't belabor you with this
9 complicated slide, but it consists of a stainless
10 steel wire that you've heard before, air dried
11 overnight, and then contaminated in a serial dilution
12 and implanted into the animal. And then the animal --
13 this happens to be a scrapie bottle of 263K in
14 hamster, and was left there for at least 365 days, or
15 until the animal demonstrates neurological problems.
16 All these animals, then histopathology is done on them
17 to confirm the presence or absence of PrP. Next
18 slide, please.

19 We believe that the formulation effects
20 are very important, as demonstrated in this slide. I
21 think there was some talk by the panel about enzymatic
22 cleaners. Not all enzymatic cleaners are equal, as

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1 this slide will show you. Enzymatic cleaner number
2 one actually decreased. Now this particular
3 experiment showed that in a porous load autoclave in
4 197 was the time to mean death, which equated to about
5 a 5.5 log reduction. When enzymatic cleaner number
6 one was used, and these are commercial products on the
7 market that are being used in hospitals every day, it
8 went down to three. Enzymatic cleaner number two was
9 used, it was 6.5, so it had an effect. And then you
10 can see the alkaline cleaners, not unexpectedly,
11 performing. Certain alkaline cleaners will give you
12 very high log reductions. And of course, this batch
13 marries with the control, where the animal did not
14 have any treatment at all. Next slide, please.

15 We thought it would be interesting to show
16 the effect of liquid versus gas in the physical state
17 of the chemistry, and this goes back to the concept of
18 formulation, as well. This slide shows that similar
19 results can be observed depending on the physical
20 state of the active reading. They could be quite
21 varied. The example given is hydrogen peroxide, which
22 is in a gas phase, especially under vacuum conditions,

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1 increases the penetration of gas, was rapidly
2 effective against prions, as you can see here. Less
3 so, but effective there.

4 Now isn't it very interesting, the
5 physical state here of the liquid, same chemistry, was
6 nowhere near as effective. And here again, as a
7 control, because this gas didn't have an effect. So
8 in contrast, liquid or condensed hydrogen peroxide was
9 not effective while the vapor phase was. This appears
10 to be due to clumping, we believe, as shown in the
11 western block in contrast of protein degradation in
12 the gaseous state. You see here, there's nothing
13 there. You can go to the next slide.

14 Lastly, we thought that it would be
15 interesting. There was some discussion on the
16 specificity of strain, the importance to determine
17 whether the method was going to be a validated method
18 or not, so we did a study with the same group again in
19 which it compared scrapie with BSE and the transgenic
20 mouse model. This testing was conducting, BSE test
21 strains in comparison to the proposed scrapie model.
22 These results would suggest that the tests of

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1 decontaminated methods were equally effective against
2 each test strain and model.

3 So, in other words, if you look at this
4 versus these, as you will see over here, these are
5 showing all zeros, likewise, and down here, of course,
6 you're getting the kind of results that you would
7 expect with that particular -- and 134 degrees for 18
8 minutes is not an uncommon cycle that's used in the
9 hospitals. As a matter of fact, this is a very common
10 cycle, and one that's recommended for everything but
11 prion decontamination.

12 It's still possible to have similar type
13 of bacterial virus activities. The prion strains may
14 demonstrate subtle differences in resistance to
15 chemical, thermal and activation. So in other words,
16 it's like we see in a virus or a bacterial strain,
17 there is a most resistant strain in most cases in I'll
18 say a spore, and each technology will have a more
19 resistant strain. In this case, I think this is true,
20 too, and I think it would be unwise to say that a
21 particular prion strain is effective for a particular
22 technology. They should be aligned with the

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1 technology in use, because in one case scrapie may be
2 more resistant to that technology, where in another
3 case BSE may be more resistant to the other
4 technology. So what I'm saying is that you have to be
5 flexible. And let me give you an example in the
6 sterilization world.

7 In sterilization, if you were to use let's
8 say vapor hydrogen peroxide, you're going to use
9 bacillus stearothermophilus as your test because it's
10 most resistant, and you will be use bacillus Atrophius
11 in the case of seeing, because here again, that's the
12 most resistant organism. So to say that one, in this
13 case, prion agent is more effective than the other as
14 an indicator, we don't believe is appropriate. It
15 should be as CDRH today mandates, the most resistant
16 organism should be used for that particular problem.
17 And it should be demonstrated it is so for that
18 particular problem.

19 Despite this, the scrapie model can be
20 practically and routinely used in most research labs,
21 and we recommend it highly due to the simplicity and
22 use of normal non-genetically altered animals. There

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1 are very few labs who can do transgenic mice studies,
2 whereas, there's much greater availability of the
3 scrapie. Just one more slide and I'll be done.

4 Lastly, in this particular, you will see
5 that we have looked at -- the people from CRH today
6 were talking about stainless steel versus plastic and
7 other things. We've started a study, it's not
8 completed yet. These further studies are underway to
9 validate the proposed test method, including
10 investigations of various test surfaces, and various
11 prion strains. The slide represent some preliminary
12 studies with plastic versus stainless steel. Both
13 materials appear to equally absorb prions infectivity
14 to the surface at two different dilutions, as well as
15 adequately decontaminating using a formulated cleaner.

16 It should be noted that a formulated
17 cleaner, this particular formulated cleaner is
18 currently labeled and in use in Europe as a Class 1
19 device, reducing the risk of prion contamination on
20 surfaces. I thank you for your time.

21 CHAIRMAN EDMISTON: Thank you, Dr. Burke.
22 Are there any questions for Dr. Burke from the panel

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1 members, please? Dr. Telling.

2 DR. TELLING: So actually just a comment
3 from the enzymatic treatment, a question related to
4 the presentation from the Collins Group earlier from
5 this year which were not commercially available
6 enzymatic cleaners. This is a combination of pronase
7 and proteinase K with SDS, but I have a question about
8 your transmission studies with BSE, or at least a mass
9 adapted variance of BSE into transgenic models over-
10 expressing PLP, so you've got a significant species
11 variant there. And in your data, I didn't see any
12 positive controls for transmission.

13 DR. BURKE: Well, there are. I mean, in
14 ten minutes, obviously, I couldn't present all the
15 data we have. There is a wealth of data. Number one,
16 the scrapie model, if you go to the Lancet publication
17 about eight months ago, the same study protocol that
18 was published in Lancet, has been used as the basis
19 for the BSE studies, so there are controls there.

20 I knew in ten minutes I was going to be
21 very rushed, so I tried to put together as limited
22 information as possible. But you're quite correct,

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1 that needs to be there, and that data is available.
2 I'll be happy to supply it to the panel.

3 DR. TELLING: Which Lancet paper are you
4 referring to?

5 DR. BURKE: Would you go back to the
6 middle slide. It has it on there. Forchette, et al,
7 2004, Lancet, 364:521-526.

8 DR. TELLING: This is from the French
9 group?

10 DR. BURKE: Excuse me?

11 DR. TELLING: From the French group?

12 DR. BURKE: Yes. That's correct.

13 DR. TELLING: Okay.

14 CHAIRMAN EDMISTON: Dr. Lurie.

15 DR. LURIE: Thank you very much. We heard
16 earlier from Mr. Brown about the statistical modeling.

17 What kind of animal numbers does your company feel is
18 sufficient to be able to make the claim that we're
19 supposed to be addressing of reducing TSE infectivity
20 from your formulating cleaner, or any other cleaning
21 method?

22 DR. BURKE: What we did at each

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1 concentration level, we used 12 animals, which we
2 thought was from a statistical point of view, an
3 appropriate number. And I think it's pretty standard
4 by most prion workers, because of the total number of
5 dilutions you must do.

6 DR. LURIE: We heard earlier I think it
7 was 300 animals would be needed to make the claim that
8 it was a more effective system, or with an element of
9 certainty. Is 300 animals a huge burden for a company
10 like your's?

11 DR. BURKE: I think 300 animals pushes the
12 limit of any laboratory would be willing to do from a
13 human rights perspective, as well as many other
14 considerations. So I would think that 300 for each
15 one of the dilutions that would be required, that
16 would be excessive. I'm not saying 12 is a perfect
17 number. I'm not a professional statistician. I could
18 certainly bring one in to talk to you about that from
19 our group, but 12 is a standard number in this
20 industry. And I think that if guidance was given that
21 a greater number was required, then I think that would
22 be appropriate, as long as it has balance to it. To

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1 get to 99 percent like the chart I saw this morning of
2 300, I think is excessive, and I'm not sure for the
3 extra say 200 animals, that you're buying a whole lot
4 for your dollar.

5 CHAIRMAN EDMISTON: I believe the FDA
6 wants to clarify that.

7 DR. RUSSEK-COHEN: The FDA was not saying
8 the particular sample size, but we wanted everybody to
9 be realistic about -- the FDA was not saying it had to
10 be 300 animals, but we wanted to be realistic, but
11 some people would like to say wow, I really want to be
12 sure that no animal will ever die as a result of the
13 treatment. And what we're saying is that kind of a
14 claim, it probably would take that kind of treatment.

15 It would be up to the panel to decide what magnitude
16 of effect is considered satisfactory, and then the
17 sample size would come after that.

18 CHAIRMAN EDMISTON: Thank you, Dr. Cohen.
19 Any further questions? Dr. Arduino.

20 DR. ARDUINO: Dr. Burke, on your studies
21 your end point was either death or no death. Did you
22 also do biopsies?

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1 DR. BURKE: Yes. Every animal that died
2 had a histopathology done on it. That's correct.

3 DR. ARDUINO: Even the survivors?

4 DR. BURKE: Yes.

5 DR. ARDUINO: Okay.

6 CHAIRMAN EDMISTON: Dr. Jarvis.

7 DR. JARVIS: Thanks for your presentation.

8 A question, FDA has raised the issue of the cage and
9 placement of animals. Can you describe what was done
10 in your experiments?

11 DR. BURKE: As typical in most cases,
12 those animals that were contaminated at various
13 concentrations were in the same cage. They were not
14 randomized, say a ten to the one randomized with a ten
15 to the ten, if that's your question. No, that was not
16 done.

17 CHAIRMAN EDMISTON: Dr. Telling.

18 DR. TELLING: I just want to be clear.
19 You say you used 12 animals be group.

20 DR. BURKE: Correct.

21 DR. TELLING: Basically incubation time
22 assays. Right?

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1 DR. BURKE: That's correct.

2 DR. TELLING: And then you're relating
3 that to a standard end point titration curve that you
4 also did in-house too, to get your log?

5 DR. BURKE: That's correct.

6 DR. TELLING: Okay.

7 CHAIRMAN EDMISTON: Are there any further
8 questions by -- please.

9 DR. MANGAIYARKARASI: You said the end
10 point is death or no death. For the no death cases,
11 when will you do the biopsy? I mean, when will you
12 kill the animal and do the biopsy?

13 DR. BURKE: We chose a period of 365 days.

14 DR. MANGAIYARKARASI: Sixty-five days?

15 DR. BURKE: Three hundred and sixty-five.

16 DR. MANGAIYARKARASI: Three hundred.

17 Okay. One year. Thank you.

18 DR. BURKE: In the hamster model, let me
19 qualify that.

20 CHAIRMAN EDMISTON: Any further questions
21 for Dr. Burke?

22 DR. ARDUINO: For each dilution, because

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1 you were titting out how much prions, how many
2 animals were done at each dilution? Was it just one
3 or another set of ten?

4 DR. BURKE: No, there was 12 done at each
5 dilution.

6 DR. ARDUINO: Twelve done. Okay.

7 CHAIRMAN EDMISTON: If there's no further
8 questions, then thank you very much. I'm sure we'll
9 have you up again. At this time, we'd like to ask Dr.
10 Marchand to join us. Please identify your
11 institution.

12 DR. MARCHAND: Hello. I'm Dr. Richard
13 Marchand. I am a medical microbiologist and
14 infectious disease specialist, Associate Professor of
15 the University of Montreal in the Department of
16 Microbiology and Infectious Disease. I've been
17 working on prion inactivation issues and prion-like
18 molecules as eventually surrogate markers for prion
19 inactivation. And actually, I'm scientific advisor to
20 TSO3, which is a company in Canada which makes an
21 ozone sterilizer, on behalf of which I'm here.

22 Now I would like to take these few minutes

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1 to guide you through some of the annual questions we
2 find in some of the model we have been discussing,
3 answers, or propose some of the answers, or some
4 answers to some of the questions that were asked to
5 the panel. And I would like to discuss mostly the
6 animal sensitivity issue, because it's an important
7 problem. A lot of presenters before me said, animal
8 models differ from one to the other, because the agent
9 cannot be seen, cannot be counted, the number of
10 copies to create the disease is not known, and what we
11 have experienced in the past is the same problem as we
12 did with viruses in the 40s, and the 60s, and the 50s.

13 At that time there was a model, what was
14 the infectious dose, 50, which is 50 percent fatality.

15 One of the problems we have also with prions which
16 are different from viral assays is that there is no
17 clean cut tail effect. This means that when we are --
18 in fact, what the hard fact is, is a sick animal.
19 When you have a healthy animal, you don't know if it's
20 bearing the disease and it will die, and some die
21 healthy in appearance of old age, but when you look at
22 their brain, they are infected. So the real hard fact

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1 is a sick animal. Next, please.

2 So when we look at different models with
3 bacteria, you can see that the number of minimal
4 copies, infectious copies to give a disease varies
5 according to different bacteria or viruses. Now for
6 prion, how many copies, of what is a minimal
7 infectious dose? Next, please.

8 These are the Karber Inactivation Kinetics
9 that were deadlocked in the 40s and the 50s. We were
10 making dilutions, and with these dilutions we were
11 seeing a reduction in infectivity. And that's the way
12 it was done. Now next, please.

13 If we look at some of the experiments,
14 especially the hamster model, which is the most
15 fluently seen, these data are carbon copied from a
16 German group that presented these. And I will try to
17 explain what is the problem with the sensitivity
18 model.

19 Here we have a 262K hamster model. The
20 extract is ten to the ninth. Maybe this works better
21 here. Okay, ten to the ninth infectious dose. Now
22 when you look at the mortality, 12 out of 12 dies in

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1 90 days. At ten to the seventh, 12 out 12 dies in 98
2 days. At ten of the sixth, 117, ten to the fifth,
3 124, ten to the fourth, 200 days, ten to the third,
4 around 200 days, so there is a kind of plateau there.

5 But if you look, the minimal infectious dose is
6 between here, around ten to the five. And if you make
7 calculations mathematic, it takes about six to eight
8 thousand molecules in this model to make sure that all
9 the animals are sick. Okay? So the minimal
10 infectious dose for 100 percent of the animals is
11 around six to eight thousand molecules.

12 When you go below that, what you see is
13 most of the time zero, but in some studies with the
14 same exact model, you see two or three of these
15 animals that will become sick, and generally most of
16 these studies stop or end at 365 days. But if you
17 look at some groups that maintain the same animals
18 over a two year period, you will see one or two
19 animals having the disease. That means that a healthy
20 animal at 365 days is not predictive of inactivation
21 of prions. Okay? Next, please.

22 This is the standard of Tg4053 mice.

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1 There you have the same type of curve, but it's
2 represented in a graph. Now if you look at this
3 model, you have the log of the quantity of infectious
4 dose, versus the number of incubation. And here what
5 you can see is that the minimal inoculation quantity
6 of molecules calculated on this slide scale here that
7 will give an incubation with 100 percent of animal
8 disease is about 600 molecules, not 6,000 or 8,000,
9 but 600 molecules. And the maximum or usual
10 incubation period will be around 95 days. So if you
11 compare these two models, you have let's say about a
12 ten-fold sensitivity in terms of molecules you need to
13 infect. Okay. Next, please.

14 Now under the minimal infectious dose to
15 kill 100 percent of animals, what you can see is that
16 the reduction is not linear with the dose, but when
17 you're under it, it's unpredictable. It's not a very
18 good predictive of inactivation, so the best way to
19 look at something is to look at sick animals, not safe
20 or healthy animals.

21 Now when you're still under this I.D. 100
22 percent infectious dose, you see that -- the

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1 infectivity rate seems to vary with each preparation,
2 and it varies also with the manipulation protocols
3 that you can see, and possibly with the moon, the
4 hormonal cycles of the animals and whatever, because
5 it's really unreliable. So once again I emphasize the
6 real hard data we can count on is a sick animal, not a
7 healthy one. Okay? And sometimes the incubation
8 period may be years. Next, please.

9 Now we've seen this previously. I would
10 like to just mimic what happens if we use a process
11 that's reduced by four logs. Okay? Now let's say
12 that we don't know our original generally when we're
13 doing the research projects, but let's say that once
14 again it's a ten to the ninth inoculation ID50
15 extract, so when we begin with an unknown sample, we
16 make dilutions to make sure we can have the proper
17 measurement. So let's say this extract is diluted by
18 100,000 so forth, so you end up -- the containing
19 inoculum would be with the ten-fold dilution, ten to
20 the eight, hundred-fold dilution, ten to the seven and
21 so forth. What we would see with these inoculum is
22 ten of the twelve animals died by 90 days. It's

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1 exactly what I've said here, that's the way we do it,
2 and we can extrapolate according to the number of days
3 what was the inoculum initially. Next, please.

4 Do the same thing with a four logging
5 activation process, what would happen? Your inoculum
6 are here, ten to the eight, ten to the seven and so
7 forth. These are, remember, unknowns in reality. Now
8 after your process, you've taken away four logs from
9 the ten to the eight, so the incubation time would be
10 201 days, with the ten to the seventh dilution, after
11 a four log process, we would have ten to the third,
12 which would be around 200 days, maybe one or two
13 animals, maybe at 200 days that would be sick. And
14 for the remaining of the one, one of them would be
15 sick at 365 days. This would mean for a lot of people
16 that this process could give a kind of safety
17 measurement, but we know that we still have a fairly
18 good amount of infectious dose in there. Next,
19 please.

20 But we don't know exactly when we do it
21 with dilutions what's in there, so if we look at these
22 post process inoculums, because we don't know what's

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1 the amount, and we don't know what we would give to
2 the animals, we would make post exposition dilutions
3 again, and with the incubation period we would be, as
4 noticed here, would be 201 days or over 365 days. So
5 once again, if you have this dilution method, and you
6 have a very low sensitivity at the end, you can expect
7 to see living animals that look fairly healthy.

8 Now just imagine that you will have a 4.5
9 log process, and all these animals here would be
10 healthy at 365 days. And in the mindset of medical
11 personnel, the conclusion would be the process is
12 fairly okay to inactivate all the prions, because this
13 animal model needs a lot of dose, infectious model
14 dose to get the disease. Next, please.

15 Now do the same thing with the Tg4053
16 model, which is a more sensitive model, you will make
17 the same types of dilutions. And now you look at the
18 mortality rate and the number of days, you have
19 heterozygote and homozygote, which means here if you
20 look at heterozygote is that you can see the reduction
21 with time, or the increase in the period of incubation
22 with time. Next, please.

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1 Now if you did it in a four log process
2 inactivation, you start from ten to the eighth, to ten
3 to the fourth, the incubation period is 76 days.
4 Where the second here with this inoculum would be 90
5 days with one more maybe not an animal sick, and all
6 the remaining animals would be healthy at 90 days.
7 Okay. This means that with this again curve - next,
8 please - higher is the capability of inactivation,
9 higher must be the sensitivity of the model in order
10 to make sure that there is no residual infectivity.

11 In other words, no one can be sure of high
12 level of inactivation with a low sensitivity model.
13 Okay? A 365-day study with the sensitive mice is more
14 than a two-year study with a hamster because we need a
15 longer and longer period to manifest the disease. And
16 when you use a high sensitivity model, level of
17 inactivation can be achieved. The object here is what
18 is an acceptable level of inactivation that we need.

19 CHAIRMAN EDMISTON: Thank you, Dr.
20 Marchand. Are there any questions for Dr. Marchand,
21 please? Dr. Grammar.

22 DR. GRAMMAR: Yes. When you say

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