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UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE

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DEVELOPING U.S. PUBLIC HEALTH SERVICE  
POLICY IN XENOTRANSPLANTATION

- - -

MEETING

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THURSDAY, JANUARY 22, 1998

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The meeting was held in the Natcher  
Conference Centre, National Institutes of Health, 9000  
Rockville Pike, Building 45, Bethesda, Maryland 20892,  
at 8:30 a.m., Amy P. Patterson, M.D., Chair,  
presiding.

PRESENT:

WILLIAM F. RAUB, PhD	Deputy Asst. Secretary
AMY P. PATTERSON, M.D.	Chair
ELETTRA RONCHI, M.D.	Moderator
LEROY WALTERS, PhD	Moderator
CLARA J. WITT, M.D.	Moderator
RACHEL ARRUNDALE	Panelist
HUGH AUCHINCLOSS, JR., M.D.	Panelist
ANTONIO BENEDI	Panelist
ALAN H. BERGER	Panelist
LOUISA CHAPMAN, M.D., MSPH	Panelist
JOHN M. COFFIN, PhD	Panelist
JONATHAN H. DARK, M.D.	Panelist
LILY O. ENGSTROM, MS	Panelist
ROGER W. EVANS, PhD	Panelist
RONALD M. FERGUSON, M.D., PhD	Panelist
JAY A. FISHMAN, M.D., PhD	Panelist
TOM FOLKS, PhD	Panelist
MICHAEL FRIEDMAN, M.D.	Panelist
ROGER R. GANZ, PhD	Panelist

1 PRESENT: (continued)

- 2
- 3 MARY GROESCH, PhD Panelist
- 4 DONNA HENRY Panelist
- 5 HAROLD W. JAFFE, M.D. Panelist
- 6 STEWART S. JESSAMINE, M.D., CHB, DPH Panelist
- 7 JEAN J. JULVEZ, M.D., PhD Panelist
- 8 ANDRE LA PRAIRIE Panelist
- 9 CAPTAIN MELODY H. LINN, PhD Panelist
- 10 MARIAN G. MICHAELS, M.D., MPH Panelist
- 11 PHILIP D. NOGUCHI, M.D. Panelist
- 12 JEFFREY L. PLATT, M.D. Panelist
- 13 ERNEST D. PRENTICE, PhD Panelist
- 14 STEPHEN M. ROSE, PhD Panelist
- 15 DANIEL R. SALOMON, M.D. Panelist
- 16 JAY P. SIEGEL, M.D. Panelist
- 17 ANNIKA TIBELL, M.D., PhD Panelist
- 18 HAROLD Y. VANDERPOOL, PhD, ThM Panelist
- 19 KATHRYN C. ZOON, PhD Panelist

20

21 ALSO PRESENT:

- 22
- 23 FRITZ BACH, M.D.
- 24 DR. MARGARET SOMERVILLE

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1 PROCEEDINGS

2 Time: 8:39 a.m.

3 MODERATOR SKIRBOLL: Good morning. This  
4 morning we're going to continue our discussion of the  
5 public policy issues related to xeno with a discussion  
6 of the ethical, legal, and social framework for this  
7 technology.

8 Many, I think, people might say this  
9 morning, in light of what's been happening in the  
10 newspapers with cloning, that xenotransplantation is  
11 perhaps just another new technology that stimulates a  
12 myriad of issues related to ethical, legal, and social  
13 issues; but in fact, I think, many of us here who are  
14 familiar with this arena would say that xeno poses  
15 some specific and unique ethical problems that deserve  
16 discussion here today and deserve broader discussion  
17 in the future.

18 These issues, such as societal  
19 risk/benefit, confidentiality, informed consent,  
20 involving not only the patient but the community at  
21 large, I'm sure, will be discussed here this morning.

22 Fortunately, scientists, the public,  
23 public advocacy groups, ethicists are not new to  
24 fruitful and public discussion of issues around  
25 emerging and ongoing science. I think you will hear  
26 later today in a part of the public policy  
27 presentation that the Public Health Service has been

1 considering this in light of our history with  
2 recombinant DNA and the RAC, in the formulation of  
3 future oversight in public policy around  
4 xenotransplantation.

5           Right now this morning, we are  
6 distinguished to have two very distinguished speakers  
7 and an illustrious panel to raise these issues, but we  
8 don't have long for a myriad, as I said, of very  
9 important issues this morning.

10           So lest you think that the only way we're  
11 going to get to every ethical, legal and social issue  
12 around xenotransplantation -- the only way we could do  
13 that is if we had the guy from the TV ads for Tyson's  
14 Corner Center who did 100 retailers in 60 seconds,  
15 that won't work here this morning.

16           So we will try to get as many of the  
17 issues out on the table. As we get them out on the  
18 table, obviously, this is not the place where we're  
19 going to solve them all. However, we would like to  
20 have a focused discussion of some specific issues, and  
21 we would like to have an opportunity for our two  
22 speakers to speak, for our panelists to speak, and at  
23 the end to have some opportunity for some people from  
24 the floor.

25           I know there are several very anxious  
26 people who are interested in having an opportunity.  
27 So what we're going to try to do this morning is to

1 try to end the panel discussion and our speakers by  
2 9:30, which will give us 15 minutes for speakers from  
3 the floor and as many of them as we will have time to  
4 fit in, so that we will have adequate time for  
5 discussion and, hopefully, some time for our panelists  
6 to come back and respond to some of the speakers from  
7 the floor.

8           So as long as we all understand the ground  
9 rules, let me move forward. Our first speaker this  
10 morning is Dr. Harold Vanderpool. Dr. Vanderpool is  
11 probably familiar to many of you.

12           He is a Professor of History and  
13 Philosophy of Medicine at the Institute for Medical  
14 Humanities at the University of Texas in Galveston  
15 where he teaches medical ethics. He lectures widely  
16 and has written on medical ethics, and speaks often on  
17 the roles of religion, science, and medicine in  
18 America.

19           Of particular note to us this morning, he  
20 has recently served on the IOM committee on xenograft  
21 transplantation. So I welcome Dr. Vanderpool, and  
22 again fair warned is fair armed where, no matter how  
23 good your oratory this morning, Leroy and I are going  
24 to keep everything moving. Thank you.

25           DR. VANDERPOOL: Thank you very much. I  
26 commend the FDA, the NIH and others for these  
27 excellent meetings, this public forum in which we can

1 talk about both the science and ethics, as well as the  
2 public policy regarding xenotransplantation.

3           The ethics of clinical trials with whole  
4 organ xenotransplants encompasses fascinating and  
5 serious ethical issues. Widely discussed issues  
6 include whether xenotransplants in humans violates the  
7 laws of nature (natural law), whether they wrongfully  
8 require animals to be sacrificed as sources for  
9 humans, whether they will expend precious medical  
10 resources unjustly on a few persons to the neglect of  
11 basic care for many, and whether they will endanger  
12 public health.

13           The last of these issues is particularly  
14 worrisome because of discoveries regarding the  
15 initiating factors for the AIDS epidemic and recent  
16 findings over the capacity of endogenous retroviruses  
17 in porcine tissue to infect human cells in vitro.

18           While these issues, especially the last,  
19 merit further discussion, four additional crucially  
20 important ethical issues have, I believe, been  
21 neglected. I should mention at the outset that I do  
22 not regard dealing with these issues as particularly  
23 daunting, such that they should delay the pace of  
24 present research and development. They are,  
25 nevertheless, both timely and essential.

26           The four critical issues that I will now  
27 identify and examine briefly include the following:

1 That whole organ and vasculated animal tissue  
2 transplants in human subjects call for considered  
3 judgments regarding permissible harm/benefit  
4 thresholds for the initiation and, more accurately  
5 put, the resumption of clinical trials involving human  
6 subjects; raise questions regarding the need to secure  
7 informed consent for medical personnel, patients'  
8 close contacts, and possibly other groups; adds  
9 serious difficulties to the securing of informed  
10 consent from research subjects; and raise problems  
11 with respect to how clinical trials should be governed  
12 and approved.

13           The urgencies of these issues runs counter  
14 to the widely held assumption that the future risks of  
15 xeno genetic infections completely overwhelms all  
16 other issues.

17           The first issue involved the imperative of  
18 making considered judgment with respect to permissible  
19 harm/benefit thresholds for the resumption of clinical  
20 trials with xenotransplants.

21           To express this issue in a form of  
22 questions, what should the balance be between expected  
23 harms and benefits of transplanted organs in order for  
24 clinical trials to be ethically permissible? What  
25 harm/benefit threshold or thresholds for human  
26 subjects should we have in mind as one of the moral  
27 justifications for the initiation of clinical trials?

1                   At the present time, suppositions about  
2 these risk/benefit thresholds are variable and  
3 uncertain. Consider the views and suggestions of  
4 various authors.

5                   In 1992 a team of Polish surgeons  
6 justified transplanting a pig's heart into a human  
7 subject in order to extend the 30-year-old man's life,  
8 because no allogenic transplant was available, and  
9 they surmised that they could overcome hyperacute  
10 rejection. The man survived for 23 hours.

11                   In 1933 Pearson and others asserted that  
12 a clinical definition of "success" is vital, because  
13 before cardiac or other xenotransplants should be  
14 attempted, they proposed that "the median survival  
15 time of weeks to months should be established as the  
16 goalpost, making attainment of a reasonable likelihood  
17 of clinical efficacy.

18                   More recently, Plant has suggested that,  
19 while hyperacute rejection can now be prevented,  
20 clinical xenotransplants will remain problematic until  
21 additional barriers of acute vascular rejection and  
22 cellular and humoral reactions to donor antigens are  
23 understood and overcome.

24                   In the same spirit, Bach and others have  
25 argued that porcine xenotransplants with human  
26 subjects should not be attempted until prolonged  
27 survival and "documented long term function" is

1 achieved with nonhuman primates.

2           Stiel and Auchincloss propose that  
3 xenotransplants should not be undertaken until  
4 patients who are too sick to be candidates of  
5 allografts can be given xenografts that offer "at  
6 least the equivalent hope of success to any  
7 allotransplant they might otherwise receive."

8           The diversity of these proposals displays  
9 a lack of consensus regarding the critical issues of  
10 thinking systematically about the morally justifiable  
11 risk/benefit thresholds for the resumption of clinical  
12 trials with animal to human transplant. The only  
13 discussion I've ever heard of this occurred yesterday  
14 within the panel.

15           Unfortunately, I've discovered that only  
16 two articles expressly deal with the question, what  
17 defines successful xenograft transplantation? As  
18 indicated by the physician authors of the articles  
19 just surveyed, the necessity of thinking about  
20 risk/benefit thresholds for xenotransplants is being  
21 voiced in the medical literature, which,  
22 interestingly, cannot be said about a number of  
23 different nonphysicians who have written articles  
24 about the "ethics of xenotransplantation."

25           Discussions of this issue are, therefore,  
26 mostly found in articles that focus on the scientific  
27 base of xenotransplantation, the authors of which are

1 sometimes unaware of the ethical underpinnings to the  
2 subject that they call "scientific or logistical."

3           This inextricably science, medical,  
4 ethical issue is more complex and more fascinating  
5 that it might first appear. It encompasses at least  
6 three factors that must be played off against one  
7 another: Scientific/medical feasibility; clinical  
8 urgency -- that is, the dire medical circumstances of  
9 patients facing no other therapeutic alternative; and  
10 the prospects of scientific discovery within the  
11 clinical trial framework.

12           Should xenotransplants be moved into  
13 clinical trials in ways similar to the trials, errors  
14 and eventual success of allotransplants? This is one  
15 of the questions that needs to inform our search for  
16 greater coherence and consensus with respect to likely  
17 scenarios involving experimental xenotransplants with  
18 human subjects.

19           Now the likely scenarios I have in mind  
20 should not be viewed as some way prophetic markers  
21 written in stone, but rather they should be both  
22 realistic and possibly very imaginative scenarios that  
23 will elicit critical thinking about what we have in  
24 mind when we talk about approving trials with respect  
25 to the balance between clinical workability and  
26 medical urgency and scientific discovery.

27           Without thoughtful deliberation about such

1 benchmark scenarios, as well as imaginative ones, the  
2 pivotal prerequisite of predicating ethically  
3 acceptable clinical trials on clearly defined and  
4 compared risks and harms may well be overlooked by  
5 local review committees, which has been the case --  
6 was the case in Poland -- and bring discredit to  
7 xenotransplant researchers and clinicians.

8           The second issue, informed consent from  
9 third parties such as patients' close contacts and  
10 family caregivers, as well as medical professionals,  
11 has been identified but rarely explored.

12           The draft guidelines of the U.S. Public  
13 Health Service opt for education over consent for  
14 third parties. They say that research subjects should  
15 follow a detailed plan that will enable each "to  
16 educate his/her close contacts regarding the  
17 possibility of the emergence of xeno genetic  
18 infections." Medical personnel must also be educated  
19 about the risk of infection, the precautions that  
20 should be taken, and so on.

21           These laudable accents on education do not  
22 negate arguments in favor of informed consent for  
23 certain third parties. I'll just make the arguments,  
24 because I think the discussion is still quite open-  
25 ended. The decisions are quite open-ended.

26           First, informed consent serves as a way to  
27 protect researchers and medical institutions from

1 harms of legal suits that could arise from medical  
2 personnel in close contacts of patients who might  
3 claim that they were never told about the risk they  
4 incurred.

5           Second and more centrally, clinical trials  
6 of xenotransplants directly affect and intervene into  
7 the lives of the patients' close contacts, who must do  
8 things to assure the success and safety of the  
9 research, including willingness to undergo serum tests  
10 and so on.

11           Since informed consent is predicated on  
12 the ethical principle of respecting the views and  
13 choices of others, as we would want to be respected,  
14 are we not morally obligated to approach these parties  
15 personally in order to secure their compliance with  
16 and commitment to the roles they are expected to play?

17           Third, consider confidentiality. The  
18 Public Health Service drafted guidelines say that  
19 baseline serum samples should be drawn from all  
20 medical personnel who deal with research subjects and  
21 from personnel who handle any of the human and/or  
22 animal tissues, cells and organs related to  
23 xenotransplants.

24           These samples are to be stored and subject  
25 to surveillance by two Federal agencies. Should not  
26 the consent of these medical workers be requested  
27 after they are told who will have access to their test

1 results, for how long, and what will happen if the  
2 serum tests reveal, for example, they have a  
3 problematic or embarrassing infection? Maybe this  
4 just goes with the medical territory, but the issue  
5 needs to be discussed.

6           Study groups need to explore the pros and  
7 cons of informed consent for third parties -- this was  
8 done briefly at the December 17 meeting of the FDA --  
9 in light of some of the questions I've raised, as well  
10 as in light of the ethical principles set forth in the  
11 Belmont report.

12           Unfortunately, the third and fourth  
13 issues, informed consent for research subjects and the  
14 approval and oversight of clinical trials, are  
15 sometimes mentioned in passing as well recognized  
16 standard issues. This detracts from their receiving  
17 the attention I believe they deserve.

18           Informed consent in clinical trials with  
19 xenotransplants needs to be thoroughly examined,  
20 because the challenges of fully informed consent in  
21 these trials may exceed those of any known research  
22 setting, including Phase I cancer chemotherapy trials.

23           The prospective subjects of xenotransplant  
24 research are likely to be sick or very sick, and  
25 desperate to have their lives extended. Nevertheless,  
26 to respect their autonomy they will need to hear  
27 about, understand, weigh, and make decisions about a

1 host of complex concerns, either/or themselves or  
2 their proxy.

3           These include understanding the stage of  
4 xenotransplant research, including discussions about  
5 mortality and quality of life data from previous  
6 experiments, the likelihood of media attention and  
7 compromised confidentiality, the risks and discomforts  
8 of contracting and dealing with opportunistic  
9 infections, information about the subject's risks of  
10 developing animal mediated or possibly genetically  
11 created infections and of transmitting these to  
12 others, the requirement of adhering to a schedule of  
13 frequent, long term or lifelong medical surveillance,  
14 of allowing public health agencies to access all of  
15 one's medical records, and of consenting to a complete  
16 autopsy at the time of death, the responsibility of  
17 educating one's close contacts about the risks of and  
18 ways to control for infections, and detailed  
19 information about the trying and sometimes traumatic  
20 psychological effects of immunosuppressive drugs.

21           Concerned over some of these complexities  
22 and over the possibility that overzealous surgeons  
23 will continue to underestimate the risks and  
24 exaggerate the benefits of these operations, the  
25 United Kingdom Nuffield Council recommends that the  
26 consent of subjects should be secured by "trained  
27 professionals who are independent of the transplant

1 team."

2                   I view this as a distrust driven policy  
3 that would keep surgical teams and their patients'  
4 subjects from openly and mutually dealing with the  
5 many faceted human dimensions of xenotransplants.  
6 Essential features of the content and process of  
7 informed consent should be set out as guidelines based  
8 upon a thorough understanding of moral autonomy, the  
9 circumstances of prospective recipients, the self-  
10 interest of researchers, for profit economic  
11 pressures, and the pros and cons of various approaches  
12 to informed consent.

13                   In addition to the specialists specified  
14 in the Public Health Service draft guidelines, every  
15 transplant team should, I believe, include a  
16 psychological counselor, and the process of consent  
17 should be spelled out by each protocol that is  
18 approved.

19                   Now some IRBs will handle these issues far  
20 better than others, but I think guidelines are very  
21 important, given the complexities of informed consent  
22 in this setting. I think it's a mistake by the  
23 authors of a very recently published article that  
24 things like extended compliance are imposed on  
25 research subjects.

26                   They will not be imposed if informed  
27 consent is observed. That's what informed consent is,

1 to inform people what the risks, benefits, problems  
2 are for becoming an experimental subject. Imposition  
3 should not be the question.

4           The fourth and final issue encompasses at  
5 least three sets of questions. I understand from Dr.  
6 Walters that he will be dealing with issues involving  
7 governments in greater detail, but the first question  
8 of which has been discussed at greater length than the  
9 others.

10           First, who should be responsible for the  
11 oversight and approval of clinical trials? Should the  
12 governance of xenotransplant research be exercised by  
13 local IRBs, a national committee, or some mixture of  
14 the two?

15           While the bottom line solution to this  
16 question will likely entail turf battles over power  
17 and control, it should reflect a carefully considered  
18 answer to the following ethical question. Which group  
19 or groups will best foster concern, protection and  
20 respect for human subjects and a commitment to balance  
21 possible harms to the public with possible benefits to  
22 persons in dire need?

23           Good reasons support the view, and this is  
24 the view I hold, that a national body -- at the  
25 present time, the FDA -- should establish mandatory  
26 rather than advisory guidelines for the make-up,  
27 resources, standards of approval and monitoring of

1 local review committees that would themselves conduct  
2 hands-on reviews of xenotransplant protocols.

3           Too many tiers of review or re-review, in  
4 my judgment, is problematic for a variety of reasons,  
5 some of which we may wish to discuss at time of the  
6 panel discussion.

7           Second, what issues should be addressed in  
8 the guidelines that are developed? While they should  
9 deal with the dangers of infectious disease, they  
10 should also expressly address the three critical  
11 issues I've just discussed.

12           The U.S. Public Health Service deserves  
13 praise for explicitly recommending the use of the  
14 Belmont report in its draft guidelines. Nevertheless,  
15 the interconnections between clinical trials with  
16 xenotransplants and the ethical principles and  
17 suggested applications of these principles in Belmont  
18 are far from obvious and should not be left merely to  
19 chance.

20           Third, what should guidelines for  
21 xenotransplant clinical trials require with respect to  
22 the membership of oversight committees? Because the  
23 decisions of these committees will hinge on  
24 understanding the complex cognitive and emotional  
25 needs of prospective subjects, committee members  
26 should include a mental health professional.

27           Furthermore, in addition to the other

1 specialists, surgeons, scientists, veterinarians and  
2 so on, specified in the Public Health Service  
3 guidelines -- furthermore, to be able to define and  
4 make reasonable determinations with respect to the  
5 risks and benefits of xenotransplants to recipients,  
6 each oversight committee should review protocols in  
7 consultation with former transplant patients until  
8 there is a sufficient literature on patients' points  
9 of view.

10                 This might or might not mean that former  
11 patients should be standing members of IRBs. The  
12 availability of consults from scholars in research  
13 ethics and religious traditions should also be  
14 considered.

15                 Why do the harm/benefit determinations  
16 required of review committees call for personal and/or  
17 social scientific based input from former transplant  
18 patients? Because every definition and assessment of  
19 risks and possible harms is inextricably derived from  
20 some frame of reference, the adequacy of which depends  
21 on the knowledge, experience, degrees of empathy and  
22 personal agendas of those who are doing the  
23 evaluating.

24                 Furthermore, the assessments of oversight  
25 committees needs to be informed by patients, because  
26 the patient subjects are the ones who will be  
27 undergoing the experimental procedures which are, in

1 turn, predicated on what they have to lose and hope to  
2 gain.

3           As a recipient's best spokespersons,  
4 former transplant patients should, therefore, have a  
5 say in what should count as the risks and benefits.  
6 I suspect that they will raise the risk/benefit ratio  
7 in regard to greater risks, as well as what levels of  
8 risk vis a vis possible benefits would be reasonable.

9           As pressures build for the initiation of  
10 new clinical trails with xenotransplanted organs in  
11 vasculated tissue, it is imperative that the four  
12 pivotal issues I've discussed are thoroughly explored  
13 and acted upon. As I say, these are not daunting  
14 questions, but they are questions to, certainly,  
15 consider here and beyond.

16           Without attending to these issues,  
17 clinical trials with xenotransplants could begin to  
18 erode the long and arduous efforts to uphold the  
19 rights of research subjects and secure the public's  
20 trust in and participation in medical research.

21           Thank you.

22           MODERATOR SKIRBOLL: Now I take pleasure  
23 in introducing my co-chair, Dr. Leroy Walters. Dr.  
24 Walters is Director of the Kennedy Institute of Ethics  
25 at Georgetown, where he is also a professor of  
26 philosophy. He has written and lectured widely on  
27 many issues related to medical ethics.

1                   He is eminently qualified to lead our  
2 discussion today of the ethical, legal and social  
3 issues related to xenotransplantation. Dr. Walters --  
4 I know Dr. Walters as the Chair of the NIH RAC for  
5 four years, where I was able to observe firsthand his  
6 considerable skill at leading broadbased discussions  
7 of science, ethics, and safety issues around  
8 developing technology. Dr. Walters.

9                   DR. WALTERS: Thank you very much, Dr.  
10 Skirboll.

11                   I had originally planned to discuss four  
12 topics this morning, but I've decided to discuss just  
13 the first of the four. So let me mention the four,  
14 and then focus on the first.

15                   The first topic is public oversight for  
16 xenotransplantation in the United States. That's the  
17 topic on which I will focus this morning.

18                   I had also hoped to say something about  
19 the moral justification for using nonhuman animals in  
20 xenotransplantation research, but that topic will  
21 surely be discussed by our panel, and it's been very  
22 well discussed in the three major reports on this  
23 subject, the one by the Nuffield Council in the U.K.,  
24 the one by the Institute of Medicine panel here, and  
25 the one by the Kennedy Committee in the United  
26 Kingdom.

27                   A third topic that I had considered

1 discussing was the selection of patients in the early  
2 clinical trials of xenotransplantation. Here, the  
3 trend in the reports to date has been to say that only  
4 adults should be involved in the early clinical  
5 trials.

6 I would agree with that judgment for Phase  
7 I studies, but based on work with gene therapy, I'd at  
8 least like to put the issue on the table of whether  
9 children should not reasonably be considered subjects  
10 in Phase II and Phase III clinical trials. I'd hate  
11 to see children excluded from the potential benefits  
12 of xenotransplantation.

13 Finally, there is a specialized topic  
14 related to neurotransplantation, both with  
15 xenotransplantation and with human fetal tissue. That  
16 is, whether the use of placebos is morally  
17 justifiable.

18 If you do a Medline search, you'll find  
19 that this is a very difficult topic to get at, and  
20 there's virtually no interdisciplinary discussion of  
21 this topic in the literature. If you look for sham  
22 surgery, for example, you'll find 131 studies of  
23 animals, but not a single human study, and yet there  
24 are studies underway with neurotransplantation of  
25 tissue from pigs, in particular, that have placebo  
26 controls. These are for Parkinson's Disease patients.

27 I think that that topic does deserve

1 public discussion.

2           Let me turn then to public oversight for  
3 selected areas of biomedical research in the United  
4 States and the United Kingdom from 1975 to the  
5 present, and that provides a backdrop then for what I  
6 think are some lessons from this 25-year or so period,  
7 and I will conclude with a few suggestions for the  
8 future.

9           I think the current situation with  
10 xenotransplantation parallels three earlier episodes  
11 in the recent history of biomedical research. The  
12 first was the debate about the potential risks of  
13 recombinant DNA research in the early 1970s.

14           The second was the public discussion of in  
15 vitro fertilization after the birth of Louise Brown in  
16 1978. The third was the preparation for the first  
17 clinical trials of human gene transfer or human gene  
18 therapy in the late 1980s and the early 1990s.

19           In the first case, a committee established  
20 by the National Institutes of Health, the Recombinant  
21 DNA Advisory Committee which we all now know  
22 affectionately as the RAC, developed guidelines for  
23 laboratory research, and these guidelines came to have  
24 the force of de facto regulations.

25           Only a few types of experiments were  
26 prohibited, but some studies had to be conducted under  
27 such strict containment procedures that the studies

1 were, in fact, delayed by several years.

2           The RAC reviewed virtually all recombinant  
3 DNA research at the beginning. Then as risk  
4 assessment data were accumulated, the RAC gradually  
5 handed over review responsibility to local  
6 institutional biosafety committees.

7           Five years after the publication of the  
8 1976 NIH guidelines for recombinant DNA research,  
9 virtually all laboratory research with recombinant DNA  
10 was being reviewed at the local level. So stringent  
11 guidelines early on, gradual confidence that the risks  
12 were quite small, and gradual decentralization of the  
13 review process.

14           On clinical in vitro fertilization and  
15 research with early human embryos, the United States  
16 and the United Kingdom have adopted remarkably  
17 different strategies for public oversight. The U.S.  
18 had a very early committee, the Ethics Advisory Board  
19 of the Department of Health, Education and Welfare,  
20 and that name reminds us that this happened quite  
21 sometime ago.

22           Within ten months of Louise Brown's birth,  
23 the Ethics Advisory Board had published a  
24 comprehensive review of IVF and embryo research.  
25 However, public officials from both major political  
26 parties in the United States have found this topic to  
27 be so controversial that Members of Congress,

1 Secretaries of health related agencies, and even  
2 Presidents have largely avoided it.

3           In 1994, an NIH committee thought to  
4 revisit the issue of human embryo research, but the  
5 committee's recommendations were immediately qualified  
6 by the President, and soon thereafter rejected by the  
7 Congress.

8           The upshot of these developments is that  
9 all human embryo research in the United States is  
10 conducted with support of private funds and without  
11 any Federal oversight or public review.

12           Clinical IVF is conducted in a highly  
13 competitive private environment, subject only to state  
14 law and exhortations to ethical behavior developed by  
15 several professional organizations. I'm not opposed  
16 to ethical exhortations. I just wonder whether they  
17 alone are likely to be effective.

18           A private sector advisory group, the  
19 National Advisory Board on Ethics in Reproduction  
20 called NABOR for short, produced several helpful  
21 reports, but seems to have had only a minor impact on  
22 the practices of infertility clinics.

23           In contrast, the United Kingdom has  
24 developed a rather robust public system for overseeing  
25 assisted reproductive technologies, including donor  
26 insemination and human embryo research. In the U.K.,  
27 the Warnock committee report of 1985 led through

1 several stages to the current Human Fertilization and  
2 Embryology Authority or HFEA for short.

3           The HFEA, a legislatively established  
4 regulatory body, licenses research facilities and  
5 clinical programs in the United Kingdom. HFEA also  
6 publishes an annual list of all U.K. research  
7 protocols involving human embryos, as well as clinical  
8 specific information about assisted reproductive  
9 technology.

10           For human gene transfer and human gene  
11 therapy, there is still a different history of public  
12 oversight. In the mid-1980s the committee that had  
13 originally overseen recombinant DNA research, the NIH  
14 RAC, gradually accepted responsibility for overseeing  
15 human gene transfer research.

16           A RAC subcommittee developed research  
17 guidelines, the points to consider, and these  
18 guidelines were in place before the first clinical  
19 gene therapy protocol was put forward.

20           In the early years, almost all human gene  
21 therapy studies were either funded by or conducted at  
22 NIH. So an NIH based committee was able to review  
23 virtually all gene therapy research conducted in the  
24 United States. Gradually, the private sector became  
25 more interested in gene therapy, and NIH funding was  
26 not necessarily involved.

27           In the early to middle 1990s, the Food and

1 Drug Administration developed impressive review  
2 capabilities for both gene and cell therapies.  
3 Gradually, a partnership between NIH and FDA has  
4 evolved in which most review of gene therapy protocols  
5 and all formal approval and disapproval now reside  
6 with FDA.

7           The NIH RAC provides initial review of the  
8 most innovative or controversial gene therapy  
9 protocols in a public setting, as well as sponsoring  
10 policy conferences on general topics like human  
11 genetic enhancement or new vectors for gene therapy.  
12 In addition, NIH and FDA have collaborated in  
13 establishing a registry to follow all patients treated  
14 with gene therapy.

15           Now what lessons can be drawn from this  
16 history? You might say it's a small sample. It's  
17 only three biomedical -- areas of biomedical research,  
18 and it's a pretty short time frame when all of human  
19 history is considered. We're just looking at 25  
20 years.

21           Nonetheless, these have been three  
22 critical areas of biomedical research and technology,  
23 and I think certain lessons can be drawn from the  
24 successes and failures that public policy has  
25 encountered in these three arenas.

26           The first lesson that I would draw is that  
27 a variety of public oversight mechanisms can be

1 devised for new biomedical technology. These  
2 oversight mechanisms can range from purely advisory  
3 private sector groups, to public advisory bodies that  
4 exercise their authority through the funding of  
5 research, to full fledged regulatory bodies; and we'll  
6 have to make a choice along that spectrum.

7           Second, the extent to which these  
8 oversight bodies conduct their work in public varies  
9 considerably. In the three examples that I cited,  
10 advisory committees have conducted most of their work  
11 in the public eye, while regulatory bodies have held  
12 public hearings or committee meetings but conduct much  
13 of their work in secret.

14           A third lesson, the absence of government  
15 oversight does not necessarily lead to greater freedom  
16 of scientific inquiry or the more efficient  
17 introduction of new biomedical technology.

18           Here, the contrast between the U.S. and  
19 the U.K. with respect to human embryo research and  
20 assisted reproductive technologies may be particularly  
21 instructive.

22           Now I know there are other variables and  
23 that abortion politics is quite different in the  
24 United States and the United Kingdom, and yet when I  
25 see what is happening in the U.K. and what is  
26 happening here with respect to clinical in vitro  
27 fertilization and human embryo research, I can't help

1 being impressed.

2           Some suggestions for the future: First,  
3 the NIH RAC model taken by itself is not likely to be  
4 well suited to xenotransplantation. It is difficult  
5 to know exactly what fraction of xenotransplantation  
6 research are funded by Federal agencies and private  
7 biotechnology companies, but it is safe to say that  
8 more than half of current xenotransplantation research  
9 funding originates in the private sector, and it may  
10 be three-fourths or even 80 percent.

11           In contrast, NIH provided most of the  
12 early funding for recombinant DNA research and gene  
13 therapy research. It would be awkward, to say the  
14 least, for NIH to oversee the work of biotechnology  
15 companies that receive no NIH research funds.

16           On the other hand, the NIH RAC has set a  
17 standard for transparency and public accountability  
18 that may be very important for the early years of  
19 xenotransplantation research. With only two  
20 exceptions in more than 20 years of work, the RAC has  
21 conducted all of its deliberations in public.

22           The NIH office that supports the RAC  
23 maintains a public list of all gene therapy protocols  
24 that have been submitted to the joint NIH-FDA review  
25 process, and each year the RAC has provided a public  
26 review of the state of the scientific art in gene  
27 therapy, broken down by disease category.

1                   For the early years of xenotransplantation  
2 research, what we may need is a new oversight model  
3 that combines the best features of both public  
4 advisory committees and regulatory bodies. Here are  
5 several specific elements that I would like to  
6 recommend for your consideration:

7                   First, regular public discussion and  
8 review of xenotransplantation protocols that typify  
9 the major lines of current research or that raise  
10 novel issues;

11                   Second, a public listing of all clinical  
12 studies involving xenotransplantation into humans,  
13 without regard to the sources of their funding, and  
14 this list could be posted on the Worldwide Web and  
15 anyone who was interested in the topic could have  
16 access to it;

17                   Third, a registry that tracks all  
18 volunteers in early xenotransplantation studies. Now  
19 an interesting question will be whether also members  
20 of their immediate families should be tracked in a  
21 registry.

22                   Fourth, an annual accounting of the number  
23 of animals used by species for transplants into human  
24 beings, and that provides another kind of  
25 accountability for the field;

26                   Fifth, an annual assessment based on a  
27 global literature review of the public health risks,

1 if any, that may be associated with  
2 xenotransplantation;

3           Sixth and finally, an external review at  
4 the end of the first five years and every two years  
5 thereafter of whether a special oversight system  
6 continues to be needed for this innovative new field.

7           Thank you very much.

8           MODERATOR SKIRBOLL: Panel members?

9           MODERATOR WALTERS: In order to have time  
10 for audience participation, we're going to have to be  
11 very efficient in the way we proceed. So I think that  
12 what we will do is simply go down the row, beginning  
13 with Dr. Platt at the far end, and ask each panelist  
14 for initial comment not to exceed about three minutes,  
15 questions that you'd like to see placed on the table  
16 or responses or questions that you have to the two  
17 earlier presentations this morning.

18           Then we will turn to the audience for  
19 comments from the audience.

20           Dr. Platt?

21           DR. PLATT: I'm a transplant immunologist  
22 and a physician who is interested and works in the  
23 field of transplantation. I must say that I'm very  
24 gratified and pleased to see the intense interest and  
25 the consideration given to the variety of issues in  
26 this field.

27           Obviously, transplantation has been no

1 stranger to controversy, but also plays a major role  
2 in the therapeutic armamentarium that we have, as was  
3 reviewed in detail yesterday.

4 I think that it's important that we have  
5 sufficient time this morning to deal with the  
6 questions that will arise in regard to this, and I can  
7 only, you know, echo my interest and thanks to those  
8 involved who so thoughtfully dealt with some of the  
9 ethical issues that were presented this morning.

10 MODERATOR WALTERS: Mr. Benedi.

11 MR. BENEDI: Thank you. First, I want to  
12 thank Dr. Amy Patterson for inviting -- including us  
13 in these talks, and Dr. Vanderpool has raised a  
14 significant number of questions that need the utmost  
15 consideration and attention.

16 I'll tell you a little bit about myself  
17 very briefly. I am a liver transplant recipient who  
18 had an emergency liver transplant with only hours left  
19 to live. If the donation from another human being had  
20 not come, I would have been dead within two hours.

21 Needless to say, I am one of the lucky  
22 ones that can stand before you today five wonderful  
23 years later and say that my life was saved by the  
24 medical miracle of transplantation and the generosity  
25 of my donor.

26 Many are not so lucky. Today as we sit  
27 here, ten people with families, dreams and the desire

1 to live will die. There are over 60,000 of us waiting  
2 as we speak for a lifesaving transplant. Can we do  
3 better as a community to increase organ donation?

4 Absolutely.

5           Should we look to other means to alleviate  
6 this very growing list of precious lives that will  
7 surely die without help? Absolutely.

8           Should we look to the scientific and  
9 medical community for new and innovative ways to save  
10 lives? Yes, absolutely, with some conditions.

11           We have heard here in the last two days  
12 fascinating and exciting new procedures and therapies  
13 that seem to address the need we all agree exists. I  
14 want to assure you that, for us recipients and for  
15 many out there waiting, that we, too, are concerned  
16 and cautious about the prospects that some have  
17 articulated relating to the spread of unknown,  
18 unpredictable viruses to the recipients and to the  
19 general population.

20           Although the lifesaving aspects to the  
21 recipient is very strong, so is the desire that we not  
22 be the ones that will endanger others for the benefit  
23 of our own survival. Informed consent by the patient,  
24 their immediate families, health care workers, and  
25 anyone that will come in contact with this possible  
26 virus is of the utmost importance in proceeding with  
27 the clinical trial.

1                   The long term expenses of the patient,  
2 their immediate families and others should also be  
3 taken into account when one puts an individual through  
4 a lifetime of exposure and testing. Insurance issues  
5 and work related acceptance of exposed individuals  
6 needs to be explored, and possible solutions mapped  
7 out. Educating the public will go along way to  
8 alleviate some of these concerns.

9                   I hate to be the one to raise these issues  
10 when we are all so excited about the possibilities  
11 xenotransplantation brings. I, for one, am one that  
12 feels that this procedure will in the near future  
13 alleviate, if not eliminate, the waiting time for  
14 those in need, and in turn save countless lives.

15                   Please keep us, the public, informed and  
16 involved in this lifesaving process, as the FDA has so  
17 thoughtfully done with these proceedings. I commend  
18 all of you that are dedicating your research, your  
19 talents, your resources and, yes, your lives to this  
20 most important work.

21                   Please continue cautiously, and let us  
22 know the bad news with the good. The public deserves  
23 no less, and our children deserve and expect our  
24 vigilance. Thank you, and God bless you.

25                   MODERATOR WALTERS: Dr. Somerville.

26                   DR. SOMERVILLE: I'm also a transplant  
27 immunologist and a transplant physician. The

1 realities of the donor organ shortage, which I think  
2 were beautifully said just now, are well known to me  
3 as well as to my colleagues.

4           Initially, when I approached  
5 xenotransplantation through the eyes of that  
6 situation, I was concerned. I thought that it was not  
7 well thought out. This was about four or five years  
8 ago. I thought that it was a lot of just let us do  
9 this, we'll take care of it; and I at that time was  
10 inspired to join what's been a four-year effort for me  
11 to grapple with those issues, to establish for myself  
12 and to make some small contribution to the dialogue.

13           During that process, I think we have to  
14 recognize that I think it's been remarkable. The FDA,  
15 the NIH, and the CDC, working together in a way that  
16 I think was unique for these organizations, came  
17 together and focused tremendous resources from these  
18 agencies with the full support of Congress, of the  
19 President, through all their various minions to deal  
20 with these issues.

21           We've dealt in multiple public situations  
22 with families, patients, anti-vivisectionist groups,  
23 animal rights, company representatives, physicians,  
24 surgeons, etcetera, again and again in open  
25 discussion, dealing with each of these issues. We've  
26 recruited all kinds of specialists in retrovirology.  
27 People that never thought about transplantation now

1 joined a growing field.

2 I think this has been a remarkable  
3 process, and I hope that it continues, and I hope that  
4 we support it, and I think it's been exactly what it  
5 should have been. I think tremendous credit goes to  
6 everyone who is involved, and I really appreciated the  
7 small chance I've had to play in it.

8 MODERATOR WALTERS: Thank you. Dr.  
9 Prentice.

10 DR. PRENTICE: I'm not a transplant  
11 surgeon. I'm not an immunologist. What I am is a co-  
12 chair of an IRB and an IACUC. I've been co-chair of  
13 the IRB at my institution for 17 years, co-chair of  
14 the IACUC for ten years, and you all know that  
15 xenotransplantation will not occur at any institution  
16 unless it is approved by both committees.

17 The issues that have been raised here are  
18 tough, difficult issues. They're not new issues.  
19 They existed back in 1984 with the Baby Fay  
20 transplant. They existed when the Pittsburgh group  
21 did their transplants in '92, in '93, but they really  
22 weren't addressed adequately.

23 I think they are being addressed now  
24 through the efforts of groups such as this, but I  
25 would like to endorse what Dr. Vanderpool said  
26 earlier. That is, we need more dialogue. We need  
27 more guidance.

1                   We reviewed at our institution our first  
2 xeno perfusion protocol about four years ago, and we  
3 struggled with the issue of informed consent and the  
4 issue of zoonosis and, quite frankly, we did not know  
5 what we were doing.

6                   I think we've come a long way since then,  
7 but we're nowhere near to the point where I think that  
8 at my institution we can perform a valid review of a  
9 xenotransplantation protocol. So I think we need to  
10 continue our efforts.

11                   I think that IRBs and IACUCs are going to  
12 need some guidance from a national group in terms of  
13 what are the protocol review criteria that we should  
14 insist upon in terms of approval of a  
15 xenotransplantation protocol.

16                   What are the issues relative to informed  
17 consent? How do we get informed consent from a  
18 terminally ill patient? What about third party  
19 consent or is it simply notification and education?  
20 We need to come to grips with all of these issues  
21 before the next xenotransplantation protocol takes  
22 place.

23                   MODERATOR WALTERS: Dr. Michaels.

24                   DR. MICHAELS: Thank you. I'd like to  
25 thank the speakers from this morning who so  
26 wonderfully articulated a lot of the issues which have  
27 come up, and also reecho the comments that have been

1 made by the previous speakers on the panel.

2 I think that a lot of these issues need to  
3 have continued dialogue and will require continued  
4 dialogue over years to come, but I do believe, as Dr.  
5 Salomon has said, that in the last four years there  
6 has been a great deal of dialogue. We have moved  
7 forward quite substantially, and I only can anticipate  
8 that we will continue to do so in the future.

9 MODERATOR WALTERS: Ms. Linn.

10 MS. LINN: Thank you. I am from a  
11 regulatory office. My office is called Office for  
12 Protection from Research Risk. The office was created  
13 to enforce the Health and Human Services regulations.

14 Clinical xenotransplantation is subject to  
15 multiple regulation for the protection of human  
16 subjects. Ultimately, it is IRB's responsibility to  
17 ensure that the rights and welfare of the human  
18 subject are protected.

19 There are four sets of regulation  
20 applicable to clinical xenotransplantation. One of  
21 them is the Health and Human Services, which OPRR have  
22 authority -- oversight authority, and there are three  
23 sets of FDA regulation in the 21 CFR 56 and 50 for the  
24 IRB and informed consent regulation, and another one  
25 is for 21 CFR 312, which the Biologics regulate.

26 All of the regulations require IRB review.  
27 There are eight criteria for IRB to review and approve

1 protocol. Protocol xenotransplantation is not an  
2 exception.

3           The interesting thing about the IRB review  
4 requirements -- one of them includes that the subject  
5 -- risk to the subject need to be minimized. In the  
6 regulation there is no requirement for IRB to consider  
7 that the subject to -- that the risk to the society  
8 need to be minimized. So that's a challenge for IRB,  
9 and I think it's important. IRB need to deal with  
10 that.

11           The PHS guideline for xenotransplantation  
12 did go beyond the additional protection, and I think  
13 that it's to be complimented.

14           Another issue that IRB need to struggle  
15 with is the informed consent issue. We heard this  
16 morning the two speakers, particularly Dr. Vanderpool,  
17 mention that informed consent issues go beyond just  
18 the subject. It goes beyond family member, third  
19 party, health providers, and public at large.

20           How do we ensure to obtain the valid  
21 informed consent when subject is so compromised and  
22 the family is in such a stressful condition? How  
23 about Dr. Walters' point about the public disclosure  
24 and public consultation? How do we define community?  
25 That is a challenge.

26           I think I agree that the current IRB make-  
27 up in most of the medical centers do not have the

1 expertise to review the xenotransplantation protocol.  
2 I think a lot of education effort needs to --  
3 extensive education effort needs to be afforded for  
4 IRB. Thanks.

5                   MODERATOR WALTERS: Thank you. This is  
6 very hard to ask all the panel members to be so brief,  
7 and I appreciate your tolerance for the brevity that  
8 we need. Ms. Henry?

9                   MS. HENRY: Thank you very much. As a  
10 member of the Patient Affairs Department at the United  
11 Network for Organ Sharing, and also as a liver  
12 recipient who once laid in the intensive care unit  
13 confronting the possibility of some form of  
14 xenotransplant bridge therapy, I cannot overstate how  
15 important this conference and also the ongoing  
16 dialogue between FDA, PHS and various organizations  
17 and governmental bodies is.

18                   It is of paramount importance that a  
19 dialogue involving all relevant communities, the  
20 public, transplant candidates and recipients, and the  
21 medical researchers involved be started now and be  
22 continued as this field develops.

23                   I applaud Dr. Vanderpool for emphasizing  
24 the role that transplant recipients can play on the  
25 IRBs, and in keeping the patient perspective alive and  
26 in front of the medical personnel so closely involved  
27 with the experimentation.

1                   I think also we should keep in mind, even  
2 with the fabulous leaps that are being made in this  
3 field, the importance of maximizing the supply of  
4 human organs. I'm hoping to avoid questions of who  
5 should get human organs versus who would be allotted  
6 animal organs, so that a disproportionate impact, if  
7 these hard decisions were made, might fall on the  
8 elderly, disabled, minorities, and pose even harder  
9 ethical questions than the ones we've been facing this  
10 morning.

11                   I was very pleased to find out yesterday  
12 at some of the clinical discussions and presentations  
13 of the many therapies involving cells and various  
14 procedures sort of a step removed from solid whole  
15 organ transplant, such as the HepAssist, perhaps  
16 displaying my bias as a liver recipient, giving liver  
17 candidates a chance to wait until they can receive a  
18 human liver, much like kidney recipients on dialysis  
19 have perhaps a longer chance.

20                   The question I would raise for the panel  
21 is much like one that has been raised by some of my  
22 colleagues earlier on the panel, of informed consent  
23 and how we can truly get informed consent of patients  
24 who are faced with the decision of do they accept a  
25 xenograft or do they die. Can informed consent be  
26 truly given in such trying circumstances? Thank you.

27                   MODERATOR WALTERS: Dr. Evans.

1 DR. EVANS: Yes. I had prepared some  
2 formal remarks which I will just summarize very  
3 briefly.

4 My interests are in the social and  
5 economic aspects of medical technology,  
6 transplantation in particular. I think there are four  
7 issues that we need to think of that have not really  
8 been covered today in this discussion, and this has to  
9 do with the -- The first one has to do with overall  
10 health care expenditures.

11 As many of you realize, we spend an  
12 increasing amount on health care. Many questions are  
13 raised as to how much we should spend. Currently,  
14 it's about \$1 trillion. By the year 2030, it will be  
15 \$16 trillion.

16 There's nothing inherently wrong with  
17 that. However, there are people who are very much  
18 opposed to spending a considerable bit more than we  
19 currently do. So we need to keep that in mind.

20 The second issue has to do with the need  
21 and the demand for xenotransplantation. I would,  
22 frankly, state quite clearly that there will never be  
23 an adequate supply of human donor organs to meet the  
24 demand, let alone the need.

25 Unfortunately, we continue to go through  
26 one charade after another where we try to convince the  
27 public that, if they chose to donate their organs,

1 there would be an adequate supply. That simply is not  
2 true. Many people still do not get on the list who  
3 could potentially benefit from a transplant, and I  
4 would say that that will continue to be the case.  
5 Therefore, indeed there is a serious need for  
6 xenotransplantation.

7 I'm also concerned about our ability to  
8 innovate in our health care system today, given the  
9 direction it has taken. If we were sitting amongst  
10 people today who were advocating a variety of  
11 different approaches to the delivery of health care  
12 services, I don't think xenotransplantation would be  
13 even on the radar screen. In fact, it would probably  
14 be under the table, as it were.

15 I think that's something we have to be  
16 concerned about as we go forward. Industry will play  
17 an increasingly critical role in the future. It's an  
18 important role. I think we'll have to look at a  
19 variety of different partnerships in order to make  
20 this even come together in a reasonable way, given  
21 what most of us are up against today.

22 The final issue, I think, is one that's  
23 even difficult to think about down the road, but I  
24 would say -- and this ties in with the issue of how  
25 much do we spend on health care, but issues related to  
26 intergenerational equity.

27 I think, eventually, what we're going to

1 have is not only an aging population but an aging  
2 population that will become increasingly large in  
3 size. I personally think, if xenotransplantation were  
4 successful, the percentage of our population that will  
5 exceed age 65 will become much more marked than it is  
6 today.

7 I think that that will raise an incredible  
8 number of social issues that, as I say, are very  
9 difficult for us to come to grips with today, but we  
10 need to start thinking about them now. Thank you.

11 MODERATOR WALTERS: Dr. Berger.

12 MR. BERGER: I'd like to try and cover  
13 some basic issues that haven't been mentioned so far.  
14 I had noticed, this is a U.S. Public Health Service  
15 policy, but I think the question of whether this is  
16 the public or not is really out there.

17 When I look around the room and I see that  
18 probably 90 percent of the people that are here really  
19 have a very strong vested interest in this particular  
20 topic, I really don't see the public participating  
21 properly in this.

22 I've been to other conferences, and it's  
23 pretty much the same audience and the same kinds of  
24 people that are, in fact, here. So the question of  
25 oversight -- do we allow the people that have really  
26 a vested interest in the process be the exact same  
27 people that are making the final decisions?

1           I've really become sympathetic to  
2 government agency officials, because I can see the  
3 enormous pressure that's being placed before them.

4           Secondly, since I do represent a national  
5 animal organization, I do think that I should be  
6 making some mention, even though I do have a feeling  
7 it will go before a deaf ear. The xenotransplantation  
8 IOM booklet that came out barely -- and I mean barely  
9 -- touched the concept of the use of animals -- barely  
10 touched it.

11           There are millions of people in this  
12 country that ethically and morally object to the use  
13 of animals in animal research. One more point on this  
14 subject: It's very curious -- The point was made  
15 yesterday. It's made over and over again, that the  
16 use of pigs is being done because people eat pigs.

17           Well, interestingly enough, people are  
18 slaughtering or eating pigs, and pigs are being  
19 slaughtered in lesser amounts year after year after  
20 year, because we will all acknowledge that meat based  
21 diets are not in our own best interests from a health  
22 perspective.

23           As a matter of fact, it's a very  
24 interesting cycle. Here we are eating pigs that, in  
25 fact, may be causing disease that require potentially  
26 a new organ. Then we blame these same pigs, call them  
27 victims, slaughter them, take the organs and put them

1 back into the same people. Somehow this doesn't  
2 appear to be correct.

3           Thirdly, and really my last point, it's  
4 really more of a discussion on the utilization of our  
5 health care resources; because this, I think, is  
6 really the major topic that we should be looking at,  
7 which is very much basic, before we even get into  
8 topics like whether we should be having clinical  
9 trials.

10           It would seem to me that there are some  
11 basic things we should be doing first. More money  
12 should be put into increasing the number of human  
13 donor organs out in this marketplace. We acknowledge  
14 that won't solve the problem, but there's no reason  
15 why we shouldn't be doing that first.

16           Secondly, we could be looking at options  
17 like a presumed consent law or something like it.  
18 Again, it may not be the answer, but it certainly  
19 might have the potential to increase the number of  
20 organs out in the marketplace.

21           Lastly, on the research allocation, there  
22 have been some very interesting reports and studies  
23 that came out. Harvard School of Public Health just  
24 came out in December about a major gap in U.S. life  
25 spans, pointing to poverty areas which are the major  
26 areas that have dramatic disease. Ninety million  
27 people live in the U.S. with chronic disease.

1           It seems to me that, if we're looking at  
2 allocating resource dollars, we should be allocating  
3 them to areas, in fact, that we know that things could  
4 actually help.

5           Just looking at heart disease alone,  
6 American Heart Association: 1995, 570,000 bypass  
7 surgeries, 420,000 angioplasties; 960,000 people died  
8 of heart disease, 41 percent of the nation's death in  
9 1995. 58 million Americans suffer some kind of  
10 disorder of heart disease.

11           We know that prevention is something that  
12 actually works. That's been proven over and over  
13 again. Why we're not putting money, first of all, in  
14 allocating money towards prevention, diet, exercise,  
15 stress management, before we look at these kinds of  
16 invasive procedures.

17           If we're looking at saving lives, it does  
18 appear to me that prevention is really the name of the  
19 game.

20           Lastly, is xenotransplantation really a  
21 public health issue or is it profits? The Salomon  
22 Brothers report in 1996 is looking at the year 2010,  
23 the need for over 500,000 pig organs. We're looking  
24 at revenues of probably \$10-12 billion in the drug  
25 industry. Is that push for profits really becoming  
26 before public health? Thank you.

27           MODERATOR WALTERS: Thank you. Dr.

1 Vanderpool, do you have anything to add?

2 DR. VANDERPOOL: Sure, but let's let the  
3 panelists finish. I have plenty of things to add to  
4 every comment, but --

5 MODERATOR WALTERS: That's remarkable  
6 self-restraint, Dr. Vanderpool. Dr. Auchincloss.

7 DR. AUCHINCLOSS: Again, I think I had  
8 enough time in front of the microphone yesterday. Why  
9 don't we move on to comments from the floor.

10 MODERATOR WALTERS: All right.

11 (COMMENT FROM THE AUDIENCE)

12 MODERATOR WALTERS: It should be in the  
13 materials that were distributed yesterday, but we can  
14 certainly go through the group, beginning with you,  
15 Dr. Platt.

16 DR. PLATT: I'm Professor of Experimental  
17 Surgery at Duke University.

18 MR. BENEDI: I'm the immediate past  
19 President of the Transplants Recipients, International  
20 organization.

21 DR. SOMERVILLE: I'm a member of the  
22 Department of Molecular and Experimental Medicine, the  
23 Scripps Institute, La Jolla, California.

24 DR. PRENTICE: I'm the Associate Dean for  
25 Research at the University of Nebraska Medical Center.

26 DR. MICHAELS: Pediatric infectious  
27 disease specialist, Childrens Hospital, Pittsburgh,

1 University of Pittsburgh.

2 MS. LINN: Deputy Director, Office for  
3 Protection from Research Risk at NIH.

4 MS. HENRY: Patient Affairs Specialist at  
5 UNOS, United Network for Organ Sharing.

6 DR. EVANS: Mayo Clinic, Rochester,  
7 Minnesota.

8 MR. BERGER: I'm the Executive Director of  
9 the Animal Protection Institute, a national animal  
10 advocacy group.

11 DR. AUCHINCLOSS: And I'm a transplant  
12 surgeon at Massachusetts General Hospital.

13 MODERATOR WALTERS: Okay. There were two  
14 people who had registered an interest in presenting to  
15 this group from the floor, and I would like to ask the  
16 first of the two people to come forward, if you would.

17 DR. BACH: My name is Fritz Bach, and I am  
18 a researcher in xenotransplantation. I decided ten  
19 years ago that I wanted to enter this field, because  
20 as everybody here, we recognize the organ shortage;  
21 but for myself as well, I recognize that the  
22 opportunities in terms of the biomedical tools that  
23 were available, especially molecular genetics, to  
24 enter this field.

25 I remain excited, optimistic, and plan to  
26 spend the next ten years doing research in  
27 xenotransplantation and, hopefully, making a

1 contribution to that field.

2           The article that we wrote in Nature  
3 Magazine was occasioned -- and I've asked myself this  
4 several time -- why suddenly did I decide this was  
5 important. It wasn't so sudden, but it was about two  
6 years ago, and came about, I think, because of two  
7 reasons that we did not previously consider such an  
8 article or talking about these things.

9           One was the excitement of the research.  
10 This is a terribly exciting field from the biological  
11 perspective. There are new insights that have been  
12 gained into problems that, I think, impact far beyond  
13 xenotransplantation.

14           The second reason, which certainly was the  
15 more proximal one, was that some individuals were  
16 beginning to speak, I think, not terribly responsibly  
17 about going into clinical trials with pig organ  
18 transplantation, and that worried me, and I had the  
19 great opportunity to make contact with one of my co-  
20 authors, the senior author on this article, Dr. Harvey  
21 Feinberg.

22           The group that finally assembled -- I will  
23 spend only one minute telling you who they are, just  
24 in case you do not know. In addition to myself, there  
25 was Dr. Feinberg. Dr. Feinberg, for many years, was  
26 the Dean at the Harvard School of Public Health. I  
27 think he is one of the most respected people in public

1 health in this world.

2           He chaired several different commissions,  
3 including one on developing ways of handling risk to  
4 the public, which was published in 1996. I found that  
5 volume exceedingly instructive and would urge anyone  
6 else to take a look at it. It's reference 14 in the  
7 article.

8           Professor Daniels is Chairman of the  
9 Department of Philosophy at Tufts University. Dr.  
10 Daniels has dealt with these issues for many years,  
11 and I found him to have incredible incisive focus  
12 which he brought to this group.

13           Lachlan Farrell is the ethicist at the  
14 Beth Israel Deaconess Medical Center and Harvard  
15 Medical School, and also brought many of the ethical  
16 considerations.

17           Everybody in this room, of course, knows  
18 Jay Fishman, in addition to the other physicians who  
19 were on this group to advise in various ways.

20           We saw this article, which was discussed  
21 for a period of well over one year, as a way to move  
22 forward in xenotransplantation, despite the discussion  
23 yesterday; but we felt the great urge that it move  
24 forward in some form of ethical context, very much  
25 along the lines that we heard so wonderfully discussed  
26 by Dr. Vanderpool and Dr. Walters this morning, and  
27 members of this panel.

1                   We began with no preconceived notions and,  
2 in fact, at the beginning discussed all of the topics  
3 that have been mentioned that I've heard at this  
4 conference and others, but eventually focused in on  
5 one, because once again we saw it as a proximal  
6 danger. That was to focus in on the risk to the  
7 public.

8                   It was our feeling that, if the public was  
9 to be put at risk, then it should be the public,  
10 through some mechanism such as the one suggested at  
11 the conference chaired by Dr. Feinberg, that it should  
12 be involved not only in being educated and educating  
13 the general public, but also in terms of helping in  
14 the decision making, a public that had no vested  
15 interest, that was interested only in the ethical  
16 impact on the population.

17                   The first ethical consideration -- it was  
18 the first, but certainly not the only one, and I think  
19 the article says that -- was that the risk to the  
20 public requires a public mechanism for determining the  
21 acceptability of and method of consent to the risk,  
22 and this is different from the technical  
23 considerations that so much of the discussion here has  
24 dealt with.

25                   We suggested a national advisory committee  
26 as one mechanism that could be used for this, and  
27 further suggested that such a national advisory

1 committee be made up of people from many walks of  
2 life, thus representing a range of philosophical  
3 principles and disciplines.

4           We thought that was very important, if the  
5 public is to be represented, and furthermore, that the  
6 education of this public representative body not be  
7 the only part. They should be educated, but then they  
8 should take a role in the decision making, including,  
9 if the trials go forward, in terms of the iterative  
10 process that is needed for them.

11           We thought that it is critical, as all of  
12 us feel, I hope, that it be made clear to the public  
13 the enormous positive impact that successful  
14 xenotransplantation would have on the practice of  
15 medicine, and this has to be explained clearly, along  
16 with the risks; but the problem cannot be dismissed by  
17 talking about education, as if the experts have to  
18 eliminate ignorance, persuade the public. The public  
19 has its own concerns.

20           Lastly, in trying to summarize this paper,  
21 we said we offer strategy to handling the ethical  
22 issues related to xenotransplantation based on the  
23 optimistic perspective that xenotransplantation could  
24 become a clinically useful procedure.

25           Why did we suggest a moratorium -- and I  
26 find a moratorium no different than the words that  
27 have been used back in December and November, whenever

1 it was, that the FDA put a hold on things. It is a  
2 hold on things.

3 We suggested it, because if the public is  
4 at risk, then the public in some way has to first  
5 consent to undergoing that risk before we put any  
6 further risk to that public, before we do any further  
7 procedures that have risk associated with them.

8 So we thought that in sequence that was  
9 the first thing that should be done.

10 Thank you.

11 MODERATOR WALTERS: Thank you, Dr. Bach.  
12 Dr. Somerville, do you have any comments that you  
13 would like to add?

14 DR. SOMERVILLE: No. I feel embarrassed.  
15 I didn't really want to be called from the floor to do  
16 this, but I suppose just two very brief comments.

17 First of all, I congratulate the ethicists  
18 this morning, because you embedded ethics in science,  
19 and that's so important. To be frank with you, I was  
20 very disturbed after yesterday's session, because I  
21 thought the science wasn't embedded in ethics, and  
22 that's a reciprocal process, and it has to go on  
23 concurrently.

24 It's not enough to do ethics as an add-on  
25 at the end of having done your science. So that would  
26 be the first point that I would make.

27 The second point is that I think it's

1 important that we identify the basic presumption from  
2 which we are working, and we haven't done that here,  
3 as far as I'm aware.

4           There's essentially four basic  
5 presumptions you can take to doing science from an  
6 ethics perspective. You can say, no, you can't do it  
7 at all. For instance, perhaps that will happen with  
8 human cloning; or, yes, go ahead and do it, which none  
9 of us do these days. We used to.

10           The other two presumptions -- We have to  
11 choose between them. They're, yes, you can do it, but  
12 we'll put some conditions on; or no, you can't do it  
13 unless you show this.

14           Now I think one of the crucial issues here  
15 is whether we're going to take a "no, unless" or a  
16 "yes, but." What I heard coming through yesterday  
17 from the scientists was a "yes, but" position.

18           I think what you would find from most  
19 ethicists, and what I hear this morning, is a "no,  
20 unless" position. They often end up at the same  
21 outcome, but not always, particularly -- and I think  
22 this is crucial to the ethics of this situation --  
23 they don't have the same timeline.

24           One of the big ethical questions here is  
25 how fast are we justified in going forward with this  
26 ethically, which means how much do we limit our  
27 original samples. For instance, how much supervision

1 and timeline do we have looking at what happens there.

2                   Now there's a big conflict between what,  
3 certainly, I would see as good ethics on timelines,  
4 and probably what -- certainly, what are commercial  
5 interests on timelines here, which I see as a major  
6 ethical issue.

7                   Another issue that I think hasn't been  
8 looked at -- We've talked about risk to the public.  
9 I would actually suggest we may want to consider the  
10 public as research subjects of this research, if we  
11 genuinely think there are risks to the public, in  
12 which case we've got to get some informed consent from  
13 them.

14                   That's a fundamental rule of the ethics of  
15 research, but one group that hasn't been mentioned  
16 except a little bit in Dr. Evans' remarks on economics  
17 this morning is, we're not just talking about risks to  
18 the present generations here. We're talking about  
19 risks to future generations. So it's not just  
20 intergenerational justice within our own context here.  
21 It's also generational justice of generations of the  
22 future.

23                   I mean, there's so much that you could say  
24 on this that, obviously, I'm not going to do that. It  
25 would be wrong for me to do that. I'd just mention to  
26 you, however, I have actually done -- We've done some  
27 work on this.

1                   I come from Canada, and we had a xeno  
2 conference up there in November, and one of the ways  
3 in which I ended the speech that I gave there was that  
4 transplantation has always been at the crossroads, on  
5 the one hand, of the new science technology in  
6 medicine, and on the other hand, the impact of these  
7 on science, including its values.

8                   It's interesting to think back that the  
9 birth of modern bioethics is often put by a  
10 bioethicist as being the date of the first heart  
11 transplant. That so shocked the public into thinking  
12 about what should we do about this.

13                   So I think that it's perhaps not  
14 surprising that we're coming back to some new issues,  
15 and, interestingly, again in the area of  
16 transplantation.

17                   There's a saying by an Australian judge.  
18 He was actually talking about law and medicine, and I  
19 think we could apply this to ethics in  
20 xenotransplantation, that science and medicine and  
21 ethics in this area are marching together or we'd  
22 certainly like to see them marching together, but I  
23 think at present, still ethics is in the rear and  
24 limping a little. So we've got to see what we can do  
25 to fix that up as well.

26                   MODERATOR WALTERS: Thank you, Dr.  
27 Somerville.

1                   Are there other comments or questions from  
2 the floor? Yes? Would you identify yourself, please?

3                   DR. FERGUSON: My name is Ron Ferguson,  
4 and I'm President of the American Society of  
5 Transplant Surgeons.

6                   We all have appreciated Dr. Bach for 25-30  
7 years, but I think yesterday and today is doing  
8 exactly what he wants done. I don't -- You know, I  
9 think we all have the same concerns.

10                  This is a process that's being put in  
11 place to solve those problems. Whether it upsets you  
12 that it isn't solved today is one thing, but certainly  
13 the process has been a remarkable one, and it is  
14 continuing and ongoing, and it's going to get at  
15 exactly the issues you bring up. So I don't  
16 understand.

17                  MODERATOR WALTERS: Dr. Bach, would you  
18 like to respond?

19                  DR. BACH: Very briefly. Ron, I'm not the  
20 least bit upset. I think the process is a wonderful  
21 one. To the extent that I've been able to dig up  
22 information about it, I'm admirous of that process.

23                  I put forward an idea which I'm delighted  
24 to hear mirrored in terms of what the plans are.  
25 This morning I had the opportunity to speak very  
26 briefly with Dr. Skirboll and Dr. Noguchi, and I find  
27 that they are planning almost exactly what we propose

1 in terms of formation of such a national advisory  
2 committee.

3 I think it is necessary, but I think it is  
4 necessary to represent the public on an ethical basis,  
5 and since they, too, feel that, I'm glad we're in  
6 concert. Whether a moratorium, a hold, should be on,  
7 I feel quite strongly it should be until the public  
8 has had a chance to speak about the danger to it.

9 I don't think we have the right to impose  
10 that, but otherwise I hear the wonderful talks by our  
11 two speakers saying a lot of the things that we said  
12 in this article. It took us a long time to develop,  
13 but I'm very pleased with it, and terribly pleased to  
14 hear the comments this morning.

15 MODERATOR WALTERS: Dr. Vanderpool.

16 DR. VANDERPOOL: For the sake of heuristic  
17 purposes and further discussion, I would like to say  
18 that I've read the article by Dr. Bach and others very  
19 carefully, and find a number of problems with it.

20 The most important problem is it seems to  
21 me to be three or four years out of date. These  
22 issues have been aired. You can almost take  
23 paragraphs out of the first page of the article and  
24 say this has been the agenda of the past three and a  
25 half years that has been going on, that is in this  
26 article being represented as a future agenda when, in  
27 fact, it's already past.

1           Second, I think to call for a moratorium,  
2 certainly, brings public visibility and perhaps alarm  
3 to these deliberations, but as a matter of fact, we've  
4 had various kinds of non-official and sometimes  
5 official holds, moratoriums or whatever you wish to  
6 call them. Whole organ xenotransplants have been put  
7 on hold, and still are for the foreseeable future.

8           So the call for a moratorium now is a call  
9 for something that essentially has been going on,  
10 perhaps under different rhetoric.

11           Third, I see this as politically naive,  
12 because it asks for a public -- "the public" to  
13 deliberate about these issues, to decide what the  
14 risks of xenotransplants are, to determine how they  
15 should be managed, and even how to deal with the  
16 respective risks through different technological  
17 stages of development.

18           Maybe my knowledge of American history  
19 escapes me, but I've never seen the public be able to  
20 do all those things with a complex issue like that.

21           Now having said that, I think the public  
22 is a misnomer. To have public input certainly is not  
23 a misnomer, and that could be increased, as several  
24 people have said, but certainly has been ongoing.

25           Finally -- I mean, I have other issues,  
26 but I think the premise that underlies part of the  
27 article, that xenotransplantation is a reverse of

1 immunization -- or vaccination, because vaccination  
2 involves the society and xenotransplants are for the  
3 individual, is a false dichotomy.

4           Xenotransplants are being flouted as a  
5 procedure for a very important and desperately sick  
6 segment of society, and at the same time another  
7 segment or segments of society may be under risk of  
8 infection.

9           So it's not -- I think the dichotomy is  
10 overdrawn and obscures the degree to which  
11 xenotransplants have the promise of not only enabling  
12 desperate patients to live, but have the spinoff  
13 possibilities of medical advancements in a variety of  
14 other areas.

15           MODERATOR WALTERS: Dr. Platt and Dr.  
16 Salomon and Dr. Michaels.

17           DR. PLATT: I'd like to make several  
18 comments in regard to the discussion that we've heard  
19 this morning.

20           First of all, there seems to be an  
21 assumption that risk exists. There may be a risk. It  
22 may be that in five years we will look back and say  
23 that there isn't a particular risk beyond what we  
24 might ordinarily anticipate through the usual clinical  
25 considerations in transplantation.

26           So let's focus on the nature of this risk  
27 with respect to infection, and I say this with due

1 respect to the issues raised by Roger Evans, which I  
2 think also were in consideration other social issues.

3           If we consider the risk of infection,  
4 there's a possibility that a xenograft could confer an  
5 infection to the recipient that could not occur  
6 through any means other than a transplant, or there is  
7 the possibility that an infection could occur through  
8 other means, such as the contact between humans and  
9 animals in various places such as farms.

10           If an infection can occur through other  
11 means, then focusing overly on one activity such as  
12 xenotransplantation and not paying any attention to  
13 other interactions will only serve to slow scientific  
14 and medical progress, and in the end won't address the  
15 public health issues.

16           If, on the other hand, an infection can  
17 only be transmitted by a xenograft and not by any  
18 other means, then in the end the value of  
19 xenotransplantation and its potential can't be weighed  
20 without some kind of a trial or a clinical opportunity  
21 that enables one to evaluate the issue of infection.

22           The second point I want to make is to  
23 reiterate a point that was made a few minutes ago, and  
24 that is that, really through this meeting and numerous  
25 other meetings, the issues have been addressed, and we  
26 do have public bodies that already exist and that may  
27 exist to take up these issues and to weigh the

1 interests of the public.

2           It's not clear to me how the public's  
3 interests can be expressed and weighed in any other  
4 way. Thank you.

5           DR. SOMERVILLE: I have two brief  
6 comments. One is I'd like to support what Dr.  
7 Vanderpool said. Dr. Bach and your colleagues wrote  
8 a beautiful article. It's extremely well written, and  
9 I agree with everything but the conclusion.

10           The fact is that you could take my slide  
11 set and that of several others in the room that's been  
12 developed over the last four years for these sort of  
13 public forums and pretty much write the article you  
14 wrote. I don't know if I'd write as well as you, but  
15 it's very similar to we'd write.

16           So I don't think that there was anything  
17 new in that article upon which the conclusion you  
18 made, that there should be a moratorium as we have  
19 more public discussion -- and I think that, in doing  
20 so -- I don't think that was your purpose, but in  
21 doing so you basically challenge or reject the very  
22 public, very successful and very remarkable work that  
23 has been done by many, many, many colleagues from all  
24 walks of xenotransplantation science over the last  
25 four years in such forums.

26           The second quick comment is vested  
27 interest. It always comes out as some ugly pejorative

1 term, like I should be embarrassed that I'm a  
2 transplant physician, because that makes me vested.

3 I think that the problem here is that this  
4 is a tremendously complicated area, the science, the  
5 ethics, the medicine, the human aspects of this. When  
6 I started, I said to you that I got into it because I  
7 thought people were just going to go do it, and now  
8 that I'm an expert, I'm suddenly vested, and you guys  
9 are using that against me as a pejorative term;  
10 because suddenly I don't represent the public any  
11 longer.

12 I really resent that. If you're going to  
13 make progress here, if we're going to be responsible,  
14 then a public dialogue has to be with the active  
15 participation of experts, and don't use the word  
16 vested as a pejorative term. We've earned that.  
17 We're vested, because we're trying to do the right  
18 thing for our patients. Thank you.

19 MODERATOR WALTERS: Dr. Michaels.

20 DR. MICHAELS: I'll make this extremely  
21 brief, because a lot of people have already said  
22 comments that I had also wanted to echo.

23 The one thing that I am very concerned  
24 about by what has now become extraordinarily public,  
25 though all of these meetings are open to the public,  
26 that's right, not all of the public come to these  
27 meetings; but what has now occurred in the newspapers

1 is the implication that there have not been these  
2 dialogues for the last several years, the implication  
3 that these issues are not being debated, discussed,  
4 and reviewed, and I find that very concerning.

5           MODERATOR WALTERS: Now I'm expecting a  
6 trapdoor to drop this whole panel from the stage at  
7 any moment, because we're so far over our time.

8           What I would suggest, just to make sure  
9 that we hear from as many points of view as possible,  
10 is that we hear the comments of the four people who  
11 are at the microphones who have not spoken before at  
12 this point. Then I think we will have to draw this  
13 panel to a close.

14           AUDIENCE MEMBER: Thank you. I'm with the  
15 Medical Research Modernization Committee. We're a  
16 nonprofit health advocacy organization in New York.  
17 We're very concerned about the public health risks of  
18 transferring zoonotic virus to the human population,  
19 and I would like to echo Mr. Berger's point that the  
20 public really has not been fully included in these  
21 discussions, and also that funds have not really been  
22 geared towards preventing illness from -- or  
23 preventable illness, which is now being looked at with  
24 xenotransplantation.

25           My question is who will be held  
26 accountable if and when a zoonotic virus spreads to  
27 the human population? I think we have to recognize

1 that the government has paid out compensatory damages  
2 to victims of government funded radiation experiments,  
3 vaccine damaged children.

4           You know, people have been infected with  
5 HIV contaminated blood, and I would like to know if  
6 the government is prepared to compensate not only  
7 xenograft recipients, should they become infected with  
8 a zoonotic virus, but members of their family,  
9 relatives, friends and members of the public at large,  
10 or who will accept that responsibility if the  
11 government declines to accept it?

12           MODERATOR WALTERS: Thank you. We'll come  
13 to this side.

14           MR. ONIONS: David Onions from University  
15 of Glasgow. I'd just like to summarize, I think, two  
16 points.

17           One is I have great respect for the  
18 authors of the Nature Medicine article. They're very  
19 distinguished and very thoughtful people. I think the  
20 final conclusion was unfortunate, although what I  
21 think is important is actually there's a great deal of  
22 consensus here in thinking between what was expressed  
23 in that article and what has been generally expressed  
24 at this meeting.

25           I want to express a personal view, in that  
26 I used to be a "no, unless." In fact, I was more than  
27 a "no, unless." I was a "no, I don't think that's

1 ever going to be possible, and I've shifted my ground  
2 as we've been involved in evaluating those issues over  
3 a period of years.

4           Had some of the experiments turned out  
5 differently, I would have a different view. The  
6 reason is -- I'm now "yes, but," and the reason I'm a  
7 "yes, but," is you think through the consequences of  
8 your actions.

9           In the United Kingdom when we had the BSE  
10 problem or still have the BSE problem, the group of  
11 experts suggested that the possibility of transmission  
12 of the disease to humans was low, very unlikely. As  
13 it happens, it looks now they were wrong and, of  
14 course, now experts are derided, but they actually put  
15 in the caveat. They didn't think it was likely, but  
16 they conceded that it was possible.

17           I think that's the position we're here  
18 with xenotransplantation. The consensus view is, I  
19 think, that probably most of these disease risks can  
20 be contained and controlled, but we might be wrong.  
21 So you must think through the next step of the  
22 consequences of those actions.

23           I think what has been forgotten by some of  
24 the outside comment, both in the press and also in the  
25 scientific press, is that it's not envisioned that  
26 everyone tomorrow is going to go into wide scale  
27 clinical trials. These are going to be closely

1 monitored trials.

2 I think it's that component of the control  
3 that makes a great deal of difference. I do not  
4 believe personally we're going to start a world  
5 pandemic, even if as a group of experts we are  
6 collectively wrong and diseases are transmitted from  
7 a xenotransplant to an individual patient.

8 The kinds of processes, controls that can  
9 be put in place, I think, are certainly there to  
10 prevent that happening.

11 MODERATOR WALTERS: Thank you.

12 DR. FISHMAN; Jay Fishman, Mass. General  
13 Hospital. I've been one of the vested interests for  
14 about four or five years as far as this process has  
15 gone on in developing approaches to safety in  
16 xenotransplantation, and as I've said yesterday and on  
17 previous occasions, I think we've done a great deal to  
18 enhance this potential safety of xenotransplantation,  
19 and there are still risks that we don't know about,  
20 maybe zero, maybe limited.

21 I think that it would be arrogant on my  
22 part to say, because I feel comfortable with this,  
23 that we can immediately transfer this to the general  
24 public. When I say the general public, and Dr.  
25 Vanderpool expressed this difficulty very elegantly,  
26 it's a dichotomy between third party risk and how do  
27 you communicate or educate or whatever we're supposed

1 to do with the great outdoors out there.

2           If you look through the audience here,  
3 it's a wonderful group of individuals who have been  
4 very proactive in developing safety monitoring and  
5 other approaches, scientific advances in  
6 xenotransplantation, but this is the same public  
7 that's been represented at each one of these  
8 conferences.

9           So I think we have to move beyond these  
10 doors, and I think this process that has been  
11 instituted by the Public Health Service has been a  
12 wonderful one and certainly has contributed to the  
13 evolution of ideas of the safety in  
14 xenotransplantation, but I think we can do more.

15           I think we can do more particularly in  
16 regard to considering the ethical concerns as related  
17 to the public interest.

18           MODERATOR WALTERS: Thank you.

19           AUDIENCE MEMBER: Marlon Levy, transplant  
20 surgeon from Dallas. I think the arrogance lies with  
21 those researchers who think that the media, press  
22 releases, articles in USA Today are a proper way to  
23 subvert the dialogue that's been going on now for  
24 several years.

25           If Dr. Bach or anyone else who perhaps  
26 hasn't held the hand of a dying patient in a long time  
27 would like, I'd be very happy to invite them to Dallas

1 and to be in our intensive care unit as our patients  
2 are dying for want of transplants. Thank you.

3 MODERATOR WALTERS: Dr. Bach, would you  
4 like to respond?

5 DR. BACH: Well, obviously, I cannot  
6 respond to everything that's been said, I'm sure, very  
7 sincerely and very thoughtfully. One of the major  
8 suggestions, if not the major suggestion, that we felt  
9 we had in our paper was to create a national advisory  
10 committee or some such mechanism to deal with these  
11 ethical issues representing the public.

12 With all due respect to Dr. Vanderpool,  
13 there's an extensive literature on how to represent  
14 the public, and we suggest that, and I'm comforted --  
15 and I have to stress it again for people who say that  
16 we're four years out of date. We made a great effort  
17 to inform ourselves of what was out there, and I hope  
18 the article pays adequate tribute -- we tried to -- to  
19 this process that's been going on, but we're  
20 suggesting how to handle this issue.

21 My comfort comes from the fact, as I  
22 mentioned before, that this is exactly what is now --  
23 now in 1998 -- being proposed by the very people who  
24 have been sitting as the regulatory authorities. So  
25 we're hardly out of date. We're directly in concert  
26 with what they're proposing, but we have a slightly  
27 different idea of how the public should be represented

1 and what should be done.

2           It's not a brand new idea. As I said, it  
3 comes very largely out of a conference that has been  
4 published in 1996. We may be politically naive. I  
5 would readily admit, I'm politically naive, and when  
6 I read the paper every morning, I realize how  
7 politically naive I am; but that does not mean that a  
8 physician who has sat with those patients, as I have,  
9 has had them die as I sit there, does not have a right  
10 to stand up and say there are other concerns here, and  
11 I think what we should be doing, since you are now  
12 suggesting this committee, is we should be having a  
13 debate.

14           I think we should be having the  
15 intercourse that is necessary to listen to each  
16 other's positions, with all due respect, Dan -- We've  
17 been friends for a long time -- not weigh back on, my  
18 heavens, we've been doing this.

19           I think there's some new ideas here, and  
20 I ask that, no matter how carefully you've had a  
21 chance to read this, perhaps read it once more. We've  
22 put a year and a half into this. As I say, I'm a  
23 minor part, but there's a lot of thought in this, and  
24 I'm delighted that it's now being planned by the very  
25 bodies that run this type of technical and now ethical  
26 considerations. Thank you.

27           MODERATOR WALTERS: Dr. Vanderpool and Dr.

1 Berger will have the last two words.

2 DR. VANDERPOOL: I just want to reiterate  
3 the significance of an issue identified by Roger Evans  
4 and commented on by Alan Berger. That is the question  
5 of the expenditure of public resources for  
6 xenotransplantation.

7 The argument can easily -- has been  
8 frequently said that this is a lot of money for the  
9 few to the neglect of the many. I think it's more  
10 complex than that. I think the -- and I think we need  
11 to think seriously about the degree to which  
12 xenotransplant, perhaps as much as allotransplants but  
13 certainly as a dramatic instance, caused into play the  
14 Judeo Christian emphasis on the inexpressible value of  
15 the individual versus the mass.

16 So we have to deal with that value, which  
17 I suspect everyone in here holds. At the same time,  
18 we don't want to neglect the large number of people.  
19 So I think more reflection needs to go on, and part of  
20 that reflection meaning that whatever spinoffs for  
21 xenotransplantation that will make it even extend well  
22 beyond the individual patients who might receive  
23 transplants, cellular, tissue or organ.

24 DR. BERGER: I'd just like to respond  
25 quickly to some comments over here. I certainly  
26 didn't mean that vested interests were necessarily a  
27 dirty word nor do I not respect and value the comments

1 and experience of people here either.

2           What I was indicating -- nor the comment  
3 about this being public. Just because you say it is  
4 a public meeting does not necessarily mean that the  
5 public is represented, and I would like to thank Dr.  
6 Patterson for having me here, since she does know what  
7 my basic comments are.

8           Just a very quick example of how the  
9 public could be better represented here: A survey,  
10 Harvard School of Public Health, found that 34 million  
11 Americans faced serious problems in getting needed  
12 medical care -- 34 million.

13           So what we're really talking about in a  
14 much broader sense is how we allocate -- how HHS  
15 allocates our health care dollars. We're looking at  
16 expensive procedures. My only point here and the  
17 point that maybe many other public interest groups  
18 might have: Maybe we should allocate those dollars  
19 differently, more for prevention and less for curing  
20 illnesses, and we might actually save more lives.

21           MODERATOR WALTERS: I'd like to thank all  
22 of the panelists and also those of you who commented  
23 from the floor, and I apologize to the groups later  
24 this morning.

25           (APPLAUSE)

26           (Whereupon, the foregoing matter went off  
27 the record at 10:27 a.m. and went back on the record

1 at 10:43 a.m.)

2 MODERATOR RONCHI: I'd like to ask  
3 everyone to please take their seats. I don't want to  
4 have to call you by name and ask you to stop talking.  
5 So please sit down.

6 All right. This next session is on  
7 international perspectives, and international  
8 collaboration and cooperation in the field of  
9 xenotransplantation is absolutely critical.  
10 Infectious agents don't respect national boundaries.

11 You and I can travel to other countries.  
12 We carry a passport. We go through customs. Our  
13 microbes do not, and it's critically important that,  
14 just as within each nation there are assessments of  
15 the risks beyond each individual patient, that we as  
16 nations look at our policies in a more global context  
17 and look at what we are doing relative to other  
18 nations, and act to address the public on the globe at  
19 large rather than just in each of our nations.

20 What you're going to hear about today are  
21 the risk assessments and the algorithms that other  
22 nations who are grappling with the ethical issues, the  
23 infectious disease issues and the need for organs  
24 available for transplantation -- what progress they've  
25 been making.

26 We're very fortunate to have two experts  
27 to be moderators for this session. Dr. Elettra Ronchi

1 is Chief Coordinator of the health and Biotechnology  
2 Products within the Directorate of Science, Technology  
3 and Industry for the Organization for Economic  
4 Cooperation and Development in Paris, France.

5 She has been responsible for coordinating  
6 reviews of socioeconomic impacts of leading edge  
7 technological developments in health and biotechnology  
8 and their regulatory framework for the 29 OECD member  
9 countries.

10 Dr. Clara Witt is currently advisor at the  
11 World Health Organization's Division of Emerging and  
12 Other Communicable Diseases Surveillance and Control,  
13 where she provides expertise, leadership and guidance  
14 in zoonotic and infectious disease prevention and  
15 control in laboratory animal medicine and science  
16 matters to senior policy and programmatic staffs.

17 These two women have been leaders in the  
18 field of catalyzing international dialogue, and this  
19 meeting is one step along a long road that lies ahead  
20 of us. Ladies.

21 MODERATOR RONCHI: I will be very brief.  
22 I'm honored to be here today. Maybe several of you  
23 are familiar with what OECD stands. It stands for  
24 Organization for Economic Cooperation and Development.  
25 You're probably familiar with the OECD indicators  
26 about how well countries are faring with their  
27 budgets, how competitive they are, and on risks about

1 new leading technologies.

2                   We've heard this morning that much of the  
3 current debate seems to echo debates about recombinant  
4 DNA research. OECD was there. On gene therapy, the  
5 OECD was there. However, I would like to point to the  
6 fact that E does not really stand for ethics, but this  
7 would undermine, actually, the broadness of the  
8 debates that the OECD usually carries out.

9                   It does stand for economics. So we will  
10 and we are particularly interested in the economic  
11 aspect, but this, for us, has the meaning of social,  
12 legal and ethical aspects as well.

13                   I was very excited to hear today Dr. Evans  
14 discuss some of the socioeconomic aspects that we are  
15 interested in looking at within this problem of  
16 xenotransplantation. We know that much of the  
17 research today is funded by the private sector.

18                   Because of the current characteristics of  
19 the pharmaceutical global market, much of the future  
20 lying ahead of us will involve a fair amount of trade  
21 of organs, and we would like to look into regulatory  
22 aspects, international regulation of this trade.

23                   We are interested in proprietary issues,  
24 and we are also interested at the end of the day at  
25 who is going to pay; because most OECD countries are  
26 very concerned with increased health care budgets.  
27 This is just a very brief introduction.

1                   I would like also to mention that the OECD  
2 is co-sponsoring with the WHO and the New York Academy  
3 of Sciences a meeting in New York on the subject, the  
4 18th of March of this year. Whoever is interested in  
5 more information on this meeting, which is a closed  
6 meeting, please do not hesitate to get in touch with  
7 me after this roundtable. Thank you.

8                   MODERATOR WITT: For the sake of time,  
9 I'll try to keep the introductions fairly brief. The  
10 more elaborate biographical information about our  
11 speakers for this morning is in your packet handout.

12                   Our first speaker is Andre La Prairie from  
13 Canada. He is a policy analyst for Therapeutic  
14 Productions Program with Health Canada, and I'm not  
15 giving you much time to reach the podium.

16                   MR. LA PRAIRIE: Well, sorry for such a  
17 low tech presentation for a high tech subject, but I  
18 find that if I stand here, I can't see that little  
19 flashing red light. So you won't be able to pull me  
20 off the stand.

21                   It's certainly been a pleasure to  
22 participate in this meeting on policy in  
23 xenotransplantation, and an honor to present on behalf  
24 of Health Canada our experience in dealing with the  
25 same kinds of issues.

26                   The depth and breadth of knowledge that  
27 have sort of been attracted here -- it leaves me a

1 little bit awestruck, and I felt sort of a similar  
2 feeling when I was at the recent WHO committee meeting  
3 on xenotransplantation, you know, because everyone  
4 else is certainly more of an expert than I am.

5           Actually, at that meeting it was Dr. Jeff  
6 Platt who, after I gave a similar talk on Health  
7 Canada's policy, he sort of challenged the need for  
8 such an overpowering regulatory oversight in  
9 xenotransplantation. I think I gave him an  
10 unsatisfactory answer.

11           I sort of said, well -- because his  
12 question was, and I heard this yesterday, too, most of  
13 the innovations in medical research have come from  
14 individual practitioners dealing with the best  
15 interests of their patients, and if we had that same -  
16 - the same regulatory oversight today that we did, you  
17 know, say, 10-20 years ago, maybe there wouldn't be  
18 transplants at all.

19           So again, my answer then was, well, you  
20 know, this is a new environment that we're dealing in,  
21 and I'm just a poor policy analyst trying to deliver  
22 the best response to the demands that the public  
23 makes, but I think the answer I really wanted to give  
24 him was in this slide that -- overhead that I didn't  
25 have at the time, which suggested that perhaps  
26 physicians today aren't looked at in the same light  
27 that they were a few years ago where, obviously, this

1 is a Dilbert cartoon talking about career choices.

2 I'm neither a physician or a scientist.

3 So I don't have to take this tiebreaker question, but  
4 if I was, the question I would ask policy analysts  
5 are, you know, just what makes you a better gatekeeper  
6 than anybody else in dealing with these new issues.

7 Certainly, in Canada we have some recent  
8 examples where policy has failed us. Our fisheries  
9 and oceans department has been criticized for its  
10 management of fish stocks, to the point where the  
11 supply is diminished to almost nonexistent levels.  
12 Closer to home, we've been criticized in the recent  
13 blood commission, a regulator that was under-  
14 resourced, underfinanced in dealing with health issues  
15 in blood.

16 Even a personal example: Just a couple of  
17 weeks ago, a bunch of us sitting around Policy  
18 Division, looking outside at the weather, and we're  
19 being told to go home because, you know, the city is  
20 being closed down; and we thought, well, just another  
21 storm, the city is probably trying to get some money  
22 for infrastructure or something like that, and of  
23 course, within 24 hours the most of Ontario and Quebec  
24 were declared a national state of emergency by the  
25 Prime Minister. Millions of people were without  
26 power. I think in excess of 24 people actually died  
27 because of the storm, and the costs are in the

1 hundreds of millions of dollars.

2           So certainly, you may be skeptical in  
3 thinking that policy analysts who can't even look at  
4 the weather and decide whether there's a risk can  
5 address the issue of xenotransplantation.

6           So hopefully, I'll be able to put those  
7 feelings at ease today as I go over the role and  
8 responsibilities of the Health Protection Branch in  
9 the area of therapeutic products, talk a little bit  
10 about our standards based risk management model  
11 addressing transplantation, its advantages, and how  
12 that can work for xenotransplantation.

13           So therapeutic products comes under the  
14 risk umbrella of Health Protection Branch and includes  
15 biologics which, of course, are vaccines, blood,  
16 organs, tissues, reproductive tissues, and  
17 xenotransplantation, as well as the other areas that  
18 we have responsibilities for.

19           Part of our policy framework is to choose  
20 risk management strategies that are appropriate for  
21 the risks that we see and the level of compliance that  
22 we want to accomplish, and these have a range of  
23 everything from just providing information to the  
24 public so they can make proper decisions, coordination  
25 of investigations, surveillance, support for  
26 guidelines and standards, all the way to forms of  
27 statutory actions such as licensure and inspection.

1                   So in many ways, the same as the U.S. and  
2 other countries around the world dealing with  
3 therapeutic products.

4                   Also similar, we look at risk assessment  
5 tools that adequately look at our responsibilities,  
6 and that's how we determine our strategies. So the  
7 strategy for transplantation, say kidney  
8 transplantation, may be different than the strategy  
9 for xenotransplantation, but that should be based on  
10 risk and science, of course.

11                   Traditionally, certainly in the area of  
12 blood and other therapeutic products, there are  
13 statutes that are broad and general principles that  
14 give the regulator authority to regulate and inspect.  
15 We have regulations that are product specific and  
16 determine what kinds of standards we want to see in  
17 our products, and then we have policies and guidelines  
18 that assist industry in reaching those levels of  
19 compliance.

20                   There are some problems with this  
21 approach. It takes a fair amount of time to change a  
22 regulation. When we say six months to two years,  
23 maybe we're being kind, and it's difficult for  
24 regulations, therefore, to keep up with the pace of  
25 technology, certainly the pace of something as new and  
26 evolving as xenotransplantation, and there are some  
27 limitations.

1                   The Food and Drug Act is product specific  
2 for therapeutic products and, obviously,  
3 xenotransplantation covers the use of animals, care of  
4 animals, ethics, medical practice. Finally, it's  
5 difficult to read, because they're written by lawyers.  
6 So I suppose we should expect that.

7                   Recently, Justice Kriever in his response  
8 to the -- I guess his final report on the Royal  
9 Commission on Inquiry in Blood clearly said that the  
10 Food and Drug Act is the appropriate act to regulate  
11 blood as a biologic, but he noted that the regulations  
12 as they're structured at present are complex, hard to  
13 read, difficult to interpret, and largely because of  
14 many amendments that are made over the years, and he  
15 notes that it's essential in any regulation to be  
16 intelligible to the regulated and desirable that it  
17 also be intelligible to the public.

18                   He goes on further to state that  
19 regulations invariably become out of date as new  
20 therapies and treatment are developed.

21                   So for these reasons, especially in an  
22 area like transplantation which hadn't had any formal  
23 regulatory oversight, we look to a standards based  
24 approach. A standard is simply a published document  
25 containing requirements, procedures, the definitions,  
26 and can be on anything from toasters to transplants.  
27 So it's not always product specific.

1           It could be safety related or whatever,  
2 but having -- being referenced in regulation, it has  
3 the full force of law, and actually, it's not a new  
4 approach in Canada. More than a third of all the  
5 national standards are referenced in some form of  
6 legislation, whether it's Federal, provincial or  
7 municipal.

8           So it's a very good tool. We like it,  
9 mostly because it's easy to update, and there's a good  
10 consultation process to it. So almost two years ago  
11 this month, Health Canada sponsored an expert working  
12 group with a similar make-up perhaps to the  
13 xenotransplant committee that U.S. has, and they were  
14 charged with the principle task of developing a  
15 Canadian general standard for organ and tissue  
16 transplantation.

17           We had an ethicist, a layperson who  
18 happened to also be a lawyer, corresponding members,  
19 including the U.S. FDA, on that committee. In  
20 addition to developing this general standard, which  
21 had principles for organization facilities, donor  
22 screening, recordkeeping, adverse event reporting,  
23 they also were responsible or charged with  
24 subcommittees or subsets for the various organs and  
25 tissues; because, clearly, there's a difference  
26 between the quality assurance measures you can apply  
27 to a kidney transplant than, say, reproductive tissues

1 or stem cells.

2           Something that was mentioned yesterday, it  
3 certainly indicates the solid organ transplants. You  
4 want to improve quality assurance. You don't want to  
5 further reduce an already diminished supply of organs  
6 and tissues. So you allow some movement and yet still  
7 address the safety.

8           In addition to their efforts at developing  
9 those standards, and they've been in draft form now  
10 for a little over a year and we've sent them out to  
11 transplant programs for initial comments, and we  
12 expect that final drafts will go out again for broader  
13 consultation. At that point we will pass them on to  
14 a standards writing body, to the Standards Council of  
15 Canada, where they will become national standards.

16           Standards Council of Canada is similar to  
17 ISO or International Standards Organization. They  
18 follow the same rules for, you know, consultation,  
19 inputs, abilities to be revised and updated, etcetera.

20           Once they're made national standards, they  
21 can be referenced in regulation, and that gives them  
22 the force of law. That means we can make programs  
23 provide adverse event reports, demonstrate their  
24 compliance through, in the case of human organ tissue  
25 transplants, third party accreditation.

26           We will still have full powers for  
27 periodic audits and reviews and full ability to

1 enforce. There will be a standards committee,  
2 essentially the expert committee that I already put on  
3 the overhead, but it will also now have the regulator  
4 as a participant and other stakeholders such as the  
5 provinces that deliver health care.

6           Again I mentioned third party  
7 accreditation through organizations such as the  
8 Canadian Council on Health Care Association -- anyway,  
9 they're the ones that regulate or accredit hospitals  
10 to make sure that they're appropriate to be teaching  
11 hospitals, and a registry and database to further work  
12 on the assessment of risk, and then, therefore, to  
13 further update the standard.

14           Of course, there's always consultation  
15 with stakeholders, and that goes without saying. So  
16 I think, in addition to producing the next round of  
17 standards, we'll also be providing them with our risk  
18 management framework and proposal for regulations  
19 before we promulgate these standards into regulation.

20           So why do we like standards? Well, they  
21 have a number of advantages. They don't have to be  
22 rewritten in a regulatory language. In format, they  
23 can address new emerging technologies in a much  
24 quicker pace. Simple edits to a standard can take a  
25 matter of weeks.

26           They can improve comprehensibility, and  
27 they can combine with areas that are not possible

1 within the Food and Drug Act. So again, the issue of  
2 medical ethics, practice, a variety of other issues  
3 that can't really go into an act can go into a  
4 standard.

5           There's a clear consensus principle which  
6 tends to help with compliance. If you're  
7 participating, obviously, you're going to be more  
8 willing to share the liability and share  
9 responsibility. They can be applied by multiple risk  
10 management systems. That means the national standard  
11 can be used by the authorities that issue licenses to  
12 physicians or other nongovernment agencies.

13           Some people have some concerns that in a  
14 standard, actually, the regulator is just dumping  
15 their responsibilities. Well, that's not true. I  
16 mean, we reference a standard, and we still maintain  
17 all those other functions that I showed earlier on the  
18 overhead, whether it's risk assessment, keeping up  
19 with research, education, ensuring proper information  
20 is made available. We don't lose any of that. We  
21 simply are finding a better vehicle to augment the  
22 regs.

23           This doesn't diminish the role of the  
24 other stakeholders, whether they are people involved  
25 in participating in the update of the standards, the  
26 transplant programs that have to develop their SOPs to  
27 meet those standards, hospitals, other manufacturers,

1 importers. They all are participating in this model.

2           So where does that leave  
3 xenotransplantation? Well, as one of the subset  
4 committees -- and again, we have a list of experts  
5 with a good range of expertise, veterinarians,  
6 ethicists, bioethicists, animal disease experts,  
7 researchers, transplant physicians. Now they take  
8 that Canadian general standard as their template, and  
9 they are looking at it in terms of writing one for  
10 xenotransplantation, but they quickly realized that  
11 xenotransplants are a little bit different in that  
12 they're not a clinical reality at this time.

13           So what they are really writing is a  
14 standard for clinical trials, and they also realize  
15 that to produce a standard and send it out without  
16 actually consulting with the public would be a  
17 mistake, and certainly, the model that we see in the  
18 U.S. is one that we are trying to follow in Canada.

19           At their advice, we've already held a  
20 national forum on xenotransplantation, addressing all  
21 the issues, asking questions as opposed to saying  
22 here's what's going to happen.

23           Even in writing their standard, they  
24 realize that they should be referencing other  
25 documents that are appropriate. In this case, the  
26 Medical Research Council has a very recent code of  
27 ethical conduct for research involving humans, and

1 there's a guide to care and use of experimental  
2 animals from the Canadian Council on Animal Care.

3           So they are linking up with other good  
4 bodies, good national bodies, that have excellent  
5 standards in areas that would be hard for us to put  
6 into the Food and Drug Act.

7           So our next steps: Again we will have our  
8 experts work on a final draft of the xenotransplant  
9 standard, so we can go out for initial comment.  
10 They've taken a lot of the comments received from our  
11 national forum and hope to incorporate them in their  
12 initial draft.

13           We'll also provide the report of the  
14 national forum, complete with all the questions and  
15 unanswered remarks, distribute them for wide comment,  
16 and continue to consult with stakeholders.

17           I thought I would just end it with a plug  
18 for a couple of Canadian authors who produced a book  
19 called Mad Cows and Mother's Milk. Their principal  
20 thesis was looking at communication, and they used  
21 examples such as Mad Cow Disease, silicon implants,  
22 the use of growth hormone for dairy and beef cattle.

23           What they noted was that many times  
24 there's a difference in how experts assess risk and  
25 how the public assess risks. Experts look at,  
26 clearly, science issues, and the public says, you  
27 know, how does this affect me; you know, is it a risk

1 or isn't it.

2                   They further noted that when there is a  
3 vacuum in this area, that's what causes your major  
4 problem. So I'm not saying that this is why Oprah  
5 Winfrey is on trial this week, because of the vacuum  
6 in the issue of Mad Cow Disease, but certainly, if we  
7 want to proceed forward with all the issues of  
8 xenotransplantation, we have to clearly tell the  
9 public what we know and what we don't know.

10                   So I think that's our current position.  
11 We, obviously, are working in collaboration with other  
12 national organizations, the FDA, WHO, the OECD, in  
13 trying to address, you know, common issues.  
14 Certainly, xenotransplantation is not limited to just  
15 one country.

16                   As Amy pointed out, bugs don't have  
17 passports, and you know, it's very important that  
18 we're all sort of at the same speed and that even the  
19 issues of moratorium can't just exist within one  
20 country, because all that will happen is the issue  
21 will simply move around somewhere else.

22                   So I think, if there is to be some kind of  
23 hold, it should be a consistent one across borders.

24                   Well, thank you very much.

25                   MODERATOR WITT: Thank you, Andre.

26                   Our next speaker this morning -- I guess  
27 we're still morning -- is Ms. Rachel Arrundale. She's

1 with the Department of Health in the U.K. in London,  
2 and was formerly a secretary to the advisory group on  
3 the ethics group on xenotransplantation, better known  
4 as the Kennedy Group, and will talk to us today on the  
5 U.K. approach to xenotransplantation.

6 MS. ARRUNDALE: If I could have the lights  
7 down, please.

8 Good morning. I'd like to start my  
9 presentation today by thanking the organizers for  
10 inviting me to speak at this meeting and for  
11 sponsoring my visit.

12 I'm going to talk about the U.K. approach  
13 to xenotransplantation, and I'm going to do that in  
14 three parts: The location of xenotransplantation,  
15 regulation in the U.K.; the current situation; and  
16 what we're going to be doing next.

17 I'm not going to dwell on the location of  
18 xenotransplantation regulation in the U.K.  
19 environment, but it is different from the situation  
20 here in the U.S., and it might just be worth  
21 clarifying that.

22 Indeed, I was asked this morning why does  
23 xenotransplantation come under Central Department of  
24 Health Control; don't you have something like the Food  
25 and Drug Administration?

26 Well, we do, but they don't actually have  
27 competence to cover all of the therapies which are

1 currently under development. I'm talking about legal  
2 competence.

3           This is the diagram of how things are in  
4 the U.K. at the moment. Xenotransplantation comes  
5 under the control of the Central Department of Health.  
6 Within that, there is a part of the department which  
7 looks after our National Health Service, which is an  
8 essentially funded health service and over which we've  
9 got some considerable control.

10           Within the National Health Service  
11 executives, there is a team which I lead which works  
12 on transplantation issues, and that includes issues  
13 around the provision of transplantation services,  
14 human transplant services, the safety and quality of  
15 human tissues, and the procurement of human organs and  
16 tissues, and now the regulation on  
17 xenotransplantation.

18           It's our team which administers our --  
19 well, not newly established anymore, but the U.K.'s  
20 xenotransplantation interim regulatory authority, and  
21 I'm going to return to talk more about that body  
22 later.

23           Just quickly through the rest of this  
24 diagram, the Medicines Control Agency and Medical  
25 Devices Agency are both bodies which do have some sort  
26 of resemblance to the Food and Drug Administration.  
27 The MCA, Medicines Control Agency, has responsibility

1 for medicinal products, and within the  
2 xenotransplantation field that's probably gene  
3 therapies which utilize viable cell lines.

4           It's also possibly some of the cell  
5 therapies we've been talking about today, but the  
6 legal position here is not clear, and we're probably  
7 going to have to proceed on a therapy by therapy  
8 basis, at least in the initial instance.

9           As far as the Medical Devices Agency is  
10 concerned, they have responsibility for the device  
11 part of extracorporeal liver assist devices. What  
12 they cannot do is consider the viable animal material  
13 point part of these devices.

14           So we do have a legislative gap, and  
15 nobody under current legal situations is responsible  
16 for whole organs.

17           The other organizations shown on this  
18 chart are the other central government departments  
19 with an interest. I'll just pick out the Home Office,  
20 which has responsibility for the use of animals in  
21 scientific procedures, so preclinical experimentation  
22 in xenotransplantation, and also the source of this  
23 tissue.

24           The other organizations with particular  
25 responsibilities are the Scottish, Welsh and Northern  
26 Ireland offices, which have responsibility for the  
27 health services within their borders, and the

1 Department of Environment and the Health and Safety  
2 Executors, which look after aspects of genetically  
3 modified organisms.

4           So we're in a somewhat paradoxical  
5 situation in the U.K., which is that there's lots of  
6 legislation around which is relevant to  
7 xenotransplantation, but we don't actually have  
8 anything which fully controls it, almost of the  
9 developments anyway.

10           Before moving on to talk about how we got  
11 to where we are at the moment, I'll just take a slight  
12 detour and talk a little bit about Europe. Europe is  
13 so important to those countries which are member  
14 states, because EU legislation supersedes domestic  
15 legislation, and indeed the Medicines Control Agency  
16 and Medical Devices Agency operate now really under  
17 control of European directors.

18           Europe hasn't really taken much of a role  
19 so far in the regulation of xenotransplantation  
20 research, and that's probably because they, too, are  
21 not sure how far their competence extends in this  
22 area.

23           This may be changing. Last June, I think  
24 it was, a new treaty was discussed in the European  
25 Union known as the Amsterdam Treaty. If ratified in  
26 about 18 months time, Article 129 of that treaty gives  
27 the EU explicit competence to take action in the field

1 of health protection, consumer protection, in the  
2 field of human blood, organs and tissues.

3           It's not clear yet how far that's going to  
4 take them or what action they are going to be taking,  
5 but I think the links to xenotransplantation may  
6 become more obvious then, and they may see more of a  
7 role for themselves in moving the work forward.

8           I've certainly had initial contacts with  
9 officials in the Public Health Directorate there, and  
10 we're hoping to take that work further forward with  
11 them.

12           To talk about where we are and how we got  
13 there, I should admit before going on to the next  
14 slide that I'm going to use a diagram that was  
15 originally produced by Amy Patterson of the FDA. It's  
16 one of my many debts to her, and I'm using that  
17 diagram to her to emphasize the similarities between  
18 our approach and to illustrate some of the  
19 differences.

20           If you can ignore the shading for a  
21 moment, I think, to summarize very briefly, the FDA  
22 started their work on xenotransplantation by consider  
23 the medical and scientific database and developing  
24 guidelines and regulatory oversight. They're moving  
25 on to considering their experience of clinical trials,  
26 developing pilot registries, databases and archives,  
27 and now considering the establishment of advisory

1 panels and extending public debate through meetings  
2 such as this one.

3           In the U.K., we've taken a slightly  
4 different approach, which is to consider initially the  
5 medical and scientific database and to establish an  
6 advisory panel and have some public debate around the  
7 ethics, and now moving on to considering regulatory  
8 oversight.

9           I think the next steps are around  
10 considering surveillance issues like archives and  
11 registries. You'll notice I haven't mentioned  
12 clinical trials. There are no clinical trials of  
13 xenotransplantation underway in the U.K.

14           The difference is, I think, in our  
15 approach that we don't have an assumption that we're  
16 going to be moving to clinical trials, probably best  
17 summed up in the "no, unless" situation. There is no  
18 ban on xenotransplantation, but the people who wish to  
19 proceed must make their case.

20           To go back and look at some of the history  
21 then to how we got to how we are, the advisory group  
22 on ethics of xenotransplantation was established in  
23 late 1995, and it was a multi-disciplinary group. The  
24 Chairman was Professor Ian Kennedy, a professor of law  
25 and ethics.

26           Its main conclusions are contained in the  
27 report, "Animal Tissue in Humans." It's main

1 conclusion was that it was ethical to use animals.  
2 That's the terms of reference of the group, and the  
3 potential developments in xenotransplantation, to  
4 review the acceptability of and ethical framework  
5 within which xenotransplantation may be undertaken,  
6 and to make recommendations.

7           There's no assumption that the group would  
8 find it to be ethically acceptable. In fact, their  
9 conclusion was that it was ethical to use some animals  
10 as sources for xenotransplantation, but that approval  
11 was conditional.

12           The report also contains the assumption,  
13 which has caused some confusion ever since, and it's  
14 "we conclude that only as the conditions which we have  
15 outlined are met could xenotransplantation be  
16 considered to be ethically acceptable." So far, they  
17 did, but what are these conditions, and have they been  
18 met?

19           A range of the conditions which they  
20 outlined the advisory group thought could be met, but  
21 it should be kept under surveillance and to be  
22 monitored, and these are around the extent of genetic  
23 manipulation of the animals, the effect of  
24 transplantation on the humans, animal welfare issues,  
25 the economic impact of xenotransplantation, and its  
26 potential effect on the allotransplantation program.  
27 Those last two points are really around the allocation

1 of resources towards the potential therapy rather than  
2 the existing therapy of human transplantation.

3           These are the conditions that the advisory  
4 group felt could not be met. These are around the  
5 issues of tissue function, tissue rejection, and the  
6 infection risks. The advisory group very much  
7 recognized that work is moving forward all the time in  
8 this field and that their conclusions were very much  
9 based on the existing scientific database at the time  
10 they were reporting.

11           They also recognized that it would not be  
12 possible to answer all the questions before going to  
13 human trials and possibly having extensive experience  
14 of human trials, but they did feel that more work  
15 could be done before taking that step and that it  
16 should be done.

17           As I say, this quote has caused some  
18 confusion in headlines in the U.K. the day that the  
19 report was published. They said both that the U.K.  
20 government had given the go-ahead for  
21 xenotransplantation and that it had been banned.

22           The situation is slightly more complex  
23 than that. We may go ahead with xenotransplantation  
24 in the U.K., if and when the evidence supports that  
25 move.

26           I'm just going to sort of detour slightly  
27 and say a brief word about primates as well, since

1 that came up yesterday, and the U.K. decision is  
2 explicitly mentioned.

3           The Kennedy report recommended that  
4 primates should not be used as sources of  
5 xenotransplantation. That was because they thought it  
6 was ethically unacceptable to keep the primates in the  
7 sort of conditions that they would need to be kept in  
8 to be suitable sources; that is, SPF conditions.

9           That conclusion was explicitly put out to  
10 consultation by the then government, the previous  
11 government in the U.K., and the issues that we're  
12 consulting on have not yet been finalized. So the use  
13 of primates is still a slightly open question in the  
14 U.K.

15           To move on to talk about the current  
16 position, I'm going to have to apologize here and say  
17 that one of my slides is missing. So again, if you  
18 ignore the shading on this, I think what we're doing -  
19 - we've done over the last year in 1997, is to  
20 consider the regulatory oversight of  
21 xenotransplantation.

22           Given the Kennedy report, the government  
23 had to consider what they did with the conclusions  
24 they had, which were that xenotransplantation may be  
25 acceptable. What they decided to do is that they  
26 needed some central control, and this is why they  
27 established the U.K. xenotransplantation interim

1 regulatory authority.

2           They also decided that they needed to  
3 start working on an infrastructure, both to consider  
4 applications and, if those applications are found to  
5 be acceptable, the monitoring then supporting the  
6 clinical trials.

7           The U.K. xenotransplantation is again a  
8 multi-disciplinary body. It's chaired by Lord  
9 Halbgood of Calverton who is a former Archbishop of  
10 Canterbury -- sorry, Archbishop of York.

11           Other members include experts in the  
12 fields of transplant surgery, immunology, animal  
13 welfare, and industry representatives, lay members,  
14 and a patient representative. We also have John Dark,  
15 who is the transplant surgeon here today.

16           Here is how the XIRA, as we know them,  
17 going to do, and these are their terms of reference.  
18 Their main role is to advise on the regulatory action,  
19 which is necessary to regulate xenotransplantation.  
20 Again, they are an advisory committee. Their  
21 authority derives from the Secretary of State, other  
22 elected politicians, and through their ability --  
23 affected states' ability. That's what the NHS does.  
24 They don't have any statutory force.

25           The other main functions of the XIRA are  
26 to consider conditions around -- the preconditions  
27 around safety and efficacy and the research. An

1 associated role is to consider what research still  
2 needs to be done.

3           To support this work, we are just now  
4 working on the establishing a systematic global  
5 literature review which will report quarterly to the  
6 XIRA meetings and help them to make those decisions.

7           We are also establishing through another  
8 government advisory group the Advisory Committee on  
9 Dangerous Pathogens, and some work to look more  
10 closely at the infection risks of xenotransplantation,  
11 and in particular, the potential differences in risks  
12 between the different sorts of therapies currently  
13 under development. That's a question that was raised  
14 yesterday.

15           Again, Judith Hilton who is a colleague of  
16 mine in the Department is here today, and she's going  
17 to be running that, too.

18           The final point of our role is to provide  
19 a focal point within government, and that was seen as  
20 quite important, given this quite diverse  
21 responsibility around agencies.

22           So now I'm now going to concentrate on the  
23 XIRA's role in advising on the acceptability of  
24 particular applications. This is probably the product  
25 of last year. It's a system we're developing for  
26 people who want to make applications to XIRA.

27           This is really the broad outline of the

1 way it's going to be done, and I should point out for  
2 all of those who are in the position of wanting to  
3 make application or who want to make applications to  
4 us that there is a document which I hope will be  
5 published shortly, which will give more details of  
6 this system and the information that we're going to be  
7 requiring.

8           To just run through the slide, the  
9 application is received by XIRA, officials like  
10 myself. It will then be circulated to around six  
11 assessors. Now we recognize that xenotransplantation  
12 therapies and their assessment require a great range  
13 of expertise, and it's not really feasible to have all  
14 the experts that we need on the one body.

15           So we're creating at the moment around 30  
16 to 40 assessors, and it's not going to be a closed  
17 list, to help us with this work. So when we get  
18 applications, the intention is that they will be  
19 circulated to around six of the most relevant  
20 assessors.

21           These assessors reports will be sent then  
22 to the full XIRA meeting. XIRA, as an advisory body,  
23 will advise the Secretary of State about their  
24 decision. So that's the national part of our  
25 framework.

26           We are then going to -- Once the Secretary  
27 of State has made the decision, the proposal, the

1 application, will either go to one of the other  
2 national bodies which has an interest, such as the  
3 Medical Devices Agency, Medicines Control Agency, and  
4 then on to local review. Our local research, ethics  
5 committees are pretty much similar to your IRBs, I  
6 think.

7           One thing to note is that the application  
8 for when we go on to these next stages if the decision  
9 by the Secretary of State is positive, that is if they  
10 decide that the trial, the application, should go  
11 ahead, in their opinion, it will then be up to local  
12 research ethics committees and the other agencies to  
13 make a decision based on their own criteria. However,  
14 if the decision with the national framework, the  
15 Secretary of State, are that the application should  
16 not proceed, then the following stages won't happen.

17           To move on to what we're going to do next  
18 then, the immediate -- in the immediate short term,  
19 I'm hoping to get the document about making  
20 applications to XIRA published. We are then going to  
21 be looking at issuing directions to our National  
22 Health Service which will require them to comply with  
23 XIRA and its decisions and its processes.

24           I should also have mentioned that certain  
25 aspects like the primates question were formally to  
26 review at the beginning of 1997, and we hope to  
27 respond to that consultation exercise shortly.

1           Over the next year, we are working on  
2 establishing the systematic review of research and to  
3 return to the FDA paradigm, we are going to be  
4 starting to consider the issues outlined in the PHS  
5 guidelines, and to look at the issues of registries  
6 and the possible establishment of tissue archives.

7           I'm very pleased that we're not going to  
8 be starting with a blank sheet here, and that we can  
9 draw on the work that's already being carried out in  
10 the States and Canada and by the WHO.

11           I think my conclusion of this part of my  
12 talk is to say that I think in our work over the next  
13 year that international cooperation is going to be  
14 most important. We've got standards. We're going to  
15 be considering standards for xenotransplantation.

16           I think we would all agree that it's  
17 important, there's going to need to be a common core  
18 of standards which will give us all some surety about  
19 any tissue which is being imported into our countries,  
20 and Amy has already mentioned the question of  
21 xenotransplantation recipients crossing borders.

22           I think it's also important to have some  
23 international cooperation around the issues of  
24 surveillance. That's not only to facilitate sharing  
25 this information, is this an adverse event, but also  
26 to enable us to look at effectiveness over a range of  
27 therapies which, admittedly, we're only going to have

1 a few people enrolled in the trials, at least in the  
2 initial stages.

3 To conclude then, the U.K. has taken a  
4 slightly different road to that taken in the U.S., but  
5 in essence still putting in place similar pieces of  
6 infrastructure to the ones you are having here.

7 The main differences are perhaps the  
8 primary emphasis we took in looking at the ethical  
9 analysis first. We also have a different legal  
10 position, which means that all our work is being done  
11 under the auspices of the Central Health Department.

12 We also are taking a slightly different  
13 approach to our assessment of clinical trials,  
14 probably one that tends towards the "no, unless"  
15 situation.

16 The final conclusion is that our work over  
17 the next year is increasingly in the realm where  
18 international cooperation is important, and I'm  
19 looking forward to continuing that work with my  
20 colleagues here.

21 Thank you.

22 MODERATOR WITT: Thank you very much,  
23 Rachel.

24 Our next speaker is Jean Julvez, who is --  
25 will talk on scientific, ethical and legal  
26 considerations in xenotransplantation in France.

27 He is a medical doctor. He holds a Ph.D.,

1 and he is a specialist in tropical diseases, public  
2 health, and epidemiology. He is currently the Chief  
3 of the Safety Unit with the -- and I'm not going to  
4 try it in French, sorry -- French establishment of  
5 transplantation, which is the French National  
6 Transplantation Agency. Jean?

7 DR. JULVEZ: Yes. Thank you, Clara, and  
8 thank you to FDA and NIH to give me the opportunity to  
9 present the French position in this field and to  
10 contribute to this important discussion.

11 Xenotransplantation has quite a long past  
12 in France, since the beginning of the century when  
13 Jaboulet in Lyons had transplanted a pig and a goat  
14 kidney into patients with adrenal failure, without any  
15 success.

16 The practice of xenotransplantation  
17 probably will happen in the near future, but without  
18 anymore precision. For most of the health  
19 professionals, xenotransplantation would bring  
20 additional benefit over the current practice of  
21 transplantation, but for the society it remains  
22 somewhat esoteric.

23 The chronic shortage of human organs is at  
24 the moment the major argument for xenotransplantation,  
25 and the dilemma of this inadequate supply is of public  
26 concern; but even if living donors' organs retrieval,  
27 cell transplantation, cellular therapy, and artificial

1 organs or other substitutive technology may play any  
2 role in this challenge, it is reasonable to think that  
3 xenotransplantation could become an essential, if not  
4 unique, solution to the problem of organ shortage.

5           Just a few medical things: I'm working in  
6 France in the field of xenotransplantation, mostly  
7 paying attention to immunological mechanisms or  
8 prevention of xenograft rejection either through  
9 xenotransplantation from animal to animal or through  
10 laboratory experiments.

11           The choice of an animal species as an  
12 appropriate source of organs, tissues or cells has  
13 never become simple. According to the risks linked  
14 with special -- related to humans, there is now a  
15 consensus about the choice of non-primate animal.

16           It is felt that the pig, with or without  
17 transgenic modifications, will provide the most  
18 suitable solid organs, tissues and cells for human  
19 beings. There is also a consensus about the limited  
20 use of some primates, Old World monkeys such as  
21 baboons or macaques, as organ recipients for the  
22 research proposals needed before clinical trials.

23           The field of xenotransplantation -- in  
24 France are the progress made by veterinary  
25 laboratories in the production of specific pathogen  
26 free pigs. This technology was first intended for  
27 agronomy research and identification of microbiologic

1 pathogens in animal breeding in the perspective of  
2 agribusiness.

3           This technology of animal selection,  
4 animal care and use, is now a well validated process.  
5 A septical hysterectomy or hysterotomy piglet  
6 extraction under sterile condition -- and then strict  
7 housing conditions to avoid any contamination from  
8 outside.

9           Staff is working as in an intensive  
10 pediatric care unit. The status of specific pathogen  
11 free is defined upon known pathogens for the pig,  
12 possibly extended to some designated pathogens for  
13 humans.

14           Principles of good practice for the  
15 production of a source animal for xenotransplantation  
16 is found under the concept of quality assurance. The  
17 control of all the stages of production of the pigs  
18 appear the only way to argue with assurance that all  
19 which can be done was done, and to think that unknown  
20 pathogens may have been warded off.

21           Good practice guidelines for the  
22 production of pigs has been already prepared by the  
23 expert committee of the Establissement Francais des  
24 Greffes, the national state confrontation agency.

25           The issues about xeno zoonosis would  
26 justify in clinical trials the real management of the  
27 infectious risks. According to the -- that

1 specificity is not a strong concept and that special  
2 barrier is just from hope.

3           If it is small, the risks remain and  
4 cannot be ruled out. The -- when faced with some --  
5 that action should be taken in advance to minimize  
6 this risk.

7           After the prevention of disease in animal  
8 source production process, measures to prevent  
9 transmission between humans have to be taken,  
10 especially in the operating room, in the intensive  
11 care unit, and later in the family environment for a  
12 long period.

13           The need of epidemiological surveillance  
14 would also be mandatory concerning the patient and his  
15 family, as well as the surgical and medical care  
16 staff. Strict operating procedure should be defined  
17 to avoid what is presently known and to collect all  
18 variable data needed to have a chance to understand  
19 the signification of an adverse event.

20           In this field, biological memories such as  
21 sera and living cell are necessary from all the  
22 protagonists. Operational research on the risk of  
23 transmission is also needed. In fact, most of the  
24 present risk assessment are speculative, based upon  
25 the notion of a close -- treated by  
26 xenotransplantation and possible retroviruses  
27 recombination.

1                   This speculation may tend to overestimate  
2 the risks maybe of animal disease spreading. After  
3 the long term guidelines prepared in 1997, the next  
4 priority for the expert committee of the Establissement  
5 Francais des Greffes is to assess the potential  
6 benefits of xenotransplantation and the risks.

7                   Product derived from animals are currently  
8 being used as medical devices without any specific  
9 ethical consideration. Man has been using animals for  
10 food and companionship, and animals provide insulin  
11 and heart valves for a long time without raising any  
12 questions, but the removal of one organ from man and  
13 its replacement by an animal one may raise issues.

14                   The ethics of xenotransplantation covers  
15 individual, professional and community issues, as well  
16 as its feasibility raises ethical, philosophical,  
17 religious, legal and also psychological implications.

18                   Considering that this topic is fairly  
19 complicated, it is essential to take as a general  
20 principle that any person involved in this question,  
21 either recipient of professional, should have the  
22 right to opt out without any prejudice. Freedom of  
23 conscience is essential, but informed consent suppose  
24 the agreement for long term surveillance and its  
25 constraints.

26                   As a new perspective of medical territory,  
27 xenotransplantation is not well known by the general

1 public, and one may see what would happen if  
2 xenotransplantation became a standard form of surgery.  
3 The general public needs a significant amount of  
4 information provided by health authorities and  
5 professionals to understand the clinical and ethical  
6 issues surrounding this practice.

7           It is absolutely necessary to combine  
8 scientific and philosophical expertise, taking into  
9 account all the positions to facilitate the general  
10 debate in an informed and understandable way. Social  
11 and ethical constraints could be important obstacles  
12 to success with xenotransplantation.

13           Actually, one could be afraid that  
14 xenotransplantation understood as a complete answer to  
15 the problem of organ shortage may decrease the  
16 perceived need for human organ donation, and thus  
17 reduce the availability of organs of human origin.  
18 This could be the main adverse result of a too large  
19 promotion of this new high technology procedure.

20           This fundamental issue must be pointed out  
21 for and by the professionals, but above all for the  
22 general public and the waiting recipients.  
23 Xenotransplantation is one of the solutions to the  
24 shortage of human organs, and only one among others.  
25 It is one of the basic information to issue in all the  
26 mass media.

27           Just a few relevant informations are

1 valuable about societal and recipient attitudes toward  
2 xenotransplantation, showing a gap among professionals  
3 themselves and between professional and public.

4           Among the general population sample in  
5 France questioned by phone, only 44 persons accepted  
6 xenotransplantation without any precision on animal  
7 source species. Forty-eight persons refused. Results  
8 confirmed the Australian study where 42 persons of  
9 potential recipients with renal failure would accept  
10 an organ of a closely related animal or a distant  
11 species.

12           A national survey is actually going on in  
13 France among patients, health workers and general  
14 population. It will be achieved within six months.  
15 The allocation of available organs, either human or of  
16 animal origin, is an important question if the ethical  
17 view is considered.

18           One, medical -- are needed to determine  
19 which organ, human or animal, should be allocated to  
20 which patient. Xenotransplantation has the advantage  
21 of catching regularly the attention of the media, and  
22 it is important to take this opportunity to state  
23 which animal species would be involved.

24           It looks ethically acceptable to use an  
25 organ from a closely related animal such as  
26 chimpanzee, but it is now clear that this species and  
27 the other nonhuman primates, especially higher apes,

1 are no longer considered as potential donors.

2           The actual international position is the  
3 pig will provide the most suitable solid organs and  
4 cells for human beings, and that transgenic  
5 modification of pig are particularly acceptable.

6           The public debate must go after this clear  
7 and uncontroversial basis to avoid any deadlock.

8           The practical implication of this  
9 position: It is the political duty to make regulation  
10 about the production and care of animals and about the  
11 process of producing pigs free from infectious  
12 organisms.

13           In addition, guidelines on the removal for  
14 organs and tissues from the animal need to be prepared  
15 by expert committee. The ethical aspects of  
16 xenotransplantation are presently in France under  
17 scrutiny by the national ethics committee.

18           Considering the absence of any specific  
19 guidelines to regulate the use and sanitation during  
20 the first period, the Establishment Francais des  
21 Greffes has formed by the end of 1995 an expert  
22 committee on xenotransplantation. We've gathered  
23 various specialists.

24           This expert committee has work in two  
25 fields and three fields, guidelines for the production  
26 of specific pathogen free, guidelines for long term  
27 epidemiological surveillance, and research on risk

1 assessments; but in fact, only one multicentric  
2 clinical trial on an extracted liver assist system  
3 with porcine pathogens was submitted to the Ministry  
4 of Health during the first period.

5           Phase I was conducted in three centers,  
6 two in the United States and one in France, and was  
7 approved for ten patients in France with acute liver  
8 failure. This Phase I is now concluded in France, and  
9 Phase II and III center examination.

10           Compassionate use of this technique was  
11 refused last month by the Minister of Health according  
12 to more recent assessments of the microbiological risk  
13 and the low benefit that can be supposed.

14           More recently, on January 14 -- that means  
15 last week -- the French Parliament adopted the first -  
16 - about a new health regulation which includes a  
17 special statement upon xenotransplantation. Firstly,  
18 that the use of such elements of animal origin must be  
19 and can only be done under biomedical research  
20 regulations.

21           Secondly, all clinical research trials  
22 need the approval of the Minister of Health after  
23 consultation of a new national health safety agency,  
24 which is going to be created, and the Etablissement  
25 Francais des Greffes.

26           The text expresses a particular concern  
27 over the potential transmission of infectious agents,

1 and allaying the idea that approval could be given  
2 provided that the long term epidemiological survey  
3 system would be established. Special guidelines about  
4 graft retrieval, conservation, transformation and  
5 transport should be followed.

6           A complete legal framework based upon the  
7 principles of the present flow is going to be heard  
8 during the year to resolve the various issues posed by  
9 this topic. Practically, every new project of  
10 xenotransplantation clinical application will be  
11 screened to define the balance between the risks and  
12 the benefits, either for the patient or upon the  
13 community.

14           As a temporary conclusion, it can be said  
15 that the majority of French scientists consider that  
16 more is to be done and learn in several fields before  
17 beginning any clinical trial. The physiological  
18 compatibility between graft and recipient is quite  
19 unknown. The mechanisms of xenograft rejection are  
20 not yet understood, and its prevention is not  
21 experimentally clearly demonstrated.

22           The effectiveness of this therapeutic  
23 choice should be more firmly established, and viral  
24 safety is not sufficiently guaranteed. The field of  
25 xenotransplantation is still presumably of  
26 experimental research concern, much more than the  
27 field of clinical application.

1                   According to the international interest  
2 shown in the topic of xenotransplantation, and  
3 according to all the projects which are multicentric  
4 projects involving several countries, the necessity of  
5 cooperation to exchange continuous information between  
6 the various agencies involved in xenotransplantation  
7 must be underlined.

8                   Thank you for your attention.

9                   DR. RONCHI: Our next speaker is Annika  
10 Tibell. Dr. Tibell is senior staff member at the  
11 Department of Transplantation surgery at the  
12 Karolinska Institute, Stockholm, Sweden.

13                   She's here to present the activities of  
14 the xenotransplantation committee recently appointed  
15 by the Swedish government. She has led, together with  
16 Karl Groth, a study of porcine islet transplantation  
17 and has a special responsibility for large animal  
18 studies and safety issues related to future clinical  
19 trials in this field.

20                   DR. TIBELL: I'd like to start by thanking  
21 the organizers, and especially Ms. Amy Patterson, for  
22 giving me the opportunity to come here and present to  
23 you the evolving regulatory guidelines for  
24 xenotransplantation in Sweden.

25                   Xenotransplant research is rather active  
26 in Sweden. We have approximately 15 groups working  
27 within the field, and three of them have programs

1 aiming at clinical application of xenotransplantation.

2           One of them is the group at the Karolinska  
3 Institute in Stockholm headed by Karl Groth, working  
4 on porcine islet transplantation, and in this group we  
5 did ten fetal porcine islet transplants during 1990 to  
6 1993.

7           These transplants were performed with  
8 approval of the local ethics committee and also the  
9 national ethics advisory board. They were discussed  
10 with a body corresponding to FDA, but we didn't have  
11 a formal approval, because it was felt that this body  
12 was not reviewing these kind of activities.

13           Also we had a group in Gothenburg dealing  
14 with vascularized grafts, and this group in 1995 did  
15 two extracorporeal perfusions with renal grafts, and  
16 we had a group in Lund presently doing allogenic fetal  
17 brain transplants in patients with Parkinson's, but  
18 also having a program aiming at porcine fetal neural  
19 cell transplants.

20           In view of this activity, the Swedish  
21 government felt that there was a need for a regulatory  
22 overview in the field of xenotransplantation.

23           The present judicial status in Sweden is  
24 presented on this slide. We do have the  
25 transplantation act from 1995. Brain related death  
26 criteria were introduced in '87, and presumed consent  
27 in '95.

1                   There are some standards relating to this  
2 act on the transmission of infectious disease by  
3 transplantation, and basically allotransplantation,  
4 but otherwise this act does not say anything in  
5 regards to xenotransplantation.

6                   We also have to take into account the  
7 animals protections act, which also has been recently  
8 revised and now states that farmed animals should be  
9 allowed to live as natural life as possible which, of  
10 course, would not be very possible with the animals  
11 bred as xeno donors.

12                   On the other hand, there is a possibility  
13 for exceptions when animals are bred for research use  
14 or medical use.

15                   In the instructions to the committee, it's  
16 stated that the committee shall lead proposals for  
17 statutory reforms. The aspects to be considered are  
18 ethical, medical, judicial, and animal protections  
19 aspects, and the committee shall only deal with  
20 clinical application of xenotransplantation. We will  
21 not discuss the ethical aspects of using, for  
22 instance, primates in preclinical large animal  
23 studies.

24                   The aspects to be covered are also  
25 mirrored by the composition of the committee. That is  
26 summarized on my two next slides. We have three  
27 members of Parliament. This is something -- the

1 Parliament, of course, but also the general public and  
2 the committee is chaired by one of these members.

3           We have one representative for the  
4 Department of Health and Social Affairs in Sweden. We  
5 had a Secretariat. One lawyer, Stefan Reimer, also at  
6 this meeting working full time on this committee, and  
7 one transplant coordinator and one transplant surgeon  
8 not involved in xeno research are also included in the  
9 Secretariate.

10           Then we have a number of experts.  
11 Professor of ethics in Lund, a psychologist, the head  
12 of the Institute for Control Infectious Disease in  
13 Sweden, the head of the Swedish Veterinary Institute.  
14 We have one retired professor of surgery who has been  
15 very active in the previous allotransplantation  
16 committee. We have two senior researchers, myself and  
17 Bruce Arnolfson in Gothenburg, who is a carbohydrate  
18 chemist, and we have one retired judge representing  
19 law.

20           The instructions given to this committee  
21 includes to propose the conditions to be met before  
22 proceeding to new clinical trials, and propose an  
23 official body, existing, one new official body, to  
24 consider and survey future xeno trials.

25           The committee shall also propose special  
26 measures to ensure that a valid informed consent is  
27 given, and take into account the special problems that

1 already have been pointed out at this conference,  
2 pediatric recipients, patients with acute organ  
3 failure, and the consequences for relatives and  
4 society.

5           The committee shall propose guidelines  
6 concerning the control of donor animals, and also  
7 propose guidelines concerning who is to receive allo  
8 organs, allo tissues, and who is to receive xeno  
9 organs.

10           The committee shall propose a system for  
11 registration and surveillance of patients that  
12 eventually will undergo xenotransplantation, and we  
13 shall propose measures to be taken if transfer of the  
14 micro-organisms from animals to man occurs.

15           You can see that the instructions given to  
16 this committee are heavily influenced by the work  
17 performed in United Kingdom and by the draft  
18 guidelines published here in U.S.

19           The instructions also include an official  
20 study the attitudes towards xenotransplantation among  
21 the general public in Sweden. There are a few public  
22 surveys already done in Sweden, one on  
23 allotransplantation that included questions on  
24 willingness to receive an animal graft, and 40 percent  
25 were willing to receive an animal graft compared to 70  
26 percent willing to receive a graft from a cadaveric  
27 donor.

1                   We also know a little about the attitudes  
2 toward gene technique. That is a great reluctance  
3 using gene technique in animals, that 60 percent of  
4 the population are negative to the use of gene  
5 technique in pigs; but we also know that the younger  
6 parts of the population are definitely more positive  
7 than older persons.

8                   The committee will also send out a  
9 questionnaire of its own, going to 1,000 Swedes,  
10 hopefully, mirroring the general public in Sweden, and  
11 also to patients on the waiting list for renal  
12 transplants.

13                   We are presently fighting about  
14 formulating the questions in this questionnaire  
15 because, as you all understand, how these questions  
16 are formulated are, of course, critical.

17                   In the instructions it's also included,  
18 official keep in close contact with the international  
19 development on regulations for xenotransplantation,  
20 and it's not at all the intention of the Swedish  
21 government that Sweden shall have some regulations  
22 that are very different from the regulations  
23 elsewhere.

24                   The committee was appointed very recently,  
25 and we had our first meeting in the beginning of  
26 January. So, I'm sorry, I can't give you any data on  
27 the work so far performed by the committee. The

1 results of the work are supposed to be presented in  
2 April next year.

3 Thank you.

4 MODERATOR RONCHI: We're trying to race  
5 ahead a little bit.

6 Our next speaker is Dr. Stewart Jessamine.  
7 Dr. Stu Jessamine will present New Zealand's  
8 perspective. As a public health expert in New  
9 Zealand, Dr. Jessamine has joined the Therapeutics  
10 Section of the Ministry of Health, and is a member of  
11 several New Zealand ministerial advisory committees;  
12 in particular, has been the author of the New Zealand  
13 interim guidelines on good clinical research practice;  
14 is a member of New Zealand gene therapy advisory  
15 committee and, as such, is responsible for the  
16 development of regulation and policy on  
17 xenotransplantation.

18 DR. JESSAMINE: I'm touched that I've been  
19 given the unique perspective of being a public health  
20 physician. I'm actually a general practitioner, but  
21 that's as good a public health physician as you're  
22 likely to get.

23 I want to start by saying hari mai, hari  
24 mai, hari mai, tenakotu, tenakotu, tenakotu, katur  
25 kiaora. Coming from Atua Aroha, New Zealand, it's  
26 only appropriate that I think I begin this part of  
27 this meeting with a traditional Maori welcome.

1                   During this presentation, I'm going to  
2 discuss the importance of culture at great length, and  
3 I want to start with this -- I'm going to really  
4 discuss four things. I'm going to discuss the  
5 cultural perspective on xenotransplantation. I'm  
6 going to discuss a legislative perspective as we look  
7 at it in New Zealand. I'm going to look at the safety  
8 perspective, but that's really been well covered.  
9 Last, I'm going to briefly touch on venture capital  
10 and how it affects small nations.

11                   I want to start with this slide, which is  
12 -- It's actually the Health Research Commission in New  
13 Zealand's emblem, and it stands for "Knowledge is  
14 Power."

15                   It comes from the Maori creation legend  
16 where Tani, the fellow in the stars, forcibly  
17 separates his mother and father to create the world,  
18 and he does this on the basis of the knowledge that  
19 there is something out there, if he separates his  
20 parents. So it's quite an appropriate and strong  
21 image for the importance of lay culture and cultural  
22 perspective.

23                   When I first was asked to talk here, I  
24 really said to myself, well, what's New Zealand got to  
25 contribute to this meeting, you know. Oh, sorry. New  
26 Zealand is bottom right, for anyone who doesn't know,  
27 and we are top left. I thought it was important that

1 I showed you just how far away we are from anyone.

2 It's over 1,000 miles between New Zealand and  
3 Australia.

4           As I said, you know, we're a small  
5 country. We're a long way from anywhere. We're about  
6 the same size as Colorado, with roughly the same  
7 population, about 3.5 million. We're dominantly  
8 Caucasian race, a nation where about 20 percent of the  
9 population of Maori or Polynesian descent, and they  
10 are the indigenous people of that country.

11           So they have a unique place in New Zealand  
12 culture and increasingly in New Zealand legislation.

13           I want to talk a lot about cultural safety  
14 and culture today, and I want you to think of lay  
15 culture as a lens through which decisions are examined  
16 or the fulcrum in which risks and benefits are  
17 balanced.

18           I think there's a great risk in meetings  
19 like this and in others, that when groups of experts  
20 meet to discuss and make decisions about scientific  
21 risks that the culture and beliefs of the members of  
22 the community are either not respected, not heard, or  
23 are lost by people who speak the technical language of  
24 risk management.

25           I think it's only through recognizing both  
26 the diversity and the importance of lay culture and by  
27 giving weight to other belief systems that the worst

1 excesses of cultural imperialism can be invited, and  
2 this is a high risk activity, I think, in what we do.

3           New Zealand has quite a unique perspective  
4 in that respect on how you develop public policy in  
5 that we do look at cultural issues, and we are  
6 actually, as I'll come to in the legislative section,  
7 required to look at cultural issues when we deal with  
8 scientific risk management.

9           I think we have to say the ethics, in some  
10 sense, is what is right and what is wrong in the  
11 community, and that they're a function of both  
12 scientific culture and lay culture. To explain the  
13 New Zealand perspective, I have to quickly touch on  
14 a very short history of New Zealand bicultural  
15 heritage.

16           New Zealand is as unique as the Galapagos  
17 Islands. This is something that I want to impress.  
18 It separated from Gonduanaland, the southern  
19 supercontinent, before the evolution of mammals. So  
20 that it is a unique case of almost prehistoric trees  
21 and plants and unique fauna and flora.

22           It was colonized about 600 years ago by --  
23 600 to 700 years ago, first by Polynesians and then in  
24 the mid-1800s by Europeans, predominantly from United  
25 Kingdom or England at that time, really.

26           At the time of colonization, there was  
27 somewhere about a quarter of a million Maori

1 established in New Zealand. Now New Zealand was  
2 settled after Australia, and anyone who has any --  
3 knows any history of the Australian settlement know  
4 that it devastated the Aboriginal community.

5 Curiously, the British government was very  
6 concerned that this did not happen to Maori in New  
7 Zealand, and as such, a treaty was drawn up between  
8 the Crown and the Maori which described the rules and  
9 responsibilities of each party under which  
10 colonization could take place. This treaty was called  
11 the Treaty of Waitangi signed in 1840.

12 The treaty really says three things, and  
13 the one to pay attention to is Clause 2 which protects  
14 by legislation Maori's -- the rate of Maori to  
15 unqualified exercise according to their custom over  
16 their land, villages, all their treasures, which  
17 refers to all dimensions of tribal groups, states,  
18 material and nonmaterial heirlooms, sacred places,  
19 ancestral law, and family trees. Fokapapa, as it was  
20 called.

21 Whilst we can certainly argue about what  
22 that treaty actually meant in 1840 when it was signed,  
23 the spirit of that treaty, the partnership concept of  
24 the treaty, has certainly come into legislation in New  
25 Zealand, such that especially when we're dealing with  
26 environmental risks, it is known that to honor Clause  
27 2 of the treat legislation requires that you must

1 consult with treaty partners on risks to the  
2 environment.

3           This consultation model requires respect  
4 for that culture and the traditional beliefs of Maori,  
5 including their world view of tapu, which is things  
6 that are forbidden to be done, and no, things which  
7 cannot or should not be done and which are punishable  
8 by -- within a tribe, and also the processes that can  
9 take place to remove these tapus or banishments.

10           The Maori world in a holistic interlinked  
11 world of place of man in his environment, and it's  
12 quite distinct from European world views and also from  
13 scientific rationalism. In New Zealand we are coming  
14 to accept the validity of this Maori perspective as  
15 being no less real than that of anyone else in the  
16 country, and it's simply becoming in the development  
17 of policy something that we must consider.

18           This has passed into what we would call  
19 ethics committees and you would call institutional  
20 review boards where, to be accredited, the ethics  
21 committee must contain a minimum number of Maori as  
22 well, and a very minimum number of medical  
23 practitioners, such that the ethics committees are  
24 predominantly laypersons.

25           Maori represent the local Iwi or sub-  
26 tribe, and they can discuss research protocols with  
27 elders from those tribes. The active involvement in

1 Maori has changed how research is done in New Zealand.  
2 It has changed the relationship between researcher and  
3 participant, to the point that the researcher -- If a  
4 researcher takes a blood sample or a tissue sample,  
5 the researcher does not own that sample. that sample  
6 is held on trusteeship of that sub-tribe, and must be  
7 given back to the members of that tribe at the end of  
8 the trial or disposed of according to Maori custom.  
9 It is an issue where trusteeship takes place.

10 In some cases, this has reached the point  
11 where, if research has been conducted predominantly on  
12 an Iwi or sub-tribe, that that tribe may have some  
13 claim on the intellectual property of the research and  
14 will hold copies of all the research papers  
15 themselves. So it's quite a different relationship.

16 To illustrate this partnership, I want to  
17 just show you a slide which is called Kororerero,  
18 which means let's talk about it. It's on a Maori  
19 health development.

20 The motif symbolizes partnership between  
21 cultures grounded in the earth and in science and  
22 looking towards the future, and the text emphasizes  
23 that progress can only be made through discussion and  
24 sharing of information.

25 I want to move to legislative  
26 perspectives. I make no apology. Originally, I was  
27 going to apologize for using Michael Crichton as an

1 author, but I really think that we haven't -- I want  
2 to give this as a lay perspective on what people  
3 outside may think about this, and in that respect both  
4 Michael Crichton is appropriate and, to some extent,  
5 in a lay environment Allen Ginsberg is quoted equally  
6 as appropriate.

7           Crichton certainly regards  
8 commercialization in molecular biology. He describes  
9 it as the most stunning ethical event the history of  
10 science has ever seen, and he's particularly disturbed  
11 by the lack of transparency in decision making, and  
12 that's probably a pretty good argument, if it's true,  
13 for strict regulation and monitoring by government.

14           In New Zealand we certainly believe that  
15 xenotransplantation is a high risk activity, given the  
16 unknowns, and we intend to try and regulate this  
17 through our current medicines legislation which views  
18 xenotransplants as a medicine. However, the concept  
19 of xenotransplantation as a medicine, we know, does  
20 not apply to solid organs.

21           So we've already got ourselves into a  
22 position akin to the U.K. where bits of  
23 xenotransplantation are medicines, but other bits are  
24 clearly not, and we don't regulate organs either.

25           It's interesting that this view of  
26 xenotransplantation as a medicine is probably still  
27 open to legal challenge in a number of countries

1 around the world, and that most medicines acts were  
2 written several years ago without even the  
3 consideration that xenotransplantation could exist,  
4 and certainly in the Kennedy Report this is made --  
5 the legal opinion expressed there is exactly not that  
6 you may need specific regulation. However, really,  
7 these things are often decided in courts of law, and  
8 we haven't had the discussion about  
9 xenotransplantation with our public, nor have we had  
10 the discussion about transgenesis either.

11           So we have really got quite a long way to  
12 go here. In the interim, we will certainly try and  
13 regulate through our medicines act, but given that  
14 this is very cutting edge stuff, New Zealand and all  
15 other small countries are nowhere near -- We're not in  
16 a position to develop our own guidelines.

17           We need guidance on policy and guidelines  
18 from fora like these before we can even begin to  
19 consider how or if xenotransplantation can occur in  
20 our countries.

21           I think we all share a number of concerns  
22 about the safety, and we've heard so much about these,  
23 I won't dwell on it other than to -- If we take New  
24 Zealand as a pastoral nation, I think we have to say  
25 that to date the underlying theme in the papers we  
26 have seen tend to be that, based on a very -- man at  
27 the center of things, it's been looking at controlling

1 and confining the donor animal and, to some extent,  
2 controlling and defining the recipient of a  
3 xenotransplant to minimize risk.

4           New Zealand has got 3.5 million people.  
5 It's got 47 million sheep, several million cattle, an  
6 unknown number of domesticated and wild pigs, and  
7 approximately 17 million possums.

8           I mentioned possums specifically, because  
9 they're an intragis species, and they have no  
10 predators in New Zealand. Australia, the natural  
11 home, they are a protected species. So we have quite  
12 -- Our experiences with rabbits, rats, deer, possums.

13           In the recent unofficial release of rabbit  
14 kilesi virus to try and destroy -- to introduce  
15 rabbit species give us quite a good understanding  
16 about the risks associated with release of exotic  
17 species into our environment.

18           One of the other issues that that brings  
19 me to, and I raise as a question for some of the  
20 experts in the hall, is that the U.K. report or the  
21 Kennedy Report points out that there's very little  
22 research on what has come to be called by some people  
23 reverse zoonosis. By this I mean whereby a xenogeneic  
24 agent mutates or has a DNA change within its -- after  
25 it has been implanted in a human and produces an agent  
26 that is not necessarily pathogenic to the human, but  
27 becomes a significant pathogen in either the original

1 host animal or in another species.

2           Now I accept that this is -- well, I was  
3 debating with someone this morning whether influenza  
4 was an example of where you may get an example of  
5 that. It may never have happened, but if we take a  
6 country, we have to look at the risks associated with  
7 that as part of our policy making initiatives.

8           The risk of reverse zoonosis may be so  
9 small that it would be entirely acceptable to an urban  
10 New Yorker, but to a pastoral trading nation where, I  
11 would be willing to bet you that the first or second  
12 person who got a xenotransplant in New Zealand would  
13 probably be either a dairy farmer or a sheep farmer,  
14 it's quite different, given that we know that New  
15 Zealanders have access to farms.

16           A large number of New Zealanders keep pet  
17 lambs, pet cattle, pet goats. We know that this is a  
18 risk, and in developing policy in this area, we've  
19 really got to go beyond the human model, I believe, in  
20 our thinking and consider risks to other animal  
21 species in addition to the donor species.

22           I think we have to take this broad  
23 intersectoral approach to policy, because if we don't  
24 do it here, there is a real risk that alternative  
25 policy may be developed and passed through trading  
26 nations which is based purely on this risk to their  
27 major exports. I'd be quite clear that the first

1 country that would buy an importation of meat, if and  
2 should this thing happen, would be the United States  
3 of America.

4           So we really want to -- I think we do have  
5 to think about that. Certainly, if we apply the  
6 principle to the Treaty of Waitangi to policy  
7 development in xenotransplantation, I think we have to  
8 look at the possible risk of transmission of new novel  
9 or genetically modified agents to our treasures in the  
10 community.

11           Arthur C. Clarke -- what can you say? --  
12 and Michael Crichton again -- The escape of kilesi  
13 virus from the secure biosecurity island off the coast  
14 of Australia would more than make the case that  
15 Michael Crichton makes here, I think.

16           I think today we've all -- in the last two  
17 days we've had some discussions that perhaps under-  
18 represent the complexity in xenotransplantation.  
19 There's a certain feeling that it's all very  
20 commonplace, and in New Zealand we certainly, in our  
21 preliminary discussions, had some difficulties with  
22 those contentions, that it wasn't really that simple  
23 and straightforward and that the idea that you simply  
24 take an SPF pig pancreas as a for instance and somehow  
25 do something to the cells and then just pour them in  
26 and everything is going to be hunky-dory.

27           I think a lot of people in the public and

1 in the scientific press in New Zealand had a lot of  
2 trouble with those ideas. I think some of those  
3 concerns are more than adequately expressed in the  
4 Kennedy Report that I referred to earlier.

5 I also -- We also have some concerns, if  
6 we do view xenotransplantation as a medicine, that  
7 there are significant gaps in the preclinical work,  
8 that if it was a chemical, we would certainly not be  
9 rushing to do some of the things that -- we might not  
10 be asking ourselves the questions we are asking  
11 ourselves today.

12 I think in developing policy we certainly  
13 have to ask ourselves some fairly basic questions  
14 about who, what, where, why, and when, and what are  
15 the underlying reasons for rushing to do some things.  
16 I also believe that we in small countries have to ask  
17 ourselves and be concerned about the very limited  
18 number of experts we have access to and the importance  
19 of -- and these kind of forum and international  
20 cooperation is massive.

21 To my knowledge, we have no publications  
22 from New Zealand on the basic science behind many of  
23 the aspects of xenotransplantation. Yet we've already  
24 received an application to perform research in humans,  
25 based entirely on other people's works conducted in  
26 other centers.

27 I think that this iterative nature of

1 research in general and xenotransplantation in  
2 particular may very well be one reason why we would  
3 prefer to see very clear policy set up before  
4 guidelines are confirmed as anything more than draft.

5           Guidelines have with them associated  
6 risks, I believe. I don't think -- I'm not saying  
7 that research shouldn't occur, but that rather we have  
8 to take this opportunity in the ethical part of it to  
9 try and define the who, what, where, why and when  
10 would be the best way for research to go forward.

11           I'm coming up to the last section, thank  
12 goodness.

13           There's no doubt in everything we read  
14 that the future in transplantation medicine seems to  
15 be about xenotransplantation. I share some of the  
16 other speakers' concerns, which I appreciate the  
17 conference is about xenotransplantation, but that  
18 there has not been a great deal said about improving  
19 the allotransplantation side of things in quite the  
20 same way as the Kennedy Report strongly came out,  
21 saying you have to push as parallel development. That  
22 is necessary rather than lots of money going into  
23 xenotransplantation and allotransplantation being  
24 allowed to wither on the vine, but I appreciate that  
25 may just be the forum in which we're in.

26           I think that there is a clear role for  
27 venture capital in the development and perfection of

1 xenotransplantation. Commercial funding has almost  
2 certainly sped this process along, and it's really  
3 government policy. However, I do have to say that I'm  
4 a lot more comfortable with funding from  
5 pharmaceutical industry here as a regulator than I am  
6 with some start-up venture capital type things.

7           In New Zealand, for example, the reported  
8 funder of our proposed study to conduct a clinical  
9 trial is a private company which has no previous  
10 experience in either the development of medicines or  
11 in biotechnology whatsoever.

12           That -- I have to ask myself, in small  
13 countries this is the reality of where research may  
14 come from, and certainly in defining policy and  
15 guidelines we may have to consider some of those  
16 aspects of where does the money come from, who is  
17 conducting the research, which you have to lock up  
18 very tightly in your guidelines. This will probably  
19 mean more government rather than less.

20           These are just another two slides I want  
21 to go back to. Science tells us what we can know, but  
22 what we know is little and, if we forget how much we  
23 cannot know, we become insensitive to many things of  
24 great importance. I think that really more than sums  
25 up a lot of the ethical perspective side of things.

26           I think it's important that we do, from a  
27 New Zealand perspective, acknowledge the importance of

1 lay culture, that we think beyond just science but to  
2 what people believe and what cultural beliefs exist,  
3 that we embrace the concepts of trusteeship which  
4 extend across generations as well, that we must have  
5 guidelines and policy that is applicable  
6 internationally and is equitable.

7           In closing, I want to show you this fellow  
8 who is a hatiki. It's a Maori image of symbolizing a  
9 way forward. It's viewed by some as a symbol of  
10 fertility, which is interesting. In this case,  
11 however, it's symbolic of tehaora, total wellbeing or  
12 holistic health.

13           The design features two figures, again  
14 symbolizing partnership between the scientific  
15 community and the lay community, if you wish, but in  
16 New Zealand between the treaty partners. Two hands  
17 each have four fingers, symbolizing the cornerstones  
18 of the Maori philosophy of health.

19           The hatiki has two heads positioned facing  
20 each other. The heads are joined at the lips to form  
21 one mouth with two tongues, the two tongues signifying  
22 two languages and two cultures working together  
23 towards one common goal. This goal is symbolized by  
24 the one mouth and is the good health of the people.

25           The two figures are joined so that they  
26 may learn to share and work together equally in  
27 unison, and the text reads quite simply: There is

1 something to be said for talking together.

2           The concept expressed in the hatiki, I  
3 believe, apply not only to the development of health  
4 services in New Zealand but also can be seen as a  
5 symbol of what you must do when you are formulating  
6 policy that is equitable on xenotransplantation.

7           Thank you.

8           MODERATOR WITT: For the sake of time, I'm  
9 going to go straight into what WHO has been trying to  
10 do for the last couple of years with respect to  
11 xenotransplantation, if we could have the slides.

12           A fundamental goal for the World Health  
13 Organization is to encourage the development of safe  
14 and effective methods for improving human health  
15 worldwide. Xenotransplantation is an area of current  
16 biomedical research which may have the potential to  
17 contribute to this overall goal.

18           Therefore, as such, even though it would  
19 be premature to either endorse or discourage its use,  
20 the WHO is greatly interested in the progress made in  
21 this technology's development; because while  
22 xenotransplantation is being investigated primarily in  
23 the industrialized world, its potential for clinical  
24 application will impact all countries.

25           It is an acknowledgement of the  
26 technology's potential significance globally. The  
27 World Health Organization has begun activities to

1 encourage its member states to appreciate the issues  
2 surrounding the technology and, if they so choose, to  
3 start considering the development of their national  
4 plans, programs and policies for dealing with this  
5 issue.

6                 Since the World Health Organization is not  
7 a governing or regulatory body, this act of  
8 encouragement is a principal mechanism for striving  
9 towards our goal of a healthier world. In this  
10 respect, the World Health Organization welcomes the  
11 efforts of the United States in taking a proactive  
12 role in its public health approach toward  
13 xenotransplantation.

14                 We appreciate your efforts in producing  
15 the PHS guideline in infectious disease issues in  
16 transplantation -- xenotransplantation, in initiating  
17 a pilot xenotransplantation registry database, and in  
18 sponsoring this series of workshops. It is this  
19 latest activity, this last activity especially, which  
20 is critically in the process of developing informed  
21 public debate which will in turn lead to the  
22 production of a sound and reasoned national policy on  
23 this technology.

24                 From a global perspective, there are  
25 several potential benefits and costs to the  
26 development of xenotransplantation, and we've heard  
27 many of them over the last day and a half. It could

1 be used, obviously, as a means to alleviate the  
2 discrepancy between the numbers of allotransplants  
3 needed and the number actually performed around the  
4 world.

5           We have heard about the problems of this  
6 discrepancy between the demand and the shortage for  
7 organs to be transplanted in the United States and  
8 some of the other industrial countries that have had  
9 presentations this morning, and in these countries  
10 where it might be assumed there may not be major  
11 overriding economic, social or religious constraints  
12 against the legal and ethical donation of human  
13 organs; but in other countries where such factors as  
14 cultural or economic constraints may play a role in  
15 the unavailability of organs for transplantation, the  
16 shortfall maybe even is quite a bit larger than in the  
17 industrialized world.

18           For example, in these numbers that I've  
19 received from Dr. Alano, who is the Director of the  
20 Kidney Foundation of the Philippines, we can see that  
21 in 1977 in Japan on the first line there, which has a  
22 population above 125 million in individuals, only 600  
23 renal transplants were performed, but there were  
24 14,000 individuals on waiting lists.

25           We might attribute this gap to cultural  
26 prohibitions against transplantation in general, and  
27 we'll go into that in a minute, or to the economic

1 capacity to sustain patients long term on dialysis.

2 One could suggest that the introduction of  
3 xenotransplantation in Japan might not help alleviate  
4 their problem, but what about other countries in the  
5 region?

6           Note that in both Indonesia, with a  
7 population approaching 200 million, and Malaysia, with  
8 a population approximately 20 million, the demand for  
9 kidneys far outstrips the supply, but the total number  
10 of persons on waiting lists are much less than in  
11 Japan in actual numbers and in proportion to their  
12 populations.

13           This could reflect the influence of  
14 religious custom. Both nations are heavily Islamic.  
15 Perhaps it could reflect an insufficient economic  
16 capacity for chronic supportive care to keep patients  
17 alive until suitable organs, human organs, become  
18 available.

19           The Philippines with a population of 68  
20 million might also have a similar problem in an  
21 infrastructure in keeping patients alive until organs  
22 become available.

23           Also note that there were no cadaveric  
24 donations used in either Indonesia or Malaysia in  
25 1997. Again, this could reflect religious custom, but  
26 it could also be a reflection of possible  
27 infrastructure difficulties in delivering viable

1 cadaveric organs to transplant centers where they are  
2 needed.

3           These numbers raise many questions which  
4 cannot, obviously, be answered here in the short time  
5 that we have, but one thing is clear. The need for  
6 transplantable human organs is not being met by  
7 existing methods in, I would venture to say, all  
8 countries on the globe. Other methods are required,  
9 and innovative approaches are, in fact, being tried,  
10 but by themselves they may not completely solve the  
11 problem.

12           The use of related and nonrelated living  
13 donors and the use of compensation for donation are  
14 alternatives under consideration in many parts of the  
15 world, but these, obviously, pose significant legal  
16 and ethical questions.

17           The use of xenotransplantation to help  
18 overcome this shortage and other potential benefits,  
19 obviously, must be weighed against its potential  
20 negative implications. Xenotransplantation presents  
21 a risk for xeno zoonosis.

22           This risk is not just local or national.  
23 In today's shrinking world, it is an international  
24 issue. It will affect all of us.

25           Also, the ethical implications of  
26 xenotransplantation could prove to be significant  
27 risks or costs. For example, what psychological

1 effects will there be on the recipient of an  
2 individual -- on the recipient as an individual  
3 person, his family members, or other close contacts?

4           As members of a society, cultural or  
5 religious group, how will the concept and fact of  
6 xenotransplantation be received by different persons  
7 and different peoples?

8           It is possible that xenotransplantation  
9 will be accepted into some societies without  
10 difficulty. This may occur where there is no  
11 preexisting or conflicting belief system or other  
12 cultural or ethical norm against which the technology  
13 will have to compete.

14           For example, in some countries it may be  
15 embraced as a demonstration of national capacity or be  
16 a symbol of national modernity. In others, acceptance  
17 may at best be conditional or selective.

18           For example, in some African countries  
19 traditional belief systems will reject the use of some  
20 species of animals and accept the use of others for  
21 this purpose, depending on the believed influence the  
22 spirit of different species of animals can exert on  
23 the personality of recipients after transplantation.

24           For some peoples, the concept of  
25 xenotransplantation will be in total conflict with  
26 existing belief systems, and the introduction of the  
27 technology will either be totally rejected as

1 unacceptable or, if acceptable, may contribute to the  
2 disruption of the traditional structure and fabric of  
3 that peoples' lives and communities.

4           The Shinto belief system in Japan is in  
5 part a good example of this. In Shintoism the concept  
6 of injuring the bodies of the dead, whether they be  
7 human or animal, by the unnatural act of removing  
8 organs or tissues for use in another is unacceptable,  
9 because it injures the spirit of the dead, and it  
10 degrades the living.

11           There is also a strong sense of bodily  
12 integrity which any transplantation violates. The  
13 implementation of xenotransplantation in Japan would  
14 probably present a major challenge to the very  
15 foundation of that country's sense of being or  
16 civilization or the need for proper human conduct.

17           Also to many people, the welfare and use  
18 of animals in xenotransplantation is considered a  
19 cultural or moral cost that may be too great to permit  
20 any use of this technology. For example, one can  
21 almost think of Hinduism and the rejection of using  
22 animals for food or any real purpose that serves only  
23 man.

24           The decision to use animals for  
25 xenotransplantation, on which animals to use, and how  
26 they will be used will influence how some persons and  
27 communities view themselves, their place in society,

1 and their role in nature and in the environment. All  
2 these potential disadvantages deserve serious  
3 consideration and thought.

4           The World Health Organization has  
5 approached these various concerns and issues through  
6 two channels. Under the World Health Organization  
7 Advisory Committee on Health Research, a task force on  
8 transplantation is reviewing the economic, social,  
9 biomedical, ethical and legal factors which influence  
10 the practice of organ transplantation in general, and  
11 includes specific discussions on xenotransplantation.

12           Also, through the Division of Emerging and  
13 Other Communicable Diseases Surveillance and Control,  
14 the WHO has produced two documents, and they should be  
15 available for you out on the table in the lobby.  
16 These documents should serve as a guidance and  
17 information source to WHO member states.

18           The first document is concerned with  
19 infectious disease issues. The second is a report on  
20 the conclusions and recommendations of a consultation  
21 on xenotransplantation that we held in Geneva last  
22 October.

23           The first document is entitled "Guidance  
24 on Infectious Disease Prevention and Management," and  
25 it presents a discussion on the infectious disease  
26 issues surrounding xenotransplantation and reviews the  
27 potential for infectious disease risk and the need to

1 perform risk assessments.

2           The type and range of potentially relevant  
3 infectious agents are mentioned, as are some possible  
4 steps for risk reduction. The document describes some  
5 animal and recipient health monitoring and follow-up  
6 procedures which could be relevant to national  
7 xenotransplantation programs, and at the end of the  
8 document there's a listing of suggested criteria for  
9 formulating infectious agent exclusion lists specific  
10 to xenotransplant applications.

11           These criteria are intended to assist  
12 deliberations on which animals may or may not be  
13 suitable for xenotransplantation from an infectious  
14 disease perspective only, and what types of infectious  
15 agents should be excluded from xenotransplants.

16           To further the infectious disease  
17 discussions and also to begin to identify the array of  
18 ethical issues surrounding xenotransplantation, the  
19 WHO has also produced a report on the conclusions and  
20 recommendations of its consultation.

21           This consultation benefitted by the  
22 participants of over 30 specialists from around the  
23 world with expertise in immunology, infectious  
24 diseases, preventive medicine, biomedical research,  
25 veterinary sciences, regulatory affairs, ethics and  
26 law.

27           The topics discussed included the status

1 of xenotransplant research and development, xeno  
2 zoonotic disease risk and prevention issues, and  
3 ethical and social considerations. The consultation  
4 concluded that, if xenotransplantation is in fact to  
5 be developed and implemented, it must be done in a  
6 manner consistent with such basically and globally  
7 accepted principles as safety, efficacy, equitable  
8 access, and respect for the dignity and rights in  
9 humans.

10           It must be recognized that there is a real  
11 but currently unquantifiable infectious disease risk  
12 associated with the technology, and that measures  
13 should be undertaken to define and minimize that risk.  
14 Safety should be maximized for individual recipients,  
15 recipient contacts, local and national communities,  
16 and the international community.

17           The proposed applications should be  
18 efficacious. They should have a reasonable  
19 expectation of benefitting the recipient and be in  
20 conformity with generally accepted standards of good  
21 clinical and scientific practice.

22           Also, scientific and technical information  
23 about xenotransplantation should be accessible in an  
24 equitable manner. Unfair or discriminatory practices  
25 denying access to the technology should not be  
26 permitted.

27           The development and application of

1 xenotransplantation should respect the dignity and  
2 rights of all humans. This not only includes respect  
3 for different countries' ethical, social, cultural and  
4 religious beliefs and legal norms, but also means  
5 respect for individuals' rights and dignity.

6           Therefore, persons should not be  
7 ostracized or discriminated against because of their  
8 xenotransplant status.

9           Based on these conclusions, the  
10 consultation made recommendations to both the World  
11 Health Organization member states and to the  
12 organization itself, recognizing that, on the one  
13 hand, member states need to develop their own  
14 policies, regulations and guidances as individual  
15 sovereign countries and as responsible members of the  
16 international community; and on the other hand, that  
17 the WHO should play a role in facilitating member  
18 state activities.

19           The consultation recommended that, if  
20 member states undertake xenotransplantation, they  
21 should promote individual and public health and safety  
22 by supporting xeno zoonosis research and developing  
23 quality assurance programs for xenotransplant  
24 processes, including animal health monitoring  
25 practices.

26           Member states should develop and practice  
27 recipient and contact infection assessment strategies

1 to detect xeno zoonotic event occurrences, and  
2 adequately management them if they occur.

3 Member states should counsel recipients  
4 and contacts on infection risks and prevention  
5 practices, and develop registries of recipients and  
6 archives of animal and recipient biologic samples for  
7 epidemiologic studies deemed necessary in the  
8 recipient's host interest, and as well as interests of  
9 public health and safety.

10 It was further recommended that member  
11 states consider the development of xenotransplantation  
12 review boards. They should have multi-disciplinary  
13 expertise and meet in a timely manner to adequately  
14 review national policies and activities, and provide  
15 a mechanism for protecting xenotransplant recipients  
16 from unreasonable limitations on their rights and  
17 freedoms.

18 These boards could also be used to promote  
19 international communication and cooperation on  
20 xenotransplant issues and events.

21 International cooperation between member  
22 states, both bilateral and multilateral, should be  
23 used as a means for promoting safety and efficacy and  
24 assuring international conformity with the generally  
25 accepted ethical and legal standards of conduct.

26 Along these lines, the consultation  
27 recommended that member states design and generate

1 their database and registry systems in such a way as  
2 to facilitate international comparative and  
3 complementary analyses of relevant data. This will be  
4 essential for detecting international patterns of  
5 xenotransplant events and will permit the exercise of  
6 international risk management strategies.

7           Finally, it was recommended that member  
8 states consider promoting and supporting communication  
9 and cooperation between national, regional and  
10 international organizations and societies having an  
11 interest in xenotransplantation, in an effort to  
12 disseminate information on and contribute to an  
13 informed decision making process on this technology  
14 internationally.

15           In addition to these recommendations, the  
16 consultation made the following recommendations to the  
17 World Health Organization.

18           The WHO should consider activities which  
19 provide guidance and facilitate national, regional and  
20 global discussion on xeno zoonosis issues, and promote  
21 informed public debate on the ethical issues involved.

22           The Organization should support the  
23 development of measures which maximize safety,  
24 efficacy and adherence to ethical principles. It  
25 should provide technical expertise and guidance to  
26 support the development of national and international  
27 archive and registry systems, and encourage

1 compatibility and cooperation between national  
2 programs.

3           In response to these recommendations, the  
4 WHO has begun distributing the consultation report and  
5 the infectious disease guidance document to its  
6 Executive Board, which is meeting this week in Geneva,  
7 and to the Ministries of Health of WHO member states,  
8 and to other groups and organizations identified as  
9 playing a critical role in the decision making process  
10 on xenotransplantation.

11           The WHO's aim is to generate and offer  
12 internationally acceptable and relevant  
13 recommendations and guidance on the implications of  
14 this technology and, when and where necessary, on  
15 measures for its safe and ethical development and  
16 usage, in an effort to attain a healthier world.

17           The WHO firmly believes that we all need  
18 to be active partners in striving towards this goal  
19 for a healthier world.

20           Thank you for your attention.

21           With that, if our panel members would like  
22 to come on up and take their seats, we can discuss  
23 some of the international perspectives raised this  
24 morning, and also we would like to be joined by Dr.  
25 Jonathan Dark, who is a cardiothoracic surgeon and who  
26 is Director of the Cardiopulmonary Transplant Unit of  
27 Freeman Hospital in the U.K., and also Dr. Peter Ganz

1 who is Acting Manager of the Blood and Tissues  
2 Division, Bureau of Biologics and  
3 Radiopharmaceuticals, with Health Canada. Welcome.

4           MODERATOR RONCHI: We will open this panel  
5 session to questions from the public.

6           MODERATOR WITT: If there are no immediate  
7 questions from the public, maybe, Andre, would you  
8 like to say something to kind of kick things off?  
9 Then we'll let Dan say something.

10           DR. LA PRAIRIE: Well, I'll be quick then.  
11 Certainly, there were lots of issues raised that are  
12 international in scope. Probably harmonization  
13 standards, the need for linking national review  
14 committees internationally maybe is something that  
15 would need to be discussed.

16           I actually do have a question for both the  
17 panel and the audience. The clear message I'm hearing  
18 today is that the public needs to be more than just  
19 informed. In fact, the questions of public safety --  
20 you almost want the public to make that decision.

21           In fact, Canada's own Margaret Somerville  
22 suggested that we have informed consent of the public.  
23 At least she stopped at not saying written consent,  
24 because, of course, I don't know how we would  
25 accomplish that; but I would ask, how do we get  
26 informed public consent on the issue of  
27 xenotransplantation.

1                   Are there any good models in public safety  
2 for this, such as the issue of Kreutzfeldt Jakob  
3 disease in blood transfusion? Is there an easy way to  
4 address that point? I'll ask that question.

5                   DR. BACH: There is no easy way, as I  
6 understand it, from what we discussed, but there are  
7 ways. In fact, the book that came out in 1996 edited  
8 by Harvey Feinberg and one other person -- and I feel  
9 terrible; I don't remember his name -- tries to deal  
10 with exactly this.

11                   The main thing is to have a body,  
12 committee, whatever you want to call it, that is very  
13 broadly representative of the public. The important  
14 issue is that, when risk is involved, we recognize  
15 that the public sees risks in many different ways, and  
16 based on their past history, their ethical beliefs,  
17 their philosophies, their religions, and that those  
18 are represented to the largest amount possible.

19                   That is not asking the public, but it is  
20 one way of at least getting an opinion that is  
21 representative, as best as one could do. But the  
22 other issue is, of course, to have public forums.

23                   We have a gentlemen in the United States  
24 who has made that a very popular kind of way of  
25 discussing issues, and that can certainly be held; but  
26 the main thing is to have this representative  
27 committee that is charged with representing the

1 public, not trying to make technical guidelines.

2           MODERATOR RONCHI: I would like to  
3 highlight two points that Dr. Jessamine brought out in  
4 his very interesting presentation and that actually  
5 reflect some of the concerns at the OECD.

6           First of all, I would say that we are  
7 concerned that in many countries right now there are  
8 a limited number of experts in the field, and I think  
9 the question of education and training is well placed,  
10 and we should also reflect on that, which is not just  
11 informing the public but, certainly, creating a  
12 reservoir of well educated and trained physicians and  
13 informed physicians.

14           The other point is that many countries do  
15 not even have had a discussion about transgenesis. In  
16 fact, right now I would like to just point out that  
17 Switzerland is in the midst of addressing the question  
18 of transgenesis in a reform -- in a referendum that  
19 they have -- Switzerland is a direct democracy.

20           So I would say that there are some basic  
21 issues that still some countries are tackling, and  
22 that whatever discussion is now carried on needs to  
23 address the technologies that are at the basis of this  
24 -- of xenotransplantation.

25           AUDIENCE MEMBER: Yes. Hello. I'm from  
26 the Medical Research Modernization Committee. I  
27 wanted to commend the presenter from New Zealand for

1 expressing some points of view that I thought were  
2 very valid and that I had not heard presented here  
3 before.

4 I wanted to again ask my question that I  
5 asked the first time, which was: Who will be held  
6 accountable if and when a zoonotic virus is spread to  
7 the human population as a result of  
8 xenotransplantation?

9 I was wondering if any of the panelists  
10 from other countries has explored this issue and,  
11 given the risk of xenotransplantation, I'm a little  
12 bit concerned that the World Health Organization might  
13 believe that xenotransplantation will lead to a  
14 healthier world, if that's something that's been  
15 implied; but the general question is who will be held  
16 accountable if and when a zoonotic virus is spread to  
17 the human population?

18 I'm talking about compensation and  
19 measures that would be taken after the fact.

20 MODERATOR WITT: Let me just respond  
21 really quickly, so that I'm not monopolizing all the  
22 time.

23 The WHO views the potential of biomedical  
24 progress as one means of leading to a healthier world.  
25 It's not the only means, but there is potential there.  
26 While we cannot say what is going to happen, whether  
27 xeno zoonoses are, in fact, going to develop, not

1 develop, whether there will be other complications to  
2 the technology, we would like as an organization to  
3 keep an open mind until that information becomes  
4 available.

5                   We think there is potential. We don't  
6 know that yet.

7                   AUDIENCE MEMBER: My question for the  
8 panel was the issue xenotourism, which to explain this  
9 term would be a patient in one country perhaps in a  
10 situation in which xenotransplantation is highly  
11 regulated or, alternatively, in a situation in which  
12 xenotransplantation is currently prohibited, going to  
13 another country -- the motivations of that country  
14 might be many -- having a xenotransplant, and then, of  
15 course, being a citizen of the first country,  
16 returning.

17                   Practical ideas from the -- To me, this is  
18 a major issue, that all our efforts to be so careful  
19 could be reversed simply by a couple of rogue  
20 countries or rogue scientists.

21                   DR. JESSAMINE: I haven't got an answer  
22 for that. I don't think anyone has got an answer for  
23 that particular question.

24                   I would, though, push the barrow that one  
25 of the things that would determine that happening is  
26 the level of public perception of risk and benefit,  
27 and that that scenario may be more or less likely,

1 depending on how well this has been debated in a  
2 community in a particular country where the risks are  
3 -- the risks and benefits are quite explicit. Then  
4 the passion, if you like, is making an informed  
5 choice, and your country's response to xenotourism, as  
6 it were, would be based on an informed decision and an  
7 informed feeling of community.

8           To pick up on Andre's thing, in the book  
9 he referred to risk -- public's perception of risk --  
10 Xenotransplantation is a classic example, I think, of  
11 you are going to -- This is a major kind of risk that  
12 public are very averse to, I believe, for several  
13 reasons.

14           Public deal badly with risks that are  
15 unavoidable, and risks that are unquantifiable, risks  
16 in which there is not a clear consensus, and this is  
17 all based on research -- it's not opinion -- and risks  
18 that are forced upon them where that links back to the  
19 unavoidability of the issue, and that the way to  
20 manage those risks most successfully is to debate and  
21 consult on those at the community level so people  
22 actually have an understanding of what the risk is.

23           It's virtually fear of the unknown, and  
24 medical procedures and this kind of biotechnology  
25 stuff is the stuff of which major public and community  
26 concerns are made from. The best way to deal with it  
27 is to open your debate so the public knows, and

1 tourism may become less of an issue once everybody  
2 knows what we're really talking about.

3 DR. DARK: To pick up your point about  
4 xenotourism, I'm sure it will occur. One hopes we can  
5 postpone it until after we've gathered a great deal  
6 more data about the potential risks.

7 I think it's incumbent upon those carrying  
8 out the initial clinical trials, and in particular,  
9 their sponsors, to be absolutely rigorous about the  
10 patients they are recruiting into those trials.

11 I would hope that we will be several  
12 hundred patients down the line, several hundred  
13 rigorously selected patients, before xenotourism could  
14 become possible, but it will depend upon the  
15 investigators and their sponsors.

16 DR. LA PRAIRIE: Can I just -- I want to  
17 answer two questions, first of all the one that I  
18 don't think we've completely answered, which was who  
19 is held accountable. Probably Peter could back me up.

20 Ultimately, the regulator is accountable,  
21 if the regulator is the one that approves an IND. So  
22 they have to, you know, take it on the chin. So I  
23 think there's a big responsibility there, although  
24 we're not alone.

25 To the issue of xenotransplantation,  
26 certainly, you can't police it by, you know, waiting  
27 at the border for these people to come back. I would

1 suggest you have to look to the same mechanisms or  
2 means that we try to address things like the commerce  
3 of organ transplantation.

4           You put an expectation on other countries  
5 to have -- even though they may have different  
6 cultural beliefs that no one else will be selling  
7 organs, and that's probably -- the best way to do that  
8 is through groups like the OECD and the WHO. You put  
9 pressure on other countries to not allow that kind of  
10 action to proceed, and that's why the issue of  
11 moratorium are very difficult.

12           Moratorium only works within borders. You  
13 want, I think, harmonization of whatever is allowed,  
14 and that should be the ground rules for everybody.

15           MODERATOR RONCHI: Just a point from the  
16 floor?

17           AUDIENCE MEMBER: It's, in fact, the point  
18 of import-export of organs has already been touched,  
19 for example, by the Executive Summary report on the  
20 xenotransplantation in the Netherlands, which have to  
21 admit that they don't have any regulation in place  
22 right now to consider how to limit the potentials of  
23 an import of organs and how to control for quality.

24           So I think, at this point, rather than  
25 xenotourism, I think the trading of organs, the  
26 import-export, could be a more immediate -- of more  
27 immediate concern.

1 DR. GANZ: Can I just follow up on some of  
2 the discussion on xenotourism or transplant tourism in  
3 general.

4 As the Canadian representative for the  
5 Council of Europe, this is an issue, obviously, that  
6 has come up at a number of meetings, and it's one of  
7 concern that we hope to address, actually, at an April  
8 meeting where we will be looking at this issue in some  
9 detail, and the xeno issue ties in as well.

10 AUDIENCE MEMBER: Okay. If I could make -  
11 - Can you hear me? If I could make a point first on  
12 the global nature of xenotransplantation, and  
13 particularly with regards to, if you like, New  
14 Zealand.

15 If you remember the -- Perhaps you weren't  
16 here yesterday -- the study that we were talking  
17 about, the Novartis study. We've actually identified  
18 20 patients in New Zealand who have already been  
19 treated with pig islets.

20 So when you say if and when  
21 xenotransplantation may be happening in New Zealand,  
22 then it has already happened, and you may be  
23 particularly interested in the results from those  
24 patients, which first indications are, I believe, that  
25 there's no retrovirus to be found.

26 Also going back to the fact that  
27 xenotransplantation patients will eventually, one

1 would assume, if the technology is successful, go on  
2 vacations like anybody else or may even move. Then I  
3 think there is some -- You have to take some regard  
4 then to the sponsors of those trials.

5           As a sponsor, it seems important to  
6 maintain a database of those patients that have been  
7 treated, and to regularly check and make sure that  
8 that monitoring is in place, wherever they are. I  
9 think that's one thing that we should take on board as  
10 sponsors of trials.

11           Another point now to Rachel Arrundale when  
12 she was outlining the process in the United Kingdom.  
13 Maybe I missed it, but it wasn't actually evident in  
14 her presentation that there was at any point the  
15 possibility of open discussions such like have been  
16 occurring today and such as the FDA have in the past  
17 had in the United States with sponsors of trials.

18           I think in an area as complex as  
19 xenotransplantation, it's possible for many  
20 misunderstandings to arise, not because of, if you  
21 like, differences in opinion, but simply because the  
22 area is so complex.

23           I think it will be unfortunate if there  
24 isn't the possibility for discussion, and also it may  
25 be unfortunate from a public perspective, because they  
26 will not be able to see the transparent progress and  
27 process going on.

1 MS. ARRUNDALE: I'll just come back on  
2 that point briefly. In fact, Corrine, before you  
3 started, during the work on the Advisory Group on the  
4 ethics of xenotransplantation, we held a major public  
5 consultation exercise, and we received around 350  
6 responses to that, not only from the companies  
7 involved but also from a large number of members of  
8 the public.

9 We also as part of the process held a  
10 public meeting with around 60 people. When the  
11 document, the animal tissue in humans document, was  
12 published, we again -- That was published before more  
13 open consultation, and we'll be looking for ways of  
14 keeping things in the public domain, particularly as  
15 in the U.K., we've now got the freedom of information  
16 white paper which make sit incumbent on us to do that.

17 AUDIENCE MEMBER: So you will actually be  
18 modifying the process that you outlined to include  
19 face to face discussions? Is that what you're saying?

20 DR. ARRUNDALE: Sorry, no. I don't think  
21 we state it at the moment as being part of the  
22 process, no.

23 DR. JESSAMINE: Can I just pick up on  
24 something from the Novartis presentation there.

25 One of the things I'd like to ask this  
26 panel and ask this meeting -- There would certainly be  
27 something to be said for there either being regional

1 archiving and databases or even a single archive and  
2 database.

3           There would be great cost efficiencies in  
4 that, but it would also be the opportunity for  
5 rapidity of advance in terms of new probes, new tests  
6 when they come along rather than have to be stuff done  
7 all around the world.

8           Certainly, speaking in purely New Zealand  
9 terms, the sort of logistics of setting up a registry  
10 and a system that holds on to samples ad infinitum and  
11 then testing them as new things come along -- It's  
12 liable to be quite a significant body.

13           There may be something to be said for  
14 trying to, at this very early stage of it, globalize  
15 that kind of -- those kind of initiatives.

16           MODERATOR WITT: I've just been instructed  
17 that we have one more question from the floor. So  
18 would the lady like to ask a question, and then if we  
19 have time, we could come back.

20           We do have two hours for discussion this  
21 afternoon, and what does not get done now -- People  
22 are getting hungry, to be perfectly frank -- we can,  
23 hopefully, get done this afternoon.

24           AUDIENCE MEMBER: I represent a vested  
25 interest. The public wants a cure for diabetes.  
26 Excuse me if my knees buckle. I'm not used to  
27 speaking publicly.

1                   With all due respect, the arguments of  
2 cultural safety cannot generally pass a test of  
3 logical reasons or reason and common sense. It  
4 suggests that the political ramifications of  
5 xenotransplants --

6                   DR. GANZA: Excuse me. We're having some  
7 difficulty. I don't know about the others. We can't  
8 hear anything that you're saying.

9                   AUDIENCE MEMBER: I'm sorry. Can you hear  
10 me now? Okay.

11                   The arguments of cultural safety cannot  
12 generally pass the test of reason or common sense. It  
13 suggests that political ramifications outweigh  
14 scientifically demonstrated benefits of any given  
15 procedure.

16                   You know, all progress entails some risk,  
17 and to avoid risk is to kill progress. We know the  
18 risk of diabetes. It's kidney failure, blindness,  
19 numerous other things.

20                   We haven't had a significant advancement  
21 in 75 years, since Bann and Vesta injected the filthy  
22 juices of dogs and pigs into children. They were  
23 ridiculed and opposed.

24                   I just would hope that logic and reason  
25 rules the U.S. -- the setting of the U.S. policy and  
26 any other country's policy as it comes along in good  
27 science.

1 DR. JESSAMINE: I think -- I'm not saying  
2 that cultural safety outweighs good science. What I'm  
3 saying is that when you come to make policy, you have  
4 to give due consideration to that point of view and  
5 that it is a meeting of minds.

6 It is science and -- It's a process that  
7 you have to work through and that you cannot just  
8 ignore those things and say the science shows it's  
9 good, and we're going to do it, even if you have a  
10 cultural -- if you haven't got -- if we haven't  
11 thought about the effects like Clara pointed out on  
12 cultural beliefs, religion, how societies are put  
13 together.

14 AUDIENCE MEMBER: I don't mean to put you  
15 on the spot, Dr. Jessamine. We've heard this argument  
16 from -- We've heard cultural safety cited frequently  
17 by Bill English, the Minister of Health. So it's not  
18 that I was trying to put you on the spot.

19 We just don't want cultural safety to  
20 outweigh scientifically proven benefits. Thank you.

21 MODERATOR WITT: Were there any other sort  
22 of final, quick comments that the panel would like to  
23 make? Sorry for the brevity of the time.

24 Just two administrative notes: The  
25 presentation by Mary Groesch on national  
26 xenotransplantation committee needs to be rescheduled,  
27 and it will be coming right after presentation by



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A F T E R N O O N   S E S S I O N

Time: 1:43 p.m.

MODERATOR RAUB: Ladies and gentlemen, for those of you who are seated, I thank you, and for those who aren't, I urge you to do so. We are about to begin our Session V.

You will note from the program that Session V carries the same title as the title of the workshop, which suggests that we see this as an opportunity to do some integrating and some further development of the ideas we've been hearing about, and that indeed is the case.

I've had the privilege over the last many months of chairing the Department-wide committee dealing with xenotransplantation issues and the pleasure of working with some of the best and the brightest of our department in this activity.

You will be hearing from a number of them today. Amy and I will be co-moderating this afternoon, and we'll begin with a presentation about the committee itself by my colleague, Lily Engstrom in the Office of Science Policy in the Office of the Assistant Secretary for Planning and Evaluation. Lily.

MS. ENGSTROM: Good afternoon. I see a lot of you still straggling back in, and I assume most

1 of you have had a chance to glance at your program for  
2 this afternoon, and some of you may have even said to  
3 yourselves, good, she's going to talk about  
4 committees, this ought to be really scintillating.

5           Now I can't make this subject matter  
6 scintillating, but I can make it brief, since we are  
7 running behind time anyway.

8           The Departmental or DHHS Interagency  
9 Committee on Xenotransplantation is made up of  
10 representatives from FDA, CDC, NIH, HRSA -- the Health  
11 Resources Services Administration -- and the Office of  
12 Science Policy. As Bill mentioned just a moment ago,  
13 he chairs this group.

14           The role of this committee essentially is  
15 to develop and to oversee implementation of an  
16 integrated, Department-wide approach and strategy to  
17 xenotransplantation and to provide policy  
18 recommendations for the Secretary; and it does so by  
19 drawing from the strengths and expertise of the  
20 participating agencies.

21           Example: FDA is the agency, as we know,  
22 that regulates drugs, devices, biologics, and clinical  
23 trials in xenotransplantation may involve one or more  
24 of these areas.

25           CDC keeps us focused on the public health  
26 concerns associated with xenotransplantation, and NIH  
27 is the agency that provides support for a significant

1 share of the research, particularly the basic research  
2 that constitutes the groundwork for today's  
3 xenotransplantation clinical trials.

4           HRS, on the other hand, has experience and  
5 expertise in facilitating human organ transplantation  
6 through its contract with UNOS to operate the organ  
7 procurement and transplantation network.

8           The Office of Science Policy has a  
9 responsibility for forging together a unified,  
10 Department-wide approach, and so this is really a case  
11 of the whole exceeding the sum of its parts because of  
12 the synergy that's really generated by the collective  
13 efforts of the participating agencies.

14           I really do want to make a personal note  
15 myself and echo what Bill said a few moments ago.  
16 We're working with a group of very bright,  
17 intelligent, competent, dedicated and very thoughtful  
18 people, and there's hardly an issue that's been  
19 discussed over the last day and a half that have not  
20 somehow or other actually surfaced in our interagency  
21 deliberations.

22           This committee is modeled after similar  
23 coordinating bodies in the Office of Science Policy.  
24 As a matter of fact, an example is genetic testing.  
25 In that area we, too, have a broad Department-wide  
26 working group which consists of representatives from  
27 various offices as well as agencies throughout the

1 Department that collectively have some role or  
2 responsibility in various aspects of genetic testing.

3           This interagency committee is not intended  
4 to take the place of any broad based national advisory  
5 committee that have been called for by various  
6 interest groups in the area of xenotransplantation,  
7 and I want to make clear that when I use the term  
8 vested interest group, it's not mean to be pejorative.

9           The interagency committee is essentially  
10 one that represents the Federal efforts to focus  
11 attention on xenotransplantation, to ensure that  
12 Federal activities undertaken by separate departments,  
13 separate agencies within the Department, are actually  
14 coordinated, integrated, and that we can, in fact,  
15 respond in an appropriate and cogent manner to various  
16 issues or concerns that are raised by  
17 xenotransplantation.

18           Now any national public advisory group  
19 that would be established in the area of  
20 xenotransplantation would be comprised of  
21 representatives of various interested communities  
22 outside the Federal government, and by that I,  
23 obviously, would include -- it would certainly not be  
24 limited to -- scientists, clinicians, epidemiologists,  
25 transplant surgeons, experts in microbiology,  
26 infectious disease and public health, and you can also  
27 imagine the other types of expertise that would be

1 represented in such a broad based committee.

2           We're talking about law. We're talking  
3 about bioethics. We're talking about patient  
4 advocacy, as well as animal welfare.

5           A couple of weeks ago, the interagency  
6 committee on xenotransplantation had an opportunity to  
7 preview the overall Departmental strategy on  
8 xenotransplantation for the DHHS leadership.

9           When I use the term overall strategy, I'm  
10 basically talking about a regulatory framework for  
11 xenotransplantation. I'm talking about the PHS draft  
12 guidelines for infectious disease issues in  
13 xenotransplantation, the national xenotransplantation  
14 registry, a centralized biological archive, and an  
15 advisory body on xenotransplantation. You will hear  
16 about each one of these components from the speakers  
17 that will follow me on the program.

18           Now the briefing that we gave to the  
19 Department's leadership a few weeks ago was really an  
20 opportunity for us to inform them of the plans and  
21 activities of the interagency committee to date, and  
22 also to make sure that they were aware of this  
23 workshop we've been having these last two days, and  
24 the general approach that the four agencies and the  
25 Office of Science Policy have agreed to.

26           In my opinion, as well as those of others  
27 who were there, the briefing went extremely well.

1 There was general agreement that there was need for a  
2 cautious but optimistic approach in this area.

3           It is expected that this interagency  
4 committee would, in fact, be providing future  
5 briefings to the senior policy makers in the  
6 Department to bring them up to date on the progress of  
7 the various activities related to the refinement and  
8 implementation of the strategies that we have proposed  
9 for xenotransplantation, and also, as issues and  
10 concerns arise and emerge from the area of  
11 xenotransplantation, that we would in fact bring it to  
12 them, if necessary, for their review, their  
13 consideration and decision making.

14           Future workshops like this one will be co-  
15 sponsored among the four agencies that have been  
16 represented throughout this workshop, and this is  
17 intended, really, as mentioned earlier -- this  
18 workshop -- as one in a series to continue to  
19 stimulate and to foster public discussions of all the  
20 issues that are so important in this arena.

21           I can tell you that no major policy  
22 decisions will be made in this Department without  
23 providing adequate opportunities for public discourse.  
24 The stakes are high, and we recognize that.

25           As we have heard over the last day and a  
26 half, this is the area that holds both promise and  
27 challenge and, therefore, it's really essential that

1 we approach it with both hope and caution.

2 I'm going to bring my remarks to closure,  
3 but I wouldn't want to do that without actually  
4 saluting my fellow committee members for their  
5 dedication, their diligence, and their commitment to  
6 developing a national strategy for xenotransplantation  
7 that not only promotes and fosters the development of  
8 a promising technology, but also ensures, to the  
9 extent possible, the protection of the public health.

10 Thank you.

11 MODERATOR PATTERSON: It's an honor and a  
12 pleasure to introduce our next speaker, Dr. Louisa  
13 Chapman from the CDC. Louisa Chapman will present  
14 highlights and revisions from the draft PHS guideline  
15 on infectious disease issues in xenotransplantation.  
16 Dr. Chapman.

17 DR. CHAPMAN: Thank you.

18 A draft Public Health Service guideline on  
19 infectious disease issues in xenotransplantation  
20 intended to minimize the public health risks  
21 associated with xenotransplantation clinical trials  
22 was prepared by working groups within the PHS --  
23 Public Health Service, excuse me -- cleared through  
24 CDC, FDA, NIH and HRSA and the Office of the Secretary  
25 of the Department of Health and Human Services, and  
26 published in the Federal Register on September 23,  
27 1996, for 90 days of public comment.

1                   The draft guideline places particular  
2 emphasis on the importance of the expertise  
3 represented on the xenotransplantation research team  
4 and the adequacy of the protocol review, the informed  
5 consent process, and the health surveillance plan.

6                   I'm aware that many of you, probably most  
7 of you, possibly all of you, have read this draft  
8 guideline, but nevertheless, in the event that some  
9 people in the audience have not, I'm going to quickly  
10 go through some of the key concepts in the draft  
11 guideline so you'll know what we're comparing the  
12 commentary to.

13                   The guideline states the following:  
14 "Xenotransplant clinical research team should contain  
15 individuals with expertise in both human and  
16 veterinary infectious diseases, and have established  
17 relationships with laboratories capable of  
18 sophisticated microbiological investigations."

19                   The review of clinical protocols must be  
20 adequate to assess the potential risks of infection  
21 for not only the recipient but also contact  
22 population, and this may require augmenting the usual  
23 membership of local review committees to obtain  
24 specific consultative expertise.

25                   Health surveillance plans are a critical  
26 part of any clinical xenotransplantation protocol.  
27 The draft guideline is built around the principles of

1 pre-transplant screening of the source animal to  
2 minimize the risk that xenographical transmit  
3 recognize zoonoses, and post-transplant surveillance  
4 of the xenograft recipient to maximize the probability  
5 that xenogeneic infections will be recognized and  
6 contained.

7           The pre-transplant screening of the source  
8 animal is nested within the husbandry practices that  
9 limit or define lifelong exposures to infectious  
10 agents.

11           The post-transplant surveillance of  
12 recipients includes recommendations for lifelong  
13 clinical monitoring of all initial xenograft  
14 recipients, as well as laboratory monitoring of  
15 specific recipients whenever a xenograft is known or  
16 suspected to contain infectious agents with undefined  
17 infectivity or pathogenicity for humans.

18           In addition, the guideline discusses  
19 hospital infection control practices, including the  
20 importance of a comprehensive Occupational Health  
21 Services program designed to educate workers about the  
22 risks associated with xenotransplantation, and to  
23 monitor for possible infection in these exposed  
24 workers.

25           The informed consent process must include  
26 education of the recipient about the uncertainty that  
27 exists at present regarding the infectious disease

1 risks associated with xenotransplantation.

2           The recipient should understand that these  
3 concerns may necessitate lifelong post-transplant  
4 surveillance, and the recipient should never donate  
5 biologic materials for the allotransplantation donor  
6 pool subsequent to the receipt of the xenograft.

7           The education and counseling process  
8 should extend beyond the recipient to include also the  
9 recipient's family or close contacts and especially  
10 sexual contacts, as well as exposed health care  
11 workers.

12           The guideline discusses the desirability  
13 of a national registry that would allow epidemiologic  
14 surveillance of populations of xenograft recipients,  
15 in addition to clinical monitoring of individual  
16 recipients.

17           The guideline emphasizes the importance of  
18 archives of biologic specimens from both the source  
19 animals and the xenograft recipient. These specimens  
20 should be maintained for use in public health  
21 investigations, should these become necessary, as a  
22 sort of public insurance policy, and the  
23 responsibility for maintaining these archives is  
24 placed on the individual investigator.

25           Over 140 comments to the public docket  
26 were received, and the published draft was formally  
27 reviewed by the CDC Infection Control Practices

1 Advisory Committee.

2           Let me just say that we received both  
3 critical commentary and -- both praise and criticism  
4 in the public commentary, and both of it was valuable.  
5 We encourage those organizations and individuals who  
6 have dissenting views to the guideline or the public  
7 process to continue to have the courage to bring those  
8 views to the public dialogue in a manner that is  
9 constructive and shoulders a share of responsibility  
10 for this progress -- progress of this process that  
11 we're all in partnership on.

12           It's not possible for me to provide a  
13 complete review of the contents of these public  
14 comments, but I'm going to attempt to summarize some  
15 of the significant ones or some of the influential  
16 ones.

17           So we'll begin with the criticism. There  
18 are 109 of these comments to the docket that express  
19 strong disapproval of the guideline. 108 disapproving  
20 comments were submitted by individuals or  
21 organizations specifically concerned with the ethical  
22 treatment of animals or the ethical development of  
23 biotechnology.

24           To condense a lot of commentary into a  
25 small summary, the comments basically argued that the  
26 suffering of animals cannot be justified for  
27 procedures that also put the human community at risk

1 and that lack documented efficacy.

2           In addition, the American Society of  
3 Transplant Surgeons argued that the draft guideline  
4 represented an unnecessary intrusion of government  
5 regulation into the performance of transplant surgery,  
6 while failing to set standards adequate to protect the  
7 public health.

8           The remainder of the comments to the  
9 docket were generally favorable, although many of them  
10 were highly critical of individual areas within the  
11 guideline. Of particular note, five organizations and  
12 two individuals representing patient populations that  
13 might benefit from xenotransplantation urged continued  
14 work to enable the safe development of the field.

15           These comments argued that the voices of  
16 those most directly affected by the therapeutic  
17 potential of the field should be heard by policy  
18 makers. The father of one patient with a degenerative  
19 genetic disease expressed specific concerns that  
20 groups opposed to the development of  
21 xenotransplantation might exaggerate the risks to the  
22 public as a tactical tool, and urged the continued use  
23 of objective scientific criteria to guide the  
24 development of national policy.

25           Thirteen organizations with a commercial  
26 interest in the development of xenotransplantation  
27 submitted comments to the public docket. Among these,

1 seven argued that an inappropriate burden for  
2 oversight of clinical trials had been assigned to the  
3 local review committees, and that that responsibility  
4 for this oversight should appropriate reside at the  
5 national level with the FDA.

6           The majority of these 13 also discussed  
7 concerns that individual clinical centers would not be  
8 able to adequately maintain biologic specimen  
9 archives.

10           A number of commentators expressed the  
11 opinion that it was possible to differentiate the  
12 infectious risk by species affiliation of the source  
13 animal, and that the use of xenografts from nonhuman  
14 primates carried a higher risk of xenogenetic  
15 infection than did xenografts procured from other  
16 species, in particular from pigs.

17           The American College of Cardiology, the  
18 American Society of Transplant Physicians, and 45  
19 specialists in infectious diseases or microbiology  
20 expressed concerns that the infectious disease risks  
21 had been inadequately addressed and that the use of  
22 nonhuman primate xenografts should be curtailed,  
23 because the baboon supply wasn't adequate to eliminate  
24 the donor shortage, therefore carrying an unnecessary  
25 risk of introduction of disease without a promise of  
26 ending the -- definitively addressing the current  
27 situation.

1                   All of these except the American College  
2 of Cardiology called for the creation of a Federal  
3 advisory committee.

4                   In addition, the American Society of  
5 Transplant Physicians also argued that the Public  
6 Health Service should take responsibility for  
7 developing a central national registry and a central  
8 biologic specimens archive.

9                   The British Nuffield Council on Bioethics  
10 reiterated their concern that it was unethical for  
11 human trials to proceed prior to further research on  
12 the infectious disease risks, without the protection  
13 of central regulatory oversight, or using nonhuman  
14 primate xenografts.

15                   The USDA noted their responsibility for  
16 oversight of animals bred, raised or kept for  
17 experimental purposes under the Animal Welfare Act and  
18 offered their assistance as appropriate.

19                   In response to these comments, as well as  
20 the evolving science and the international policy  
21 development, the draft guideline has been revised in  
22 the following ways.

23                   The revised document states that all  
24 xenotransplantation clinical trials in the United  
25 States will proceed under FDA oversight, and it  
26 consolidates responsibilities for all aspects of  
27 safety under the sponsor.

1           The revision acknowledges the complexity  
2 and the importance of issues of animal welfare, of  
3 human rights, and of community interests, but it also  
4 emphasizes that these issues are appropriately  
5 addressed in other publications and other public  
6 discussions, both in the past, ongoing in the present,  
7 and in the future.

8           The revision does discuss a national  
9 advisory process that may consider aspects of these  
10 issues that are beyond the scope of this guideline  
11 document. Let me divert from my prepared comments to  
12 reiterate, this guideline is a guideline on infectious  
13 disease risks associated with xenotransplantation, and  
14 deferring discussion of certain issues to other forums  
15 is not an indication that we consider them  
16 unimportant.

17           It is, rather, an acknowledgement that, if  
18 we're going to accomplish anything, we're going to  
19 have to take it step by step, define our goals, and  
20 complete the process in a step by step manner; and  
21 it's also an acknowledgment that those of us who are  
22 appropriate by expertise -- most appropriate by  
23 expertise to develop the guideline on infectious  
24 disease issues are not necessarily the most  
25 appropriate experts to address some of these other  
26 issues that need both a different forum and a  
27 different body of workers.

1                   The revisions clarify and strengthen the  
2 informed consent process for xenograft recipients and  
3 the education and counseling process for both  
4 recipients, their contacts, and the associated health  
5 care professionals.

6                   The need to comply with long term or  
7 lifelong surveillance, regardless of the success of  
8 the experiment or the duration of the xenograft or the  
9 removal or rejection of the xenograft, is emphasized.

10                  The prohibition against xenograft  
11 recipients contributing to the allotransplant donor  
12 pool is reiterated, and consensus is currently being  
13 sought on whether or not it's appropriate to extend  
14 that ban to also include close contacts of xenograft  
15 recipients. The public comment was divided on this  
16 point.

17                  The revised document acknowledges that  
18 some experts consider a differential risk of cross-  
19 species infection to exist among source animal  
20 species. However, it does not differentiate risk by  
21 species affiliation. Rather, it delineates a minimal  
22 level of animal husbandry and pre-transplant  
23 infectious disease screening that must be met before  
24 any animal is an appropriate source for xenograft  
25 procurement.

26                  The guideline emphasizes the importance of  
27 appropriate husbandry, including procuring source

1 animals from closed herds or colonies raised in  
2 facilities employing appropriate barriers to the  
3 introduction or spread of infectious diseases. It  
4 emphasizes that the risk minimization precautions  
5 appropriate to each xenograft protocol should be  
6 employed in all steps of production, regardless of the  
7 species of the source animal.

8           Because I notice the hall is much more  
9 full than it was last night at about six o'clock when  
10 we discussed this before, maybe it's worth reiterating  
11 redundantly some comments I made last night.

12           There's been a lot of discussion about  
13 whether it's appropriate to differentiate between  
14 species on the basis of the risks they pose as sources  
15 of xenografts. There has been disagreement among  
16 people of goodwill who are not in disagreement on the  
17 basic facts, and I think a lot of that disagreement  
18 has come out of the fact that it's actually a rather  
19 vague statement to talk about a risk differential on  
20 the basis of species, and it allows interchange about  
21 actually a number of specific levels of associated  
22 risk.

23           The first level is the risk that is  
24 present in an animal species by virtue of the extent  
25 that that animal has been removed from a feral source  
26 towards domestication with the attendant diminution of  
27 adventitious agents carried by the animal. There is

1 no disagreement.

2           It's very clear that baboons are at best  
3 one or two generations at present removed from feral  
4 animals, where pigs are largely domesticated, and that  
5 results in that large differential you tend to see in  
6 the number of persistent viruses listed when you talk  
7 about baboons than pigs.

8           On a second level, you can talk about a  
9 differential between the species on the basis of  
10 husbandry techniques that are available to be applied  
11 to decrease infectious agents in the animals, and  
12 there's also no difference of opinion on the facts  
13 presented yesterday that there's certainly far more  
14 developed techniques at present in terms of  
15 hysterectomy, barrier precautions, that decrease the  
16 load of infectious agents carried by pigs compared to  
17 baboons. Those techniques have not been developed and  
18 may not be developable for baboons.

19           There is also no disagreement about  
20 whether at present there's a difference in the degree  
21 of infectious risk associated with available pigs.  
22 You can obtain pigs tomorrow from very clean specific  
23 pathogen free colonies. You cannot do the same with  
24 baboons, and we heard data yesterday that suggests it  
25 will be minimally an investment of 20 years and a lot  
26 of dollars to see if we're able to obtain the same  
27 degree of cleanness with baboons.

1                   In developing the guideline, we don't  
2 ignore those facts, but each of those differences  
3 between species can also be looked at in terms of a  
4 difference between husbandry techniques, currently  
5 available herd, and infectious disease screening; and  
6 we chose to address those principles.

7                   If you equalize all of those, you're left  
8 with two species, both of which have endogenous agents  
9 that cannot be removed at present, that can infect  
10 human cell lines in vitro, and may or may not be able  
11 to infect human cell lines in vivo. So we've chosen  
12 to address the standards that must be obtained and to  
13 say they must be obtained across the board, regardless  
14 of species affiliation.

15                   The revisions also clarify and strengthen  
16 the acceptable standards of infectious disease  
17 screening and surveillance. The revisions address the  
18 appropriateness of employing established relationships  
19 with off-site consultants as sources of expertise.  
20 This was a matter of concern in a lot of the public  
21 commentary.

22                   The revisions acknowledge the need to  
23 tailor all screening, quarantine and surveillance  
24 protocols to the specific process and xenograft  
25 product, as well as to the source animal and the  
26 husbandry history of that animal. They emphasize the  
27 need to review and update all these protocols as

1 knowledge progresses.

2           The revisions clarify the extent and  
3 nature of preclinical research that should be  
4 completed prior to the onset of clinical trials.  
5 Specifically and minimally, it is critical that  
6 adequate diagnostic assays and methodologies for  
7 surveillance of known infections agents from the  
8 source animal are developed prior to the initiation of  
9 a clinical trial.

10           The revisions discuss the necessity of  
11 maintaining health records and archive biologic  
12 specimens for a defined period of 50 years. This was  
13 left indefinite in the initial document, and that was  
14 again the source of a lot of public commentary.

15           This preliminary duration was selected on  
16 the basis of the latency periods of known human  
17 pathogenic persistent viruses, and also the presence  
18 of OSHA record keeping. However, the appropriate  
19 duration of maintenance is really unknown at present,  
20 and it will need to be continually reconsidered as our  
21 knowledge advances.

22           Expert review of specific language  
23 inserted to address the biosafety level recommended  
24 for manipulation of biologic specimens procured from  
25 xenograft recipients is currently underway, and  
26 preliminary revisions discuss the creation of a  
27 national advisory committee, a national

1 xenotransplantation registry, and a central biologic  
2 archive.

3 I should emphasize that these proposals  
4 are still under review and development and discussion,  
5 and may not persist in the final document. You'll be  
6 hearing more about them from the speakers who follow  
7 me.

8 When completed, the revised guideline will  
9 again undergo clearance at the four agencies and with  
10 the Office of the Secretary prior to publication in  
11 final format, and we hope that finalization and  
12 publication will be completed in the first half of  
13 1998.

14 MODERATOR RAUB: Thank you very much, Dr.  
15 Chapman.

16 The guidelines, obviously, are an  
17 important facet of the overall approach to  
18 xenotransplantation. An equally important facet is  
19 that of the regulatory structure for this, and Dr.  
20 Kathryn Zoon of FDA will describe that.

21 DR. ZOON: Thank you very much, Dr. Raub.  
22 It's a pleasure to be here as one of the Public Health  
23 Service partners in this important initiative.

24 Today I would like to present to you the  
25 regulatory framework that the agency has been actively  
26 engaged in with xenotransplantation.

27 To introduce biologics, what I'd like to

1 do is cover essentially what is, briefly, a biologic,  
2 and then go on and speak about the local and Federal  
3 oversight of this area, then proceed to talk briefly  
4 about the differences between human  
5 allotransplantation and xenotransplantation, the FDA  
6 regulatory framework, our initiatives, and finally,  
7 summarize.

8           Biological products span a wide range of  
9 products. They include tissues, whole blood, blood  
10 components, plasma derivatives, vaccines, products  
11 prepared from biotechnology, including monoclonal  
12 antibodies, recombinant DNA proteins, somatic cell and  
13 gene therapy and xenotransplantation.

14           The mechanisms that we use to regulate  
15 biologics are really founded on science and law, and  
16 they include a variety of activities such as review,  
17 research, education, enforcement, use of advisory  
18 committees for outside input, a variety of meetings to  
19 which we get scientific and other ethical/social  
20 input, and workshops in order to have the best  
21 possible information in our regulatory decision  
22 making.

23           In looking at the process for the review  
24 and development of biological drug products, this is  
25 just to make sure everyone is on a level playing field  
26 with respect to understanding this. Many of these  
27 products are in the research and development phase.

1 Many of the preclinical issues are being addressed,  
2 and the development of new products.

3           Oftentimes the agency will interact with  
4 those sponsors early on in what we call pre-  
5 investigational new drug meetings. These are very  
6 important for understanding the scientific issues  
7 surrounding a new product as well as to provide input  
8 into the sponsors on how to deal with safety issues  
9 for the first phases of their studies.

10           This goes on with the introduction of  
11 these products into humans, and initially, the first  
12 stage of development in the clinic is to look at  
13 safety. As the product goes through clinical  
14 development, one continues to look at safety, but then  
15 also activity and, finally, in Phase III studies  
16 safety and efficacy for supporting the approval  
17 process of these products.

18           This is generally covered in what we call  
19 the licensure phase or approval phase of a product,  
20 and that would result in a biologics license  
21 application, a new drug approval, etcetera.

22           That's not where our job ends. Our job  
23 continues to follow with post-marketing surveillance,  
24 making sure that there is a safe profile and an  
25 accurate use of the products as well as new  
26 developments are made with respect to the safety and  
27 efficacy of these products.

1                   In looking at clinical trials in  
2 xenotransplantation, there are actually multiple  
3 points of oversight, some of which include the FDA and  
4 some of which include other organizations. Clearly,  
5 the local review has been discussed during the course  
6 of the meetings, which is very important.

7                   Each of these committees provide an  
8 assessment of the protocols, some of which look at  
9 risk/benefit, some of which look at community safety,  
10 and others which look at animal use. These include  
11 the institutional review board, the institutional  
12 biosafety committee, and the institutional animal care  
13 and use committee, respectively.

14                   There is also another mechanism which  
15 involves the NIH funding, and this would, obviously,  
16 relate to the final Public Health Service guideline,  
17 as that evolves.

18                   Finally, the FDA plays a major role in  
19 oversight of clinical trials in xenotransplantation,  
20 and this is something that we have been doing, as  
21 stated yesterday, for the past several years.

22                   In looking at human allotransplantation  
23 and xenotransplantation, we have heard a lot about  
24 this over the past day and a half. There are a number  
25 of lessons and limitations one can learn from human  
26 allotransplantation, and we look at these very hard as  
27 to their application to xenotransplantation.

1                   There is much we can learn, but yet there  
2 is much, in addition, that must be taken care of in a  
3 greater level of oversight that would normally be left  
4 to allotransplantation.

5                   The life saving successes in  
6 allotransplantation have raised many challenging  
7 issues, particularly with regard to the limitations of  
8 the availability of these organs. So this has,  
9 obviously, led to the situation of looking at  
10 xenotransplantations; but there are many important  
11 differences between human to human organ  
12 transplantation and cross-species transplantation.

13                   There are limitations within the  
14 applicability of allotransplantation to a regulatory  
15 scheme for xenotransplantation. This has actually led  
16 to the need for new public health tools to make that  
17 distinct regulatory infrastructure.

18                   The spectrum of infectious agents  
19 transmitted by human allotransplantation has, for the  
20 most part, been well established, while with  
21 xenotransplantation, clearly, we still have an awful  
22 lot to learn. We are constantly learning of new  
23 agents daily.

24                   I think our ability to make sure we have  
25 appropriate science that goes into this, that will  
26 help develop a good regulatory framework, is very,  
27 very key.

1                   In allotransplantation, demand vastly  
2 exceeds supply, and we have a closed system for  
3 procurement and allocation of human organs as a rare  
4 national resource. Each transplant center must comply  
5 with the accepted standards in order to be eligible to  
6 receive an organ, and indeed the National Organ  
7 Transplant Act of 1984 prohibits the sale and barter  
8 of human organs.

9                   In contrast, the supply of animal grafts  
10 may greatly exceed demand. Much as animals are  
11 currently commercially bred and raised as food  
12 sources, animals could be, certainly, commercial bred  
13 and used as a source of xenograft products, as we've  
14 heard, for xenotransplantation.

15                   This creates an open system, and a system  
16 of sale and barter. As demand and commercialization  
17 increases, clearly, there are concerns that there may  
18 be pressure that might erode the application of  
19 appropriate donor screening standards and appropriate  
20 quality control, and thus the amount of tension a  
21 subject is getting during the course of a variety of  
22 public discussions and PHS policy decisions.

23                   In human organ transplant, there's an  
24 inherent presumption of clinical efficacy. If the  
25 immunological hurdles of allograft rejection can be  
26 overcome, the donor organ has been empirically shown  
27 over the past few decades of experience to carry out

1 its intended function in the new host.

2           Currently, xeno products are  
3 investigational, and their efficacy is not presumed.

4           So what is the framework that FDA is  
5 looking at? Well, first of all, animal cells, tissues  
6 and all organs intended for therapeutic use in humans  
7 are subject to regulation by the FD&C Act and the  
8 Public Health Service Act.

9           Xenografts are subject of IND  
10 applications. Furthermore, sponsors are highly  
11 encouraged to interact with the agency in order to  
12 make sure we have a clear understanding before you  
13 come in with your clinical trials of what the issues  
14 are for your particular product. These are very  
15 important in the case of xenotransplantation.

16           Some of the FDA initiatives involve  
17 actually three regulations and guidance documents to  
18 date. These are needed to refine and extend our  
19 regulatory infrastructure to provide reasonable  
20 assessment of the safety and efficacy oversight of  
21 these products.

22           The first of these, in trying to really  
23 look into the area of xeno, because as pointed out,  
24 one needs to titrate very carefully the regulatory  
25 oversight to guidance to the level of risk identified  
26 in the course of the studies, both preclinical and  
27 clinical studies, and try to balance that oversight

1 with the scientific advancements, and so that we are  
2 not inhibiting future new medicines to patients with  
3 life threatening illnesses or conditions.

4           Clearly, this is often a delicate balance,  
5 and one that we constantly need to make sure there's  
6 a good public discussion in doing so.

7           The proposed rule on xenotransplantation  
8 will be one mechanism which will then get public  
9 comment on, and finalize. We will also be working on  
10 draft guidances to the industry on xenotransplantation  
11 to try to provide as much specific information to  
12 guide the industry on the issues that we believe need  
13 to be addressed in their clinical trial development.

14           In addition, as raised many times during  
15 the course of the past two days, is the issue of  
16 public disclosure and openness, transparency when it  
17 deals with these very important public health  
18 programs.

19           On this, I would like to address that we  
20 are looking at proposing a rule on public disclosure  
21 of gene therapy and xenotransplantation clinical  
22 trials.

23           The FDA has been dealing with a number of  
24 xenotransplant products over the past several years.  
25 To assist us, we have recently formed a subcommittee  
26 of our Biologic Response Modifier Advisory Committee  
27 to deal with xenotransplantation issues.

1                   We feel that the openness of that public  
2 process -- and Dr. Hugh Auchincloss gave a summary of  
3 that first meeting that we have held, and I think it's  
4 very important, and I wish to thank all that  
5 participated as panel members in that process to make  
6 sure that we get the very best advice from all sectors  
7 as we move forward into this area.

8                   In addition, FDA has research initiatives  
9 in the area of xenotransplantation. With the  
10 knowledge of porcine retroviruses, our staff have  
11 implemented programs to assess the safety of many of  
12 these xenotransplant products.

13                   In particular, Carolyn Wilson and her  
14 colleagues have recently made known at several public  
15 meetings and a prepared paper on the presence of Type  
16 C retroviruses from porcine primary peripheral blood  
17 mononuclear cells, which can infect human cells in  
18 vitro.

19                   I think these are just some of many  
20 questions, scientific questions, and there will be  
21 need for much research in this area as we move  
22 forward.

23                   In looking at the proposed rule on  
24 xenotransplantation, we would like very much to have  
25 a proposed rule out in 1998. This will go out for  
26 notice and comment to get all the suggestions from the  
27 various communities that will be incorporated.

1                   In the scope of this proposed rule, we're  
2 hoping to touch on the procurement and screening of  
3 animals, post-transplant infectious disease monitoring  
4 of patients, archiving of biological specimens, and  
5 participation in a national registry.

6                   As I mentioned earlier, we will be  
7 developing guidelines. This will complement the broad  
8 principles outlined in the Public Health Service  
9 guideline by providing a reasonably detailed and  
10 timely guidance to sponsors regarding xenograft  
11 screening and clinical safety.

12                   Finally, the proposed rule on public  
13 disclosure of gene therapy and xenotransplantation  
14 clinical trials, public awareness and understanding of  
15 xenotransplantation is vital because of the potential  
16 infectious disease risks posed by cross-species  
17 transplants which extend beyond individual patients to  
18 the public is large.

19                   Therefore, looking at this, we believe  
20 that there needs to be a more transparent process. In  
21 looking at this, we would -- We believe that such  
22 items should be covered as having a select subset of  
23 information from all INDs of xenotransplant and human  
24 gene therapy available to the public.

25                   Similar information has been made  
26 available from human gene therapy transfer protocols  
27 through the Office of Recombinant DNA Activities and

1 the Recombinant DNA Advisory Committee of the NIH. I  
2 think this will be very important to continue in this  
3 area in a similar tradition.

4 I think it's important, because it will  
5 enable public knowledge of preclinical and clinical  
6 research, and I think it will be also important to  
7 stimulate further research and clinical trial  
8 development, and it will provide a mechanism which we  
9 hear today is so important on public input.

10 Support information on databases, you will  
11 hear about shortly.

12 So in summary, I would just like to close  
13 and say xenotransplant has extensive local and Federal  
14 oversight. FDA regulates all xenotransplantation  
15 protocols, encourages early pre-IND interactions, and  
16 we support continued public discussions related to the  
17 safety, efficacy, ethical and societal issues which  
18 will be a feature of xenotransplantation.

19 Thank you.

20 MODERATOR PATTERSON: Our next speaker is  
21 Dr. Mary Groesch from the Office of Science Policy at  
22 NIH. Dr. Groesch will talk to us about the proposed  
23 national advisory committee.

24 DR. GROESCH: I'm speaking today as a  
25 member of the Health and Human Services or HHS  
26 Committee on Xenotransplantation. On behalf of the  
27 Committee, I would like to outline the National

1 Xenotransplantation Advisory Committee. We would like  
2 to share our thinking on this topic as well as ask for  
3 your input.

4           Over the past four years there have been  
5 a number of important ad hoc public discussions of  
6 xenotransplantation. Many of these meetings have been  
7 Federally sponsored. For example, over the course of  
8 three meetings, the FDA Biologics Advisory Committee  
9 has discussed the public health risks associated with  
10 xenotransplantation, new technologies that have led to  
11 increased interest in this research, lessons learned  
12 from known zoonotic diseases, protocols for using  
13 xenotransplantation in the treatment of Parkinson's  
14 and AIDS, and early considerations of the PHS  
15 guideline on xenotransplantation.

16           The National Academy of Sciences,  
17 Institute of Medicine, convened two meetings to  
18 examine the scientific, medical, social, legal,  
19 ethical and economic aspects of xenotransplantation.

20           The Public Health Service has launched a  
21 series of public workshops on the different aspects of  
22 xenotransplantation. This is the second in the  
23 series, and yesterday you heard a summary from John  
24 Coffin of the first workshops which focused on cross-  
25 species infectivity and pathogenesis.

26           We've also heard about the FDA Advisory  
27 Committee which recently established a Subcommittee on

1 Xenotransplantation. We've heard a summary of their  
2 discussion of xenograft product testing, patient care,  
3 informed consent, and public risks with respect to  
4 porcine endogenous retrovirus.

5           In addition, there have been many  
6 excellent public meetings sponsored by the transplant  
7 community, the scientific community, and industry, as  
8 well as by other nations.

9           Collectively, these meetings have provided  
10 much needed public forums for not only keeping abreast  
11 of scientific progress in xenotransplantation  
12 research, but also for discussion of the accompanying  
13 social, legal and ethical issues.

14           The HHS committee strongly holds, however,  
15 that regular public review and discussion of  
16 xenotransplantation research is imperative to ensure  
17 broad public awareness, understanding and feedback on  
18 this line of study.

19           While clinical studies involving  
20 xenotransplantation are not new, recent biomedical  
21 advances has significantly changed the nature and  
22 feasibility of these studies, giving rise to renewed  
23 and growing interest in a century-old field of  
24 investigation.

25           Advances in transplantation, molecular  
26 biology, virology and immunology have brought us to  
27 the point where we are no longer saying "could we" but

1 "should we" about xenotransplantation. We now have to  
2 decide whether the potential benefits of  
3 xenotransplantation, which we have seen to be  
4 extraordinary, outweigh the potential risks.

5           This is a critical analysis, and is  
6 complicated by the fact that the possible infectious  
7 disease risks extend beyond the individual to close  
8 contacts, health care workers, and the community.

9           So there's a pressing need for both public  
10 education and comprehensive public involvement in  
11 addressing the broad range of complex issues raised by  
12 ongoing and proposed xenotransplantation protocols.  
13 Many of these scientific, medical, public health,  
14 ethical, legal, social and economic issues have been  
15 identified during this meeting.

16           For example, we've heard about the issues  
17 of valid informed consent from seriously ill patients,  
18 gaining informed consent from third parties or close  
19 contacts, and communities, intergenerational  
20 implications, welfare and use of animals, the  
21 allocation of scarce resources, patient selection, use  
22 of placebos, and confidentiality.

23           These are just a few of the relevant  
24 issues. We've heard about many others during the  
25 course of just this meeting.

26           Because these are issues in which we are  
27 all stakeholders, we must all engage in the continuing

1 dialogue. Sound public policy in xenotransplantation  
2 is based on broad public input from researchers,  
3 physicians, health care providers, policy makers,  
4 patients and their families, public health officials,  
5 the news media, and the public at large.

6           There is certainly precedent for the  
7 establishment of a national advisory committee. Some  
8 of the concerns surrounding xenotransplantation  
9 research are strikingly similar to widespread  
10 apprehension that emerged at the inception of genetic  
11 engineering research.

12           In 1975, a group of scientists involved in  
13 genetic engineering research convened an international  
14 conference at Asilomar. They discussed how this new  
15 technology could have potentially dangerous  
16 consequences in the absence of appropriate oversight  
17 and safeguards.

18           In response to the Asilomar discussion and  
19 recommendations, the NIH established the Recombinant  
20 DNA Advisory Committee or RAC. At first, the RAC was  
21 composed entirely of scientific members, but it soon  
22 became clear that ethical issues needed to be  
23 addressed, in addition to safety concerns, and RAC  
24 membership was expanded to include public  
25 representation, in addition to scientific expertise.

26           This was a case where widespread public  
27 concerns about an emerging field of research could

1 have halted what we now know to be a critical line of  
2 investigation. However, the establishment of an  
3 advisory committee provided a means for public  
4 education and examination of the issue and,  
5 consequently, allowed the field to move forward with  
6 essential oversight, including of ethical issues and  
7 public health safety precautions.

8           In thinking about the function and purpose  
9 of a national xenotransplantation advisory committee,  
10 the HHS committee has discussed a number of potential  
11 roles. First and foremost, a xenotransplantation  
12 advisory committee could discuss in a public forum the  
13 full range of scientific, social, and ethical issues  
14 raised by xenotransplantation and could make  
15 recommendations for the conduct and oversight of these  
16 studies.

17           Some specific examples of this include:  
18 reviewing all classes of ongoing xenotransplantation  
19 research initiated prior to establishment of the  
20 advisory committee; providing formal expert advice to  
21 HHS agencies about the current state of knowledge and  
22 technology regarding xenotransplantation and the  
23 potential for transmission of infectious diseases as  
24 a consequence of it; discussing novel experimental  
25 approaches of individual xenotransplantation protocols  
26 and making formal recommendations to HHS agencies such  
27 as HRSA, CDC, and NIH and, in particular, the FDA

1 which has regulatory authority for this research.

2           Other possible roles include: identifying  
3 additional diseases and conditions which may benefit  
4 from xenotransplantation; discussing new scientific  
5 developments that have implications for or potential  
6 application to xenotransplantation; convening  
7 xenotransplantation policy conferences to enhance the  
8 depth and value of public discussion of this research;  
9 consulting with xenotransplantation recipients, their  
10 close contacts, and health care providers on the real  
11 and perceived risks and benefits of  
12 xenotransplantation and the realities of ongoing and  
13 proposed xenotransplantation policies; without  
14 disclosing proprietary information, publicly reviewed  
15 data collected through the xenotransplantation  
16 registry, coordinate with national and international  
17 organizations concerned with xenotransplantation; and  
18 recommend changes to the PHS guideline and other  
19 government policies or guidance in this area.

20           We've also considered the composition of  
21 a national xenotransplantation advisory committee. In  
22 order to successfully function as envisioned, the  
23 advisory committee would need to include and/or have  
24 access to a broad array of expertise and  
25 representation.

26           This would include at a minimum a balance  
27 between scientists and clinicians actively engaged in

1 xenotransplantation research, experts in scientific  
2 areas that are highly relevant to xenotransplantation.  
3 This includes epidemiology, virology, microbiology,  
4 infectious disease, veterinary medicine, and  
5 transplantation surgery, among others.

6           It also includes bioethicists, legal  
7 experts, representatives of patient communities and  
8 their families, representatives of various public,  
9 religious and cultural perspectives, and animal  
10 welfare advocates.

11           My remarks today provide a thumbnail  
12 sketch of the deliberations of the HHS committee on  
13 the need for and potential function of a national  
14 advisory committee on xenotransplantation. Our  
15 intention in previewing this today is to solicit wide  
16 public input as to the necessity and function of such  
17 a committee.

18           We have heard a number of suggestions  
19 already, and we welcome your additional comments.

20           MODERATOR RAUB: Thank you, Dr. Groesch.

21           Phil Noguchi of the FDA spends a lot of  
22 his waking hours thinking about cell based therapies  
23 in general and xenotransplants in particular, and he  
24 will share with you some of our thinking related to  
25 the xenotransplantation registry database. Phil.

26           DR. NOGUCHI: Thank you for those kind  
27 words, except you did remind me of all the things we

1 do need to do.

2 I'm very pleased today to represent the  
3 Department and our consensus deliberations of how we  
4 actually were able to come up with an approach to a  
5 national registry, but as an FDA representative, I  
6 want to also take this opportunity to specifically  
7 acknowledge the help of Ms. Debbie Knorr, who is the  
8 Acting Director of the Office of Recombinant DNA  
9 Technology.

10 She and I have been working very closely  
11 together for the last five years on making available  
12 all clinical protocols for gene therapy, and Ms. Gwen  
13 Mayes, who I'm not sure is still here or not, but she  
14 has helped us immensely in understanding the human  
15 allotransplantation system and took us on a very  
16 extended tour of the UNOS facilities.

17 What we're presenting today is actually an  
18 amalgam of all that experience, and -- well, I'll get  
19 right into it here, if I could have the first slide.  
20 I get a signal from the back. Well, I can just talk  
21 a little bit from the upcoming slides here.

22 Basically, I'm going to talk a little bit  
23 about what the goal of this preliminary pilot is going  
24 to be determined about. I'll have a diagram which  
25 will be fairly complicated, and we won't go through  
26 all of it, of -- I hear them talking in the background  
27 here. I'm sure it's coming.

1                   Then finally, I'll describe the ongoing  
2 process right now and assure you that the process to  
3 develop this database is ongoing. We don't have any  
4 real data yet to show you, but we anticipate being  
5 able to do that in the very near future.

6                   Ah, thank you. That's what we just said.

7                   Next slide, please. The goals of this are  
8 to provide a repository for the long term assessments.  
9 In any strategy that allows xenotransplantation to go  
10 forward, we absolutely need to know what happens to  
11 the patients, not just in the short term, but in the  
12 long term over a course of many years.

13                   This will assist us in identifying those  
14 things that are epidemiological in nature and specific  
15 to xenotransplantation, and through coordination with  
16 HRSA we'll be able to compare that to that of human  
17 allotransplantation. Some of these may overlap. Some  
18 of these may be unique.

19                   One of the most important goals is, should  
20 anything happen that we want to investigate, this will  
21 enable us to track patients and track occurrences of  
22 events; and this will provide a framework for safety  
23 assessments of patient outcomes.

24                   Next slide, please. Now this will be a  
25 receipt point for a number of bits of information  
26 which are above and beyond the IND. For example, we  
27 will have a registration of the facilities and

1 procedures in which this is done. This is a little  
2 bit unusual.

3           There will be a place for a clinical  
4 follow-up of individual patients. Patient adverse  
5 events report do get reported to FDA, obviously, all  
6 the time anyway, but these will also be flagged and  
7 put directly into the database so that we can try to  
8 monitor events in a somewhat real time fashion.

9           Most importantly, in terms of the  
10 correlation of is this due to the disease or is it due  
11 to the animal, is it due to the transplant, we will  
12 keep track also of animal health events.

13           The question of how far shall we take this  
14 kind of monitoring is, obviously, still being debated,  
15 but we are building into this at least a mechanism  
16 whereby close contacts -- that is, family contacts --  
17 may also be tracked by this particular system.

18           At a previous format, the Institute of  
19 Medicine, this issue came up. We want to assure  
20 everybody we're not talking about every six months  
21 everybody has to troop in and be re-registered, but  
22 we're trying to examine how can this be done on a for-  
23 cause type of basis. So one of the main issues is how  
24 to be nonintrusive and yet maintain continuity.

25           We will be, within this whole framework,  
26 support the notification of recipients, should  
27 anything happen that we feel the recipients do need to

1 be notified. Again, the long term analysis and  
2 scientific studies will be a logical outcome of all  
3 these functions.

4           Now in your handouts, you actually have  
5 something where, I think, all the gray things are now  
6 black, and you still can't quite see what's going on  
7 here; but the main thing that I think you should focus  
8 on here is, because all xenotransplantation protocols  
9 will be under IND, this is the IND sponsor.

10           In the case of this registry, as we  
11 develop it, we're concentrating on the commercial  
12 firms, because they have already built in their own  
13 database that will be tracking an animal facility,  
14 the clinical center, and I think this is another  
15 manufacturing sort of center.

16           The sponsor is also responsible for  
17 maintaining records that will enable tracking of  
18 patients as each one is entered. All this here, CBER  
19 itself, FDA is building a corporate database even as  
20 we speak. So this national registry and our corporate  
21 database are being developed simultaneously as  
22 separate databases, but they will be integrated  
23 eventually.

24           The main reason that FDA has taken the  
25 lead on this is because for the IND submission most of  
26 the information -- in fact, all of the information  
27 that is necessary to track will be coming to FDA. We

1 will have to review that anyway. So it was trying to  
2 take advantage of that process.

3           Here we have in the future members of the  
4 PHS xenotransplantation committee, and we will be  
5 having, in fact, the ability to monitor relatively in  
6 real time, and from this sort of notification we have  
7 in plan and have identified who will be called upon  
8 should an event, adverse event, come up that will  
9 trigger a response.

10           We will go through the usual sorts of  
11 things of trying to find out is this specific to the  
12 animal or to the patient or a combination of both, and  
13 we have procedures in place that will enable us to  
14 actually respond to that.

15           Now the process that we're looking at:  
16 We're just getting started, although I think we're  
17 about three months into this. There will be a pilot  
18 phase, and the pilot is going to be somewhat bare, but  
19 will be functional. Then we are also looking at long  
20 term enhancements with an intermediate and a longer  
21 term phase.

22           When we say target system, this is sort of  
23 like what will be in place for full time use. Now the  
24 pilot at the current time: We are working with three  
25 sponsors. As you had seen before, the amount of data  
26 that's required is fairly comprehensive, and the  
27 intricacies of keeping them in a database is rather

1 comprehensive.

2           We will be looking at trying to make sure  
3 there is a control vocabulary with FDA standards being  
4 built in. We will also be looking very closely at  
5 what international standards exist for reporting. For  
6 example, the ICH standard for safety reports will be  
7 incorporated.

8           This will be, as we said, a pilot, but  
9 everything we do will be transferable, and we're  
10 looking for how we can make sure that whatever we do  
11 today will be compatible with the future -- for  
12 example, electronic data interchange formats.

13           Finally, as we mentioned, at the present  
14 time there's a stand-alone database. That is, it will  
15 be a small database somewhere over here, but then it  
16 will be integrated with the FDA corporate database.

17           It will have capabilities by necessity,  
18 since not all the data will be in the database, but  
19 there will be specific links to IND sponsored  
20 databases. Obviously, this will also play directly  
21 into the whole concept of -- it's true, viruses don't  
22 have passports. So we need to be able to link up with  
23 the international community, and we're already in  
24 discussions with several international potential  
25 sponsors to make sure that we understand how they  
26 collect the data and that they understand how we would  
27 like the data to be submitted to us.

1           Austere is not an acronym. That is really  
2 what it is. Because it's very easy in any database  
3 development thing to say, oh, wouldn't it be nice if  
4 we had this, and oh, we have to have that and  
5 everything, Austere is really what we're doing.

6           We're combing through each requirement  
7 that has been proposed, and on an almost hourly basis  
8 we go through the process saying, is that nice to have  
9 or must we have that to protect the public health.

10           I can tell you it sometimes is not too  
11 easy, but when you just stress the public health, I  
12 think we are rapidly getting toward those very basic  
13 kinds of data elements that will ensure that, should  
14 something happen, we will be able to respond in an  
15 intelligent and a responsible manner.

16           Finally, this is just to reiterate that  
17 this is not just a prototype so we could see what's  
18 happening out there and then try to figure out what we  
19 will do. Coincident with this development, we'll also  
20 have, and we do have in place, specific individuals to  
21 respond to any particular event.

22           Thank you.

23           MODERATOR PATTERSON: Our next speaker is  
24 Dr. Stephen Rose from the NIH. Dr. Rose will speak to  
25 us about strategies for archiving biologic specimens.

26           DR. ROSE: I have the distinct pleasure of  
27 preaching to the choir. Dr. Noguchi just described

1 one of the important instruments necessary to ensure  
2 the ability to effectively deal with any possible  
3 public health risk for xenotransplantation, i.e., the  
4 registry.

5 I will describe the second arm that is  
6 necessary to any public health investigation, the  
7 xenotransplant biologic specimen archive.

8 Now this archive is meant to keep  
9 biological samples from xenograft recipients, exposed  
10 health care workers, and source animals which are  
11 essential for a public health investigation.

12 The absence of such samples has already  
13 been noted and has prevented our ability to do  
14 retrospective analysis that might, in fact, have  
15 answered some of the questions we are already trying  
16 to get at, and that is the spread of infectious agents  
17 from porcine tissues or even nonhuman primate tissues  
18 into xenograft recipients.

19 We had originally proposed in the draft  
20 guidelines for infectious agents to have a  
21 decentralized archive. Upon review, we've determined  
22 that these decentralized archives that are maintained  
23 by independent investigators or companies are  
24 inadequate, compared to a central archive, and that's  
25 for the following reasons.

26 First off, this type of decentralized  
27 archive would rely on academic or company

1 investigators who do not have stable or dedicated  
2 support for this very important effort.

3           Secondly, loss of archive continuity as an  
4 academic or company investigator moves between  
5 institutions or companies would be a distinct possible  
6 problem.

7           Thirdly, there would be an unacceptable  
8 variability in sample preparation, preservation and  
9 storage.

10           For this reason and in response to the  
11 comments received from the proposed draft guidelines,  
12 the PHS committee came to the conclusion that only a  
13 central archive with a sustained stable source of  
14 funding operated by the PHS can adequately and  
15 completely ensure immediate access to biologic samples  
16 for a public health investigation.

17           This central archive would serve as a  
18 source for biologic samples from xenograft recipients,  
19 exposed health care workers, and source animals for  
20 public health investigations.

21           You've also heard a discussion about the  
22 possibility of including close contacts of xenograft  
23 recipients, and that is, obviously, something that the  
24 national review board, if it is established, or  
25 certainly comments from the community would have a  
26 great impact on determining whether those samples  
27 would also be important to be collected.

1                   This would store the biologic samples for  
2 a defined period of time. As you heard Dr. Chapman  
3 talk about, it has been proposed that that time period  
4 would be 50 years, based on the latency of known  
5 infectious agents as of this moment, but again that  
6 period would be reviewed on a regular basis to  
7 determine if, in fact, it was necessary for that  
8 period.

9                   This would also, in an added wrinkle,  
10 serve as a source of pooled biologic samples for  
11 competitively awarded investigator initiated research  
12 grants administered through existing National  
13 Institutes of Health grant processes. This, we feel,  
14 is an extremely important issue that needs to be  
15 addressed.

16                   There is a dearth of information and a  
17 dearth of research going on into xeno infectious  
18 diseases. There is very little being done outside of  
19 what is happening inside the corporate culture at the  
20 moment with respect to new diagnostics, determining  
21 what sort of transmission happens in these agents,  
22 what the possibilities are, and we feel the National  
23 Institutes of Health, as they have in the past in any  
24 other area of research, can help in this area and  
25 provide a great impetus to allow this type of research  
26 to go forward.

27                   I'm going to stop for a second and give a

1 commercial message. That is, a while ago the NIH  
2 published an announcement, an NIH guide for grants and  
3 contracts, specifically requesting grant applications  
4 dealing with this particular issue.

5           Again, I would say to anybody, we are  
6 open to receiving applications, reviewing them, and  
7 funding them, if they receive a meritorious score,  
8 dealing with xeno infectious disease transmission and  
9 agents, as well as immune response to xeno antigen.

10           The grants, as I said before, would be to  
11 investigate xeno infectious diseases and devise new  
12 and improved current detection methodology, and also  
13 to investigate the immune response to xenotransplants  
14 in order to prolong functional graft survival.

15           That takes care of the presentation on the  
16 archive. We feel this is an extremely important  
17 function but, like I said, I feel I'm preaching to the  
18 choir in that it's been called for by many people out  
19 in the community, and that this is something that we  
20 have heard and have responded to accordingly.

21           Thank you.

22           MODERATOR RAUB: Thank you, Dr. Rose. We  
23 may not be under budget, but we are under time. I'll  
24 ask the members who spoke, as well as a few others  
25 whom we've dragooned to be on this panel to join us  
26 here on the stage, and we'll be open for comments and  
27 questions from the members of the audience.

1 Dr. Friedman, would you like to join us?

2 MODERATOR PATTERSON: Any questions from  
3 the audience? Yes, sir? Please identify yourself.

4 AUDIENCE MEMBER: I'm Earl Blewett. I'm  
5 a microbiologist virologist. Actually, I'm a  
6 recipient of a grant under the program he was just  
7 discussing.

8 I was interested in: Is this archive  
9 going to be -- go back and try and get data from the  
10 initial xenotransplants that occurred in the last  
11 decade or so or are they just going to be doing stuff  
12 from now on?

13 DR. ROSE: The archive itself, as  
14 proposed, would be a prospective archive. However,  
15 there are efforts being conducted at the moment to, in  
16 fact, go back and obtain samples and monitor those  
17 patients.

18 I know of two particular studies that are  
19 going on, one of which actually is in for review at  
20 the moment.

21 MODERATOR PATTERSON: Yes, Dr. Berger.

22 DR. BERGER: Has there been a study done  
23 to estimate the cost of the registry, the central  
24 archives, when we're looking at a future -- and again,  
25 I use the same number of an estimate in the year 2010  
26 -- of 500,000 pig donors, the accumulated effects of  
27 all of those transplants, the cost of archiving

1 samples and keeping a national registry. Has there  
2 been any type of study done, any type of future cash  
3 forecast in terms of what that's going to cost the  
4 public?

5 MODERATOR PATTERSON: I'd like to call on  
6 Dr. Rose and Dr. Noguchi to answer those questions.  
7 The answer is, yes, limited but yes.

8 DR. NOGUCHI: Yes. We have done some  
9 preliminary things, at least for the registry. You  
10 saw the word Austere there, and that's deliberate,  
11 because it's quite evident that the more patients you  
12 have, the bulkier it can get.

13 I'm not sure. Do we want to say about how  
14 much we estimate? We estimate that, for the registry  
15 as we anticipate it somewhere on the order of \$250,000  
16 to \$300,000 per year.

17 DR. BERGER: What about for the archiving  
18 of samples?

19 DR. ROSE: The archiving of samples -- The  
20 estimates on that are based on a number of very good  
21 examples, including the ATCC as well as the AIDS  
22 archives that are currently being supported.

23 The answer is it is felt that this can be  
24 done, including all the computer records and the  
25 cross-referencing, for probably no more than about a  
26 million dollars a year.

27 DR. BERGER: As that continues to grow?

1 DR. ROSE: I cannot hear you.

2 DR. BERGER: As that continues to grow,  
3 year after year?

4 DR. ROSE: Again, that depends upon how  
5 fast it grows. While I understand the report that was  
6 put out and the numbers that you're quoting, not  
7 everybody necessarily adheres to that number.

8 So my answer to you is that is based on a  
9 relatively good example, but not as high as the number  
10 you're quoting, no.

11 MODERATOR PATTERSON: Yes?

12 AUDIENCE MEMBER: Good afternoon. Michael  
13 Langan from the National Organization for Rare  
14 Disorders. We're a patient advocacy organization  
15 representing literally millions of Americans with  
16 rare, usually genetic diseases and their national  
17 organizations that represent them specifically.

18 I'd like to first comment and then ask a  
19 question. My first comment is that the patient  
20 community that stands to benefit the most from the  
21 success and the efficacy of xenotransplantation  
22 maintains a great deal of hope for its future, that it  
23 may be their cure. It may save their lives. However,  
24 this segment of the patient community also maintains  
25 a great deal of fear.

26 Unfortunately, that fear at the present  
27 time of the risks of either infectious disease or the

1 risks of clear unsafety, for whatever reason, perhaps  
2 outweighs that hope.

3 I would like to say first, thank you, to  
4 many of the speakers and panelists yesterday and today  
5 and members of the audience who have urged that Public  
6 Health Service guidelines, regulations, whatever the  
7 policy may be, that it be developed in the public  
8 arena. This meeting is clearly an example of that.

9 The presentations we just heard regarding  
10 the proposed rule for public disclosure with respect  
11 to clinical trials is something that we applaud  
12 greatly and hope to see become effective, as well as  
13 the creation of a national advisory committee for  
14 xenotransplantation.

15 What I would like to ask members of the  
16 panel and perhaps Dr. Zoon specifically to clarify is:  
17 Will there be connection between a public advisory  
18 committee and that information that is disclosed?

19 It's been our experience in the patient  
20 community that very often the FDA has been perhaps too  
21 conservative in its interpretation of what is  
22 proprietary information or confidential or what ought  
23 to be considered a trade secret, and will those  
24 clinical trials be discussed in some public forum  
25 rather than just allowing an advisory committee to  
26 discuss theory or to discuss broad social or policy  
27 implications?

1 DR. ZOON: I'd be happy to discuss.

2 Actually, the proposed rule on public disclosure for  
3 gene therapy and xenotransplant clinical trials is  
4 just under development.

5 The experience that we have with gene  
6 therapy has been quite vast in terms of our ability to  
7 make information available, and that subset of  
8 information clearly will be an issue that is necessary  
9 that public discussion in the area of health and  
10 safety can be addressed.

11 The specifics of the disclosure with  
12 respect to parts of commercial confidential  
13 information are clearly still subject to other FDA  
14 rules, but I think that the issues and the public  
15 comment period on the proposed rule will help guide us  
16 into making that proper area, and we invite all those  
17 interested, clearly, when this comes out, to give  
18 their input into this proposed rule.

19 DR. NOGUCHI: Amy.

20 MODERATOR PATTERSON: Yes, Dr. Noguchi?

21 DR. NOGUCHI: I'd just like to expand upon  
22 what Dr. Zoon has said.

23 This is an example of where the integrated  
24 interactions between agencies has been extremely  
25 beneficial. Again not to embarrass Debbie Knorr, but  
26 just to say that she has shown us very dramatically  
27 that almost everything that has been considered

1 commercial confidential by companies when they submit  
2 things, she's gone back and asked them personally is  
3 this page confidential, is this; and invariably, over  
4 the course of the last, I think, ten years, there have  
5 been two pages that actually were.

6                   So, actually, we're taking our lead for  
7 this rule from our interactions and from the ability  
8 that is given us to respond in a very rapid way to  
9 public events.

10                   MODERATOR PATTERSON: Yes, Dr. Pollard?

11                   AUDIENCE MEMBER: Harvey Pollard. I'm at  
12 the Uniformed Services Medical School across the  
13 street.

14                   By way of full disclosure, I guess I  
15 should say I'm an enthusiast about xenotransplants.  
16 Twelve years ago we invented the method as an  
17 intramural scientists of implanting chromaffin cells  
18 for treatment of chronic pain. These are bovine  
19 chromaffin cells that came from an abattoir, and we  
20 asked no questions except to say is it infected or  
21 grossly.

22                   Now the problem, of course, is that this  
23 technology is bigger than us. It's not so difficult  
24 now that you can't do it elsewhere. My question  
25 actually has to do with the fact that we have to be  
26 careful about regulating ourselves into irrelevancy,  
27 because as we speak, people are taking chromaffin

1 cells from cows that came off of the local abattoir  
2 and sticking them into people in France and in Spain.

3 No one is asking any questions, and the  
4 question has to do with, in terms of this registry,  
5 how are you going to deal with the outside world, and  
6 what's the strategy for dealing with that?

7 DR. NOGUCHI: I'll take a crack at that.

8 AUDIENCE MEMBER: I figured you would,  
9 Phil.

10 DR. NOGUCHI: You heard this afternoon  
11 from the international community, which is forging a  
12 very strong alliance to really determine what are the  
13 necessary components for xenotransplant trials.

14 I will take issue as a representative of  
15 FDA, saying that, in fact, I think if you look very  
16 closely, more innovation takes place under FDA  
17 regulation than without it, and for the precise reason  
18 that we're all here today.

19 How many times have you heard people say,  
20 oh, we'd love to do that, but FDA will never let us?  
21 They never actually asked us, and most of the time  
22 they're surprised at what we can allow to go forward,  
23 and actually, most of the time we help to improve the  
24 protocols, because we have a vast knowledge of a lot  
25 of different things.

26 So I would just say that we are very  
27 sensitive to the fact that, no, we don't want to chase

1 people offshore, but we would encourage them to really  
2 look very closely at what has happened.

3           The advances in gene therapy, the advances  
4 in cellular therapies, are far and away far more  
5 advanced in this country than anywhere else, and  
6 that's in spite of the fact that they are regulated.

7           AUDIENCE MEMBER: Is there a strategy for  
8 dealing with the people who are not taking part in  
9 this program?

10           MODERATOR PATTERSON: Dr. Zoon.

11           DR. ZOON: Well, I think it's very clear.  
12 We as representatives of the FDA and -- Food and Drug  
13 Administration and the Public Health Service have been  
14 asked to participate in the World Health Organization  
15 activities, OECD and other activities to share where  
16 we are, our ideas and directives with respect to the  
17 future.

18           I think the communication has been very  
19 good, and I think there's a common understanding of  
20 the baseline needs and requirements for this area. So  
21 I think it's going to continue to take a lot of  
22 discussion and outreach, because the science is going  
23 to evolve over time.

24           I think where we are today is trying to  
25 develop the baseline at which we can all share that  
26 information, and I think people have worked very hard  
27 to make sure, as you can see from the meeting today,

1 that we've gotten other participants from other  
2 countries.

3 I think one of the things that has been  
4 important, certainly, from the perspective that I sit  
5 in, many of the common issues and concerns have all  
6 raised many of the same points, the use of registries,  
7 archiving, the importance of infectious disease  
8 testing and the importance of monitoring this seems to  
9 be universally accepted as general principles.

10 MODERATOR PATTERSON: Thank you. Yes?

11 AUDIENCE MEMBER: Thanks. I'd like to  
12 follow up with an issue that Dr. Berger raised about  
13 the costs involved.

14 As one of the 34 million uninsured  
15 Americans in this country, I feel that the costs for  
16 archiving and for the registry are vastly  
17 underestimated. In fact, I hope that the FDA and NIH  
18 will make those figures public, because I think the  
19 public should have a right to look at them.

20 I believe that -- I wanted to know if the  
21 \$1 million figure for archiving samples also included  
22 the cost of testing, and I also wanted to know if the  
23 breeding and housing and feeding and medicating of  
24 source animals was also included.

25 I wanted to know who was going to pay for  
26 those tests and procedures, and who, in fact, would  
27 eventually pay for the xenograft procedures

1 themselves, particularly if insurance providers don't  
2 agree to pay for them.

3           Another question, which I still feel  
4 really hasn't been answered by any U.S. panelist is  
5 who will pay for compensatory damages if the zoonotic  
6 virus spreads to the human population. I still  
7 haven't really received any kind of answer to that  
8 question from anybody on the U.S. panel.

9           DR. FRIEDMAN: May I just ask for your  
10 views on that?

11           AUDIENCE MEMBER: My views?

12           DR. FRIEDMAN: Yes. This is a public  
13 discussion. We'd be interested in who you think  
14 should bear those costs.

15           AUDIENCE MEMBER: I'd like to hear your  
16 views on that subject.

17           DR. FRIEDMAN: I'm sorry?

18           AUDIENCE MEMBER: I'd like to hear your  
19 views on that subject.

20           DR. FRIEDMAN: I do understand, but would  
21 you share yours with us?

22           AUDIENCE MEMBER: I'd like to hear yours  
23 first.

24           DR. FRIEDMAN: I'd be happy to share mine  
25 with you. I think those are very difficult questions  
26 that deserve -- and I'm not being coy. I'm not being  
27 tricky. I think these deserve full public discussion.

1                   There are, obviously, a variety of payers.  
2   There are a variety of organizations, individuals and  
3   groups who could serve as the indemnifiers of these  
4   activities, but I think what the optimal configuration  
5   is for reimbursement or for cost recovery in the event  
6   of harm or for whether patients or organizations or  
7   sponsors should bear the costs of the archiving and  
8   virologic and other evaluation of tissues -- those are  
9   issues that I think really deserve public discussion.

10                   So it's not a reluctance on our part, but  
11   I think rather in the best interests of what people  
12   have been talking about for two days. Let's have a  
13   public discussion. There are many ways in which this  
14   could go. What are the pros and cons?

15                   AUDIENCE MEMBER: Well, my -- I mean my  
16   view is, you know, on a general basis, drawing up an  
17   analogy, if I were a homeowner and I wanted to buy a  
18   home, I'm not going to go out and buy a home without  
19   having the money to buy it first.

20                   So I really believe that the FDA or the  
21   NIH and maybe the CDC have a fiscal responsibility to  
22   formulate a budget for xenotransplantation procedures,  
23   and everything that they entail, and present it to the  
24   public before any of this should be allowed to go  
25   forward.

26                   I mean, how can you spend money that you  
27   don't have and make plans for a very expensive

1 technology without knowing what the costs involved are  
2 going to be to the public eventually?

3 DR. NOGUCHI: Can I take a little crack at  
4 this, not to address the case of indemnity, because I  
5 think that's assuming that we aren't taking an  
6 appropriate and responsible course here. The whole  
7 purpose of what we're doing is to ensure that it's  
8 everybody's responsibility to participate in this.

9 Just to set the record straight, however,  
10 the funding for the initiatives that you've heard have  
11 been not specifically allocated, but have been  
12 scritchted and scratched out of existing budgets by the  
13 various services that you've heard.

14 I will also say that the bulk of the  
15 investment into xenotransplantation has not been by  
16 the public funding, but has been by corporate funding.  
17 The amount that has already been spent in preclinical  
18 studies probably dwarfs by many orders of magnitude  
19 what you've heard about today.

20 So it's difficult to respond when the  
21 assumption is that this is a public venture funded by  
22 NIH. It is not. It is being driven by a lot of  
23 concerns, and there is a lot of corporate backing in  
24 this.

25 So as Dr. Friedman indicated, these are,  
26 obviously, very important issues. The questions you  
27 are raising are entirely appropriate, but they're not

1 entirely accurate at the moment.

2 AUDIENCE MEMBER: Right, but the goal is  
3 to integrate it into public health programs.

4 DR. NOGUCHI: Yes.

5 AUDIENCE MEMBER: So eventually, the  
6 taxpayers will be, you know made to bear any kind of  
7 burden, financial burden, of the technology. I think  
8 that should be made clear to the public.

9 DR. NOGUCHI: Yes, you are quite right.

10 MODERATOR PATTERSON: Yes, ma'am?

11 AUDIENCE MEMBER: Just an aside to the  
12 lady in black over here. The cost -- indirect and  
13 direct costs of diabetes per year to American  
14 taxpayers and public is \$100 billion. So whatever is  
15 spent on this is going to be -- to get the proper  
16 protocols in place -- is minuscule compared to that,  
17 in my opinion.

18 My questions, though, have to do with the  
19 call for public -- keeping the public involved. Will  
20 you be calling for -- Will there be a formal call for  
21 public comment like you did in the previous xeno  
22 guideline?

23 In the contact protocols -- I brought 20  
24 letters with me already, but you know, there's at  
25 least a half a dozen people on this list that look  
26 like they should have a letter. So we're going to  
27 need to know who we address our comments to.

1                   MODERATOR RAUB: On the issues of public  
2 comment, the generic answer is yes. In particular, as  
3 far as the guidelines are concerned, based on today,  
4 our collective hope is the committee is to complete  
5 this version of the guidelines, issue it, such that it  
6 can be out there in the world and be used, but by  
7 definition guidelines are meant to be flexible.  
8 Guidelines are meant to change. So it's out there all  
9 the time for public comment, and we'll be both  
10 receiving and seeking them.

11                   With respect to the particular letters you  
12 talked about, I'll certainly be glad to receive them  
13 on behalf of the Department and to follow up as  
14 appropriate, and beyond the guidelines, as Dr. Zoon  
15 indicated, those elements that need to play out to  
16 complete or refine the regulatory structure all go  
17 through what, from Civics 101, we might find a  
18 ponderous process, but the Notice of Proposed  
19 Rulemaking, the Administrative Procedure Act, is  
20 designed precisely to ensure that ideas get published,  
21 out there for comment, and as you've seen with the  
22 guidelines, we listen and respond, and so does the FDA  
23 systematically on its rulemaking.

24                   AUDIENCE MEMBER: Okay. You did have a  
25 formal call for public comment. It was posted on your  
26 Web site. What I wanted to know, would you be doing  
27 something like that with this, too?

1                   MODERATOR RAUB: Yes, and we also  
2 appreciate suggestions of other media and other forums  
3 to do it.

4                   AUDIENCE MEMBER: Okay. As far as  
5 letters, are you going to have a committee that there  
6 are specific names of people that we can address, or  
7 will it be put in with your call for comment, the  
8 contact person?

9                   MODERATOR RAUB: As far ahead as we can  
10 see now, we intend to maintain our internal committee.  
11 The individuals you see here are the members of it,  
12 and plan to continue meeting from time to time and  
13 working together for what other steps are needed.

14                   AUDIENCE MEMBER: Okay, thank you.

15                   MODERATOR RAUB: As the needs change, we  
16 can expand or otherwise change the composition of the  
17 group or perhaps go to some other forum, but for now  
18 what you see is what you get.

19                   AUDIENCE MEMBER: So if I have anymore  
20 questions, I'll write to you?

21                   MODERATOR RAUB: Please do.

22                   AUDIENCE MEMBER: Okay. Thank you.

23                   MODERATOR PATTERSON: Yes, Dr. Allan?

24                   DR. ALLAN: Yes. John Allan from  
25 Southwest Foundation.

26                   First of all, I wanted to, in one way,  
27 praise the FDA for the way they've set up the

1 xenotransplant subcommittee. I think it looks to me  
2 as though it's very effective in handling infectious  
3 disease risks at a regulatory level. I think it looks  
4 like it's going to work very well, and so I praise the  
5 FDA for that.

6           Coming back at the issue of nonhuman  
7 primate use, I'm baffled. I'm absolutely baffled. We  
8 submitted, and many other groups have submitted and  
9 talked about the inherent infectious disease risks  
10 associated with nonhuman primates.

11           It's a substantial risk. It's something  
12 not to be taken lightly. We submitted a letter in  
13 response to the guidelines of 44 virologists, some of  
14 the top virologists in the world, stating that  
15 nonhuman primates at this point should not be  
16 considered as transplant donors, and that there needs  
17 to be something specifically in the guidelines to  
18 address that.

19           What I heard was that that's been ignored.  
20 The American Society for Transplant Physicians in an  
21 open letter in response has said that nonhuman  
22 primates are a significant risk and should be  
23 considered specifically in the guidelines.

24           Again, it seems to me that this has been  
25 ignored. I really believe you need to address this  
26 issue. Not to do that and to take the tactic of just  
27 trying to regulate it may be a mistake, because there

1 are other countries that are going to look at those  
2 guidelines and say there's no difference between  
3 primates and pigs.

4 I think that's something you really need  
5 to reconsider and take back and take a really close  
6 look at.

7 MODERATOR PATTERSON: Thank you, Dr.  
8 Allan. That's a very important comment. Dr. Chapman  
9 or Dr. Jaffe.

10 DR. CHAPMAN: Thanks, John. I guess I  
11 didn't express myself very clearly before. So let me  
12 try again.

13 We take very seriously your concerns and  
14 the other concerns that were expressed with the  
15 nonhuman primates, but when people talk about  
16 differences between pigs and primates and the  
17 infectious disease risks that they pose, they are  
18 usually thinking very precisely but talking very  
19 generally.

20 I would propose that, when you and the 43  
21 other scientists and the additional couple of  
22 scientists in the other groups in the public  
23 commentary express concerns about the infectious  
24 disease risks posed by nonhuman primates, and that  
25 they exceeded those posed by pigs -- when you  
26 dissected the reasoning behind that, there were some  
27 specific reasons.

1           One reason is that pigs that are available  
2 presently and could be considered a source animal for  
3 xenografts have a husbandry history for multiple  
4 generations that can produce an animal that is very  
5 clean of infectious agents in a way that currently  
6 available nonhuman primates do not.

7           We addressed that concern in the  
8 guideline, but we didn't address it by talking about  
9 the difference between species. We addressed it by  
10 talking about the minimal level of husbandry that must  
11 be obtained before you can begin to consider any  
12 animal as a source of a xenograft.

13           The fact is no nonhuman primate that  
14 exists at present, unless there's some exceptional  
15 ones I don't know about, could meet those criteria.

16           DR. ALLAN: But that's exclusionary,  
17 though. I mean, the thing that I'm saying is that  
18 it's an inherent risk. It's not about husbandry.

19           What I'm saying is you shouldn't try and  
20 say, well, if we draw these very carefully, by nature  
21 it may exclude primates. I think that's what you're  
22 saying. Is that -- Am I missing that?

23           DR. CHAPMAN: I think I'm saying something  
24 a little differently. Let me -- but I'm not,  
25 apparently, saying it real well.

26           I think risk of infection that's carried  
27 by a source animal is due to one of three things.

1 It's either due to what I'll call exogenous infectious  
2 agents that persist in that anima, by which I mean  
3 infectious agents the way we usually think of them,  
4 agents that can be transmitted horizontally from one  
5 living creature to another by infection, or --and part  
6 of your concern, as I understand it, and other  
7 people's concern, is that at present nonhuman primates  
8 who are a couple of generations removed from a feral  
9 state, who are generally raised in open large corrals,  
10 have a very long list of exogenous infectious agents  
11 that are or may be in them that are recognized and  
12 possibly a longer list of those we don't recognize, in  
13 contrast with pigs that have been domesticated for  
14 thousands of years, maybe raised with extreme  
15 precautions in barrier facilities, and with whom there  
16 is actually probably a very narrow range of identified  
17 persistent infections that cannot be eliminated from  
18 them or are not already eliminated from them.

19           That concern is very real, and we take it  
20 seriously, but we chose to address that particular  
21 concern not by talking about difference between the  
22 species but by talking about the standards necessary  
23 in terms of cleaning up an animal, any animal,  
24 including the pig, before you could consider it as a  
25 source of xenotransplant.

26           The second way a source animal could pose  
27 an infectious risk through a xenograft that was

1 produced form it is through endogenous infectious  
2 agents, the only ones of which I know about at present  
3 at endogenous retroviruses; but basically, infectious  
4 agents that are passed vertically from one animal to  
5 another through inheritance as part of a genom of the  
6 animal, and that cannot at present be removed from  
7 those animals, although there's been discussion about  
8 theoretical possibilities of removing them by breeding  
9 or by transgenic techniques.

10 Up until a year or so ago, the existing  
11 science suggested that nonhuman primates clearly had  
12 an endogenous retrovirus. They have an endogenous  
13 virus that had been demonstrated to infect human cell  
14 lines in vitro in the laboratory.

15 Therefore, clearly, we had to be concerned that  
16 it might be able to infect humans in vivo. That had  
17 not been shown with pigs, but pigs had been relatively  
18 less explored, and the evolving science over the last  
19 year, year and a half, that's been discussed here has  
20 told us that, in fact, pigs also have an endogenous  
21 retrovirus.

22 DR. ALLAN: But you can't equate pig  
23 endogenous retrovirus that barely infects human cells  
24 in tissue culture with endogenous viruses that are  
25 found in baboons or even exogenous viruses.

26 If you take any solace from the fact that  
27 an exogenous viruses in baboons are highly infectious

1 in human -- in tissue culture in the natural setting,  
2 nonhuman primate viruses are inherently more  
3 infectious and much more pathogenic and dangerous in  
4 humans than are pig viruses. Then you might take that  
5 same tactic and suggest that endogenous viruses in  
6 baboons are probably going to be a lot more likely to  
7 be a risk than is a pig endogenous retrovirus.

8           So what I'm saying is that there are  
9 inherent species differences in terms of infectious  
10 risks that need to be considered. It's not simply  
11 whether or not one has a virus or not, but the  
12 inherent risks associated with the species.

13           DR. CHAPMAN: We've also put in additional  
14 language on preclinical studies that argue, before you  
15 put -- You know, there is discussion of husbandry  
16 techniques and screening that, basically, if I could  
17 summarize it, argue that before you procure a  
18 xenograft from an animal and put it into a human  
19 being, you need to have cleaned it from virtually all  
20 identifiable exogenous infectious agents that may pose  
21 a hazard.

22           Now there is another section that  
23 discusses the preclinical science that should be  
24 accomplished before you take a xenograft and put it  
25 into a human being. That, basically, discusses two  
26 things.

27           One is that, with agents you cannot remove

1 like these endogenous viruses, you should have done  
2 preclinical studies before you moved to the clinical  
3 trials, in which you've done everything that you can  
4 to characterize the ability of that agent to infect  
5 human cells, short of moving to human trials, and you  
6 need to have the diagnostic tools in place on your  
7 initial safety trials on limited numbers of people who  
8 are closely monitored to monitor those recipients  
9 post-transmission for any evidence that, actually  
10 infection has taken place.

11           So what we tried to do -- and what we've  
12 tried to do is dissect out the specific issues that  
13 present a risk and develop strategies to address those  
14 risks in a responsible manner. It's a sort of  
15 philosophical difference, I suppose, but I think it's  
16 the same thing that the FDA has sort of done when they  
17 have chosen not to impose a global moratorium but  
18 rather to put clinical trials on hold and define the  
19 specific safety criteria that sponsors need to be able  
20 to meet before those trials can come off hold, but  
21 then impose -- you know, lift that hold on a trial by  
22 trial basis.

23           DR. ALLAN: Do you think there will ever  
24 be a -- I can't see in the near future at least that  
25 you could consider using a nonhuman primate that would  
26 be considered safe, based on the fact that they have  
27 these endogenous retroviruses.

1 DR. FOLKS: I'd like to ask a question  
2 back to John. I think we know that allotransplant is  
3 clearly a practice of medicine. We really don't  
4 anticipate -- I don't think anyone here anticipates  
5 the baboon entering in an arena that will be a  
6 practice of medicine in xenotransplantation. We're  
7 talking about research.

8 Yeah, we're talking about research here.  
9 We don't know -- There aren't even enough animals. I  
10 think enough people have shown that there aren't  
11 enough animals to really utilize the baboon in a  
12 practice of medicine for --

13 MODERATOR PATTERSON: Tom, could you  
14 clarify something when you get your mike back on?  
15 Could you clarify, when you say research, are you  
16 referring to clinical research, because I think that's  
17 a difference, and I think that's one thing that John  
18 was concerned about.

19 DR. FOLKS: Well, yeah, I was really  
20 throwing the question back to John, where he thinks  
21 the danger is going to come. Is it one more  
22 xenotransplant of a baboon? Is it five more from a  
23 baboon? Where is the danger limit that you feel like  
24 surveillance and public health monitoring will break  
25 down, and this will become a serious threat?

26 MODERATOR PATTERSON: Before John answers,  
27 Phil, would you like to put this in a little bit of

1 context in terms of where some baboon colonies stand?

2 DR. NOGUCHI; Well, based on a lot of the  
3 public discussion, we have been in contact with  
4 several sponsors who have indicated that they have  
5 perhaps at least something that they would like to  
6 propose as potential sources of nonhuman primates.

7 I think that -- and that just -- As the  
8 regulators and the ones on the hot seat and, as Andre  
9 said, the ones who always get blamed, that does give  
10 us some concern.

11 We're willing to examine every case that  
12 comes before us in great detail, obviously, and now  
13 that, in a way, the public disclosure part is sort of  
14 being heralded by everybody, you can rest assured we  
15 will do that.

16 I think that it's like everything else in  
17 science, especially if somebody says it can't be done  
18 -- We saw slides today. Somebody is going to really  
19 try to prove you wrong. So I think that, from our  
20 point of view, John your point is very well taken --  
21 from FDA's point of view.

22 DR. ALLAN: So let me answer the question  
23 that Tom raised. That is -- and I've written about  
24 this extensively over the last three, four years. So  
25 what I'm going to say right now isn't any different,  
26 and I'm very blunt.

27 The bluntness is this, is that it only

1 takes one transplant to start an epidemic. So it only  
2 takes really one. So what you're doing is you're  
3 playing Russian roulette. You're basically betting  
4 that this transplant is not going to transmit a virus,  
5 because if you transmit a virus, all the surveillance  
6 in the world -- and you focus your attention on  
7 containment, you're already behind the eightball,  
8 because you've already transmitted that virus.

9           If it's a retrovirus, all you're going to  
10 be able to do is say there it is, there it is, there  
11 it is. We got HIV. How good are we at containing  
12 that? Terrible, because it's a retrovirus, and it  
13 just spreads, and we know how to stop it. We just  
14 tell people to not do those behaviors, and yet they  
15 continue to do them.

16           So you transmit a baboon virus, and it  
17 gets transmitted from patient to patient, all you're  
18 going to do is follow it. So I think we really need  
19 to be very careful about using baboon organs, and I  
20 believe you really need to make that distinction, not  
21 only myself but many others.

22           DR. NOGUCHI: Jonathan, there's two ways  
23 of handling it, in my view, strictly my view. One is  
24 you can say thou shalt not use baboons, period. The  
25 other way, which I think you've heard Louisa express,  
26 is to set out a set of criteria that must be met.

27           It's what we heard this morning, "no,

1 unless." That's sort of the way that this has been  
2 structured, and the way it's been structured in the  
3 infectious disease area is you shall not unless you  
4 meet these criteria, and these criteria are you will  
5 not have these agents which can be transmitted. You  
6 shall not have the retroviruses in tests in vitro and  
7 maybe even some in vivo models of concordant  
8 transplant that would show transmission between even  
9 monkey strains.

10           There's enough safeguards put in before  
11 you can even go forward to even trying a human trial.  
12 What if I said to you -- I mean, you know, I'll use  
13 the one that the press uses all the time -- you  
14 cannot clone?

15           Well, we've been proved wrong. What if I  
16 said to you that three years down the pike by a  
17 concerted effort supported by whomever I showed you a  
18 baboon that had no infectious agents that could be  
19 transmitted either in vitro between monkey cells and  
20 monkey cells or monkey and human cells, and that  
21 includes the endogenous retroviruses?

22           I'm not saying it's going to happen, but  
23 I'm saying, as was said earlier, science has a way of  
24 finding a way to do what we want to do. I think that,  
25 to me, is the important thing, is not to say a blanket  
26 no, but to set up a set of criteria that must be met  
27 and are stringent enough to actually preclude the type

1 of scenario that you're talking about.

2 DR. ALLAN: I agree with that. I actually  
3 agree with that. The reality of the situation can be  
4 far less than that, and we've already seen that happen  
5 with the AIDS patient who received a baboon bone  
6 marrow. In spite of the fact of the infectious  
7 disease risk associated with that, in spite of the  
8 fact that the science may or may not have been there,  
9 it went forward.

10 I was on the committee. So there's the  
11 reality of the situation. Really, when you look at  
12 those two species, one is that "no, unless" and the  
13 other one is a "yes, but" essentially -- "yes, if."  
14 In other words, a pig is sort of a "yes, if you meet  
15 these criteria," and a baboon is a "no, unless." So  
16 you're really dealing with two different things, and  
17 we're back to the same problem.

18 MODERATOR PATTERSON: Walid, and then Dr.  
19 Vanderpool.

20 DR. HENEINE: Yes. My comment is  
21 regarding the issue raised by John that, by  
22 definition, baboon endogenous virus being a nonhuman  
23 primate virus is likely to be more infectious than pig  
24 endogenous retroviruses.

25 We all shared that thinking with you until  
26 we did the screening of the patient that received the  
27 baboon bone marrow, and to our surprise, so far we

1 have seen no evidence of transmission of baboon  
2 endogenous virus in this patient who had underlying  
3 immunosuppression, who was also additionally  
4 immunosuppressed for the procedure.

5           So to start with the definition that  
6 nonhuman primate endogenous viruses are exogenous --  
7 or let me limit myself to the endogenous. These are  
8 the difficult ones to eliminate, by definition more  
9 infectious. We have to provide data for that.

10           This is one case we can extract  
11 information as much from a single case, but again it  
12 demonstrates that we're not dealing with apparently a  
13 very infectious virus.

14           MODERATOR PATTERSON: Dr. Vanderpool.

15           DR. VANDERPOOL: Gosh, when someone talks  
16 that long, I can't keep but making one comment on that  
17 subject. I thought the thrust of a lot of what we  
18 said was that baboons could be used with porcine  
19 transplant experimentations but extremely rarely used  
20 for baboon to human. It seems to me that baboons have  
21 more or less at the present time confined themselves  
22 due to their disease propensity to being experimental  
23 animals for xenotransplant trials with pigs to  
24 baboons, but very rarely baboons to humans. At any  
25 rate, I have a question that may be a forecast of the  
26 panel to come and, if so, I hope Amy appreciates this,  
27 because people may be inclined to go fairly soon.

1                   That is the following. That is, first, to  
2 express a great appreciation for what all of you have  
3 already done in terms of a variety of regulatory  
4 mechanisms and very basic institutional developments  
5 that will most certainly assure safety and so on.

6                   Now my concern has to do with the culture  
7 of research. I am in a large medical school where we  
8 do a lot of biomedical research, and I have written a  
9 recent book on the ethics of human subject research  
10 which takes me either as attendant or speaker to  
11 numerous PRIMAR conferences -- PRIMAR, Public  
12 Responsibility in Medicine and Research, a group in  
13 Boston that many of you surely know.

14                   PRIMAR puts on major conferences every  
15 year both for animal and human subject research and  
16 research with animals.

17                   Well, the university people I know, the  
18 IRB members, all track to PRIMAR. I mean that's the  
19 place they go, and in PRIMAR the people who are there  
20 most prominently are Gary Ellis and Melody Linn and a  
21 few people from OPRR, obviously, a very small division  
22 of NIH.

23                   I see Paul Gerbils from FDA there, but  
24 he's a fairly rare person from the FDA. Now my  
25 concern is this. How are these large number of  
26 university researchers going to figure out how to go -  
27 - how to do an IND?

1                   I mean, the researchers in the  
2 universities aren't attuned to that level of form  
3 filling out and sophistication. At least many of them  
4 I know aren't.

5                   So my challenge for the future is, okay,  
6 how -- With the FDA being the fundamental organization  
7 that is the regulatory agent through which  
8 xenotransplant research is done, how do you  
9 communicate what you do to the people who can be the  
10 superb researchers, and how can there be a fair  
11 playing field between the researchers at Merck and  
12 SmithKline Beecham and so on, and I own stock in some  
13 of those companies but no xenotransplant company --  
14 otherwise, I wouldn't have been here or at least I  
15 couldn't have served on the FDA committee -- but these  
16 organizations find drug firms are extremely skilled in  
17 IND processing.

18                   I think the university researchers are, by  
19 and large, neophytes in that area. So I think that's  
20 a question for ongoing education to think about panels  
21 who want to get these issues out to the public. One  
22 way to do it is through the IRBs at universities, all  
23 of whom have at least one non-university member on the  
24 committee.

25                   So this is maybe something for the next  
26 hour in terms of future developments, but I want to  
27 see the culture of the university researcher and the

1 work of FDA brought closer to each other, because the  
2 perception fundamentally -- FDA and industry go  
3 together. I know that's not entirely true, but OPRR  
4 and universities go together.

5           Seems to me, that's an area for future  
6 consideration.

7           MODERATOR PATTERSON: That's a very  
8 important point, and I think we have a volunteer on  
9 the panel to respond. Dr. Friedman.

10           DR. FRIEDMAN: Yes, if I may respond. I  
11 think it is a very important observation. I think  
12 that what you're asking is a rather special case of  
13 the general issue which has been of great concern and  
14 interest to the National Institutes of Health. It's  
15 been a great concern and interest to organizations  
16 like the Association of Medical Colleges.

17           I dare say, there's virtually no component  
18 of the biomedical research community that isn't  
19 concerned about what's usually called how to best  
20 foster clinical investigation in developing  
21 scientists, to assure that that tradition continues.

22           There's so many threats to that currently  
23 that there are many organizations that are very  
24 worried about how to do exactly what you're saying.  
25 You make a very good case for xenotransplantation.

26           You could have made an equally good case  
27 for some forms of genetic therapy or any other special

1 technology that has unique science, that has special  
2 ethical concerns, that has important biologic  
3 differences.

4           I think that, rather than say this is  
5 something that we solve for xenotransplantation, we  
6 recognize that it is essential that we solve it there,  
7 but it's not sufficient, and that what we really need  
8 to do is to pay attention to what is the university  
9 infrastructure that allows this kind of research to  
10 continue. How much responsibility is put on  
11 individual investigators versus institutional  
12 resources that are applied to do this? What special  
13 granting and funding mechanisms exist?

14           Also, your question implied something even  
15 larger, which was what will be the nature of  
16 public/private partnerships in the future? A lot of  
17 research is currently co-sponsored or partially  
18 sponsored by industry as well as non-vested -- non-  
19 directly vested research sponsors.

20           This is again a very important theme that  
21 academic centers and academic investigators are  
22 looking at very carefully right now. There is no  
23 simple answer to that except that I think that  
24 investigators will have increasingly difficult time  
25 with competing needs of these different scientific  
26 disciplines as well as competing needs from their  
27 institution to meet certain practice guidelines or all

1 sorts of other things that they'll have to do.

2 I think that the way to solve this is  
3 recognizing the enormity of the issue and asking to  
4 what extent all the public agencies involved, but also  
5 all the private organizations involved, wish to  
6 support an unbiased scientific infrastructure that  
7 allows medical progress to be made.

8 DR. VANDERPOOL: I guess one point I would  
9 make is I think FDA, through your work -- I think,  
10 superb work on these issues and leadership on this  
11 issue -- You have an opportunity to make a new  
12 presentation of yourself, a new image of yourself. I  
13 don't mean just window dressing, but I mean a serious  
14 -- for university researchers.

15 I think that, if certain processes and  
16 relationships with universities can be built at this  
17 time, maybe with the counseling back and forth with  
18 the OPRR person, I think this is an opportunity to  
19 break down some of those biases and blockages that up  
20 to this time continue, I think, to be in the minds of  
21 a lot of university researchers vis a vis the FDA.

22 I think it's time to get past that.

23 MODERATOR PATTERSON: Dr. Scirboll.

24 DR. SCIRBOLL: Yes. Thank you for making  
25 those comments. I actually was at PRIMAR this year  
26 talking a little bit about the range of ethical issues  
27 at NIH and its emerging scientific areas we're dealing

1 with, and I spoke I think, just before Stu Nightingale  
2 from the FDA. So we have been making efforts at the  
3 leadership level from many agencies to get to PRIMAR  
4 to talk to the IRB members, the IRB chairs.

5 I think Bill and I were discussing the  
6 same as Michael was saying, that issues related to  
7 genetic testing and gene therapy all have raised  
8 before us a series of new burdens, new needs for  
9 education to the IRBs, and it's something that not  
10 only the Public Health Service is grappling with, but  
11 the National Bioethics Advisory Committee is grappling  
12 with.

13 To that end, I think there are a number of  
14 initiatives that are going to be proposed that you'll  
15 start to see with making efforts to educate IRBs that  
16 have these new burdens, and perhaps not the full  
17 amount of expertise they may need to adequately  
18 evaluate research as it moves forward, so that it can  
19 move forward but move forward with the appropriate  
20 local review.

21 To that end, I point to the history of the  
22 RAC, which has over time, I think, provided a great  
23 deal of guidance to institutional IRBs and IBCs about  
24 the broad issues, both scientific safety and ethical  
25 issues, that IRBs need to consider when they're  
26 looking at protocols.

27 As we conceptualize the NXAC, if you will,

1 it would be able to offer those same sorts of broad  
2 and sometimes specific guidance to local review  
3 committees so that they can move forward with their  
4 task, doing it well but doing it expeditiously.

5           MODERATOR PATTERSON: Thank you. We'll  
6 take two more questions from the floor, starting with  
7 the gentleman in green, then Dr. Bach, and we will  
8 take a 15-minute coffee break, and I beg all of you to  
9 come back. You've been stalwart in your stamina so  
10 far, but the next session is very important as we talk  
11 about the road ahead.

12           Yes, sir?

13           AUDIENCE MEMBER: Thank you. My name is  
14 Pete Matthews. I'm a veterinary consultant. One of  
15 my clients is the NeoCrin Company, and you all heard  
16 from Dr. Scharp about encapsulated islets for therapy  
17 in insulin dependent diabetics. I have a very  
18 specific question for Dr. Chapman.

19           It is about the guidelines, the proposed  
20 guidelines, and I realize that you could not hone in  
21 on the very specific comments for a very specific  
22 section, but I am going to ask that question.

23           The specific requirement of no recycled or  
24 rendered animal materials in feed -- The way I do  
25 business to eliminate specific pathogens from  
26 potential porcine donors is to use segregated early  
27 weaning or medicated early weaning techniques to

1 eliminate those specific -- certain specific  
2 pathogens.

3           If this requirement as it is written -- if  
4 that's the guideline, then it will become very  
5 difficult to use those techniques, because of the  
6 special requirement of the early weaned pig for  
7 certain diets that are highly digestible and very high  
8 in protein and, of course, we use porcine plasma,  
9 spray dried plasma. We use fish meal.

10           Sometimes we use blood meal, and also  
11 whey, cheese and other, you know, milk products. So  
12 could you address that for me, and set my mind at rest  
13 or otherwise I have to go back and write my protocols  
14 all over again.

15           DR. CHAPMAN: I'm happy to address it.  
16 Actually, Tom Eggerman from FDA spoke to it last  
17 night.

18           Let me just say in preparation for the  
19 next question that's aimed at me, I'm happy to be the  
20 point person in responding to questions about the  
21 guidelines, because I do have the advantage of having  
22 just reviewed all the public commentary in preparation  
23 for this talk, but in my own defense, in case a  
24 question comes up I don't want to answer, I do want to  
25 also point out that everyone at the table here and  
26 many of the people in the audience from the Public  
27 Health Service are also actively involved in the

1 guideline and are perfectly qualified to answer these  
2 questions.

3           Your specific concern -- There were  
4 several commentators. In fact, if I remember  
5 correctly, you wrote one of the public comments that  
6 raised this issue. There was specific wording in the  
7 guideline that was inserted to address concerns with  
8 prion mediated diseases and talked about documenting  
9 an absence of rendered or recycled -- I think the  
10 original wording was mammalian tissue, protein  
11 materials for several generations.

12           There were several commentators that  
13 brought to our attention the problem that creates with  
14 segregated early weaning that you're talking about,  
15 and that language has been revised in response to that  
16 and with expert veterinary consultation to make  
17 appropriate allowances for the nutrition of those  
18 suckling pigs.

19           AUDIENCE MEMBER: I really appreciate  
20 that, and I appreciate the fact that we are allowed to  
21 make comments, and this is a democratic society.

22           I'd like to read a little poem I've  
23 written, if that's all right with you.

24           DR. FRIEDMAN: You may be stressing the  
25 limits of democracy.

26           AUDIENCE MEMBER: This is four lines --  
27 four lines, four lines. We're coming back. We're all

1 coming back.

2 My kidneys were failing, my heart was no  
3 good,

4 I needed a transplant as quick as I could.  
5 The surgeon said in his best beside voice,  
6 "xeno or allo, you make the choice."

7 I'll take the xeno, I said with a grin,  
8 Because I know where the pigs have been.

9 (APPLAUSE)

10 MODERATOR PATTERSON: Dr. Bach.

11 DR. BACH: It is very hard to say anything  
12 right after that. I'll make a very short comment and  
13 a very brief question.

14 The comment is: I'm hesitant to see too  
15 much emphasis put on any form of testing in the  
16 recipient of baboon bone marrow. The reason is that,  
17 at least from what I know, there was never a real take  
18 of that bone marrow. I saw the data to effect that  
19 there were some baboon cells maybe, but without a take  
20 and without the cells residing, I don't know what one  
21 can conclude.

22 My question is -- I just want to be sure  
23 I understand. These revised guidelines now will be  
24 the basis for the FDA to decide, if an investigator  
25 fulfills all of the requirements of the guidelines,  
26 that that investigator can go ahead with a trial in  
27 xenotransplantation?

1 DR. ZOON: The guidelines are the  
2 framework of the Public Health Service for the area of  
3 xenotransplantation. There's a variety of regulations  
4 and guidances that govern the conduct of clinical  
5 studies that would have to be adhered to.

6 In addition, as I mentioned in my talk,  
7 there will be a number of specifics with respect to  
8 new regulation as well as guidance documents in the  
9 area of xenotransplantation.

10 DR. BACH: But if all of those are met,  
11 the existing ones, all of these, then it will be all  
12 right to move ahead, presumably. Is that right?

13 DR. ZOON: Well, there are currently INDs  
14 filed for xenotransplantation. So I didn't want --  
15 There is currently activity in this area as we speak,  
16 and people need to follow the regulations that are  
17 included in the Code of Federal Regulations. The INDs  
18 are specifically the 312, I believe, is the right  
19 number.

20 DR. NOGUCHI: If I could just amplify on  
21 that, since we see all of these in our shop.

22 I think the guidelines you should consider  
23 as being a necessary component, but not sufficient to  
24 allow entry of any specific protocol. Actually, we  
25 were reflecting, one gene therapy protocol, which is  
26 a form of a xenotransplant, was not included here, and  
27 the requirements there were far in addition to all --

1 what was required would go far beyond that.

2           So I think it's fair to say that the  
3 guidelines are intended to be, if any institution  
4 would like to start into xenotransplantation, these  
5 are the minimum sorts of considerations you have, and  
6 each specific protocol will add onto that. We will  
7 not be requiring things that aren't in the guidelines,  
8 but it will be more than that. I should say it will  
9 be more than that.

10           DR. BACH: Thank you very much.

11           MODERATOR PATTERSON: At this point, we'll  
12 have a ten-minute coffee break, 12 minute coffee  
13 break. If you could be back in here by 4:10, thank  
14 you.

15           (Whereupon, the foregoing matter went off  
16 the record at 3:57 p.m. and went back on the record at  
17 4:26 p.m.)

18           MODERATOR RAUB: Ladies and gentlemen, if  
19 you will take your seats, we're prepared to begin the  
20 final session. Anybody who is still here, obviously,  
21 wants to be still here, and we're doubly grateful for  
22 that.

23           As the transition into getting some  
24 comments about what next from our panelists here, I  
25 call on Mike Friedman of FDA to make that bridge from  
26 our last session and offer some further comments.  
27 Mike.

1 DR. FRIEDMAN: Thank you. I just want to  
2 offer a couple of comments, if I may. Unfortunately,  
3 I won't be able to stay through the completion of the  
4 conference, and so there are a couple of things I  
5 wanted to convey, and appreciate this moment to do so.

6 I realize that there were a lot more  
7 people here earlier in this meeting, but for those of  
8 you who remain, can I express my personal appreciation  
9 for your attendance and your participation.

10 As I implied just a little bit ago, the  
11 purpose of this and other meetings is to garner the  
12 best input in its full diversity from all the  
13 different segments of our citizenry who have vested  
14 opinions, vested interests, and positions that they  
15 want to convey to us.

16 This is an enormously complex and subtle  
17 topic. Scientifically, it's enormously interesting  
18 and exciting. Therapeutically, it has real promise  
19 for the future, but there are clear hazards, and there  
20 are clear areas of unknowns that we must deal with,  
21 and your participation and your colleagues' who were  
22 here earlier is very much appreciated. This will  
23 continue to be a part of how we proceed in the future.

24 That's my first point. My second point is  
25 much briefer, which is to say that a number of people  
26 have come to me and asked whether there's any hidden  
27 agenda in this meeting, whether there's anything going

1 on that isn't perfectly obvious.

2           The answer, refreshingly, is no, that this  
3 is a meeting to discuss the status of the guidelines,  
4 the status of the scientific issues as we recognize  
5 them today, to help us all collectively chart a course  
6 for the future.

7           There is no regulatory action which is  
8 unanticipated, which is going to take place.  
9 Protocols that people are submitting will be dealt  
10 with in the way in which the process has been  
11 described here.

12           Someone asked me whether we were going to  
13 announce a moratorium on all trials. The answer is,  
14 no, we are not going to do that. Each trial, each IND  
15 that is submitted will be scrutinized carefully.  
16 Appropriate questions will be asked, but then we want  
17 to proceed in a responsible, in a thoughtful, in an  
18 ethically and scientifically appropriate way, and  
19 that's what we're struggling to do.

20           I have appreciated the short time that  
21 I've been able to sit in and listen to the  
22 presentations, which were of high quality. I thank  
23 you all again, and I thank you all for putting up with  
24 my back for a few minutes and for your really  
25 excellent participation and leadership today.

26           Thank you, and thank you, Bill.

27           MODERATOR RAUB: Thank you very much,

1 Mike.

2           The format of this last session is  
3 deliberately informal. We've managed to persuade  
4 several of our former panelists to return. What we  
5 would like is if each of them as they see fit would  
6 offer their views as to what next, where we go from  
7 here, in particular, what issues you would hope the  
8 agencies of the Public Health Service specifically and  
9 the rest of us in general might confront as we move  
10 along within the spirit of what Dr. Friedman was  
11 saying of let's keep it moving, but let's do it right.

12           DR. FISHMAN: Okay, I'll make the first  
13 bid.

14           As somebody who has been involved in this  
15 process for a fairly long time, I've been impressed  
16 first, after overcoming my fear of the 12 regulators  
17 sitting on the stage in the previous panel, that this  
18 really has been a four-year odyssey which has been  
19 done with remarkable openness to comment and input  
20 from a wide variety of individuals.

21           What has also happened because of the  
22 variety of individuals in the various forums that  
23 we've participated in is that there has been a gradual  
24 evolution of a sort of consensus, not that we agree,  
25 as you can tell, on all issues, but that in the broad  
26 strokes that there tends to be a consensus.

27           What has emerged out of that for me is the

1 setting of an agenda for future research, areas which  
2 Steve Rose touched on, but for me in particular the  
3 gaps in our knowledge about the microbiology of  
4 interspecies infections, the behavior, in particular,  
5 of pathogens in human hosts, the development of  
6 diagnostic assays for studying those infections really  
7 provides an exciting venue for basic research, which  
8 will go hand in hand with the evolution of clinical  
9 xenotransplantation, if and when that really occurs.

10 I think there are some open questions  
11 which apply to this area as well as other areas, which  
12 are: If we wanted to, how do we go about educating  
13 the public, whoever they are? Do we have town  
14 meetings? Do we have more meetings like this? Do we  
15 go on the road?

16 I don't think there's a precedent for  
17 that, and those are the kinds of questions that would  
18 be very valuable not just in xenotransplantation, but  
19 if you wanted to set up a new vaccine program, if you  
20 wanted to set up any kind of interaction on a  
21 prospective basis with the general public.

22 So I think there's a lot to learn. The  
23 research agenda has been, in part, set because  
24 consensus has evolved. I think it's been a very  
25 positive process.

26 DR. MICHAELS: I think Jay Fishman has  
27 really said it quite eloquently, and the one thing

1 that I might add to that as the future comes to us, I  
2 think that this whole process should continue in the  
3 fashion that it has started where the open dialogues  
4 have been there.

5 I agree with Jay that anyone that has  
6 suggestions for other ways to get out to the general  
7 public should certainly give their opinions and their  
8 perspective to people.

9 I think the national registry and a  
10 centralized archives bank absolutely should be  
11 supported. I think there's a lot to learn in terms of  
12 the epidemiology of infections that are shared between  
13 species, not just with xenotransplantation, that might  
14 have wider implications as well, and I certainly  
15 support that.

16 DR. VANDERPOOL: I have two initial  
17 observations. One comes from a trip this last summer  
18 to China, which I was invited at the Chinese Medical  
19 Ethical Association to speak about American  
20 developments.

21 I thought for a long time and decided,  
22 well, I'm going to give a speech on the history of the  
23 regulation, ethics and regulation of research in the  
24 U.S. I thought that was a good topic, but I had to  
25 think quite a while as to what point I would make.

26 This is the point I came up with, and I  
27 think it's true. I want to share it with you. That

1 is, in the Chinese setting the worry is that  
2 regulation of research will stifle research and will  
3 give the state a finger in the pie and possibly  
4 another surveillance mechanism.

5           Without missing any of the possibilities  
6 of what happens in China, the thesis I argued was that  
7 ever since the guidelines and regulations of research  
8 began in greatest earnest in 1974, although there were  
9 some earlier guidelines, research has flourished, and  
10 the public's trust shifted from being concerned that  
11 another Tuskegee, another San Antonio abuse of  
12 Hispanics with contraceptives and all the other abuses  
13 at the time -- Instead the public's being worried  
14 about that, and having a jaundiced eye toward  
15 research, the public in about 20 years started  
16 shifting to think, hey, you know, our group needs to  
17 get in on the research, too, because that's the  
18 promise for better medicine and a better cure.

19           My thesis, therefore, was that regulation,  
20 good regulation, actually facilitates research and  
21 assures public trust. So I give that to all of you  
22 and occasionally to myself when I get to the point of  
23 seeing myself as contributing to the regulation of  
24 research and seeing this is not bureaucratic in the  
25 worst sense. This is really a facilitative process.

26           I think the upshot has been a very  
27 important contribution to greater and more responsible

1 and more socially acceptable research. So the  
2 challenge here would be that on xenotransplants, good  
3 regulations and good organizations that can maintain  
4 those regulations in a nonrepressive way --  
5 communicated in a nonrepressive way, can actually be  
6 one of the finest things that can happen to the  
7 development of effective xenotransplantation.

8           So that's maybe the moral of the point.  
9 The thing would be to say keep going, because this is  
10 a real social contribution.

11           The next point is: I was so pleased when  
12 Clara Witt and I were sitting together, and I heard  
13 her talk about the World Health Organization, and some  
14 of the things that are happening on the international  
15 level.

16           One of my concerns -- and where the funds  
17 and where the energy comes from, I don't know, but one  
18 of my hopes is that there will be a forum for far  
19 greater international cooperation and collaboration.  
20 I don't know where that comes from, but you all are  
21 closer to the source of power than I am off the Texas  
22 coast in Galveston, though I come to Boston and  
23 Washington when I get a chance.

24           We need greater collaboration and  
25 cooperation. One of the sections of the book I've  
26 just authored on the ethics of human subjects research  
27 deals with research in cross-cultural settings. A lot

1 more attention needs to be given both to the ethics  
2 and import of that kind of research.

3           When we worry about the terrible things  
4 that have happened, we can say that some of the worst  
5 things happened because of AIDS in Africa and, even if  
6 we close the doors and keep the floods away, there may  
7 be researchers, and likely will be researchers, in  
8 Eastern Europe and the Far East, wherever, who will do  
9 things that may be appalling.

10           So as leaders in xenotransplant research,  
11 I hope that Americans -- we Americans can also set  
12 examples and make inroads into the regulation of  
13 research elsewhere, not as people with all the  
14 answers, not in the old 19th Century colonialist  
15 fashion, but in an open and supportive and  
16 communicative way with other nations.

17           MODERATOR RAUB: Clara?

18           DR. WITT: Just sort of to build on what  
19 Harold was saying: I love the concept of good  
20 regulations, and to use good regulations not just as  
21 a format for building public confidence, but also as  
22 a format for public education and fostering an  
23 awareness of the issues and the problems involved.

24           I think, if in -- As countries start  
25 addressing the issues surrounding xenotransplantation  
26 and addressing the technology, if the countries such  
27 as the United States, the U.K., and France and others

1 can be used as examples, as templates to other  
2 nations, ways of demonstrating how a process of  
3 dealing with this technology can be evolved and  
4 developed in these other countries, it will go a long  
5 way to helping the public education, information  
6 dissemination in these countries also.

7           It will help in some respects make a more  
8 universal or a global network of taking advantage of  
9 the potential benefits of this technology, but also  
10 trying to take care of some of the major disadvantages  
11 and risks of the technology more possible.

12           MR. BENEDI: Yes. I'd just like say  
13 something really a little lighter than I talked about  
14 earlier this morning, is to really thank the FDA and  
15 the HHS for including us recipients in this debate, in  
16 this conversation.

17           There are a lot of -- There were a lot of  
18 myths 15-20 years ago about human to human  
19 transplants, and they still exist, even in the medical  
20 community, whether we're normal individuals after  
21 transplants or whether we take on some weird  
22 characteristics.

23           When I came out of the hospital after  
24 spending some time there after my transplant five  
25 years ago, I had a friend ask me if I wanted to go to  
26 lunch, and I said, sure. They said, well, do you have  
27 to bring equipment with you? I told them I did travel

1 with an ambulance, but they could wait outside, and I  
2 would be in radio contact with them.

3           There are a lot of myths. I don't travel  
4 with an ambulance, but there are some things that I  
5 think we all need to really be aware of. That is that  
6 the quality of life after transplantation, human to  
7 human and, hopefully, in the future xenotransplants,  
8 is very good and very productive, and we enjoy life to  
9 the fullest.

10           I have a basketball practice at 7:15 that  
11 I'm the head coach of a 12-year-old team, and I'm very  
12 grateful to be here five years after my transplant.

13           Public involvement, the recipients -- I  
14 hate the word patient, because I only go to the  
15 hospital once a year to get my blood tested. So  
16 recipients in this debate is very important. I hope  
17 that we can add some debate and some good intelligent  
18 conversation to the debate.

19           Some of the medical and scientific  
20 conversations kind of go right by us, like any of the  
21 general public, I think, but the public debate about  
22 xenotransplantation and any other areas in scientific  
23 research that is new, I think, we can keep up with,  
24 and I'm very glad and pleased that you included us.  
25 Thank you.

26           MODERATOR RAUB: Thank you, and before  
27 your transplant, you couldn't slam dunk either.

1                   May I raise an issue that builds on the  
2 comment that Harold made from the floor before. It's  
3 on the theme of how do we get to the public in very  
4 different ways.

5                   We were talking about the institutional  
6 review boards, the institutional animal care and use  
7 committees in the context of how do we give them more  
8 help in various kinds of specialty areas. Another  
9 side of that is those are institutional processes.  
10 All of them have public members, in part because the  
11 institutions want that, in part because we require it,  
12 but that's also a potential vehicle for accessing a  
13 community at that stratum.

14                   I'd be interested in the comments of  
15 members of the panel as to -- without putting yet  
16 another unreasonable burden upon those institutional  
17 processes, is that not another means that we might  
18 engage more community participation?

19                   DR. VANDERPOOL: Can I make a comment to  
20 that? I mean, I initiated this conversation earlier.

21                   The OPRR, as everyone in FDA knows and  
22 most people in the audience know -- not all -- is a  
23 very small group of people, but you know, what's  
24 happened over time is OPRR -- and this is partly due  
25 to Charles McCarthy's very effective leadership --  
26 really developed a following, because Charlie McCarthy  
27 had a way of saying, hey, would you like a conference

1 on research ethics, I bet we can give you \$5,000 seed  
2 money; would you like to do this and that; you know,  
3 I think we're going to be able to come do this, that  
4 and the other thing for you.

5           Then, of course, they have ongoing, I  
6 think, as Melody Linn could confirm this or not, a 24-  
7 hour hotline for IRBs to call. What they've done over  
8 the years is develop really close relationships,  
9 ongoing relationships, appreciative relationships, as  
10 being a helpful agent, in spite of the fact that it  
11 has to enforce certain initially perceived egregious  
12 regulations.

13           So my question would be: Would it be in  
14 the FDA's interest for you all to sit around and say,  
15 okay, are there ways to improve our relationships with  
16 these university IRBs? Do we want to do that? Are  
17 there ways to approve it? What can we do to do that  
18 effectively? Can we co-sponsor more conferences? Do  
19 we have the funds for that? What kind of things do we  
20 do to make more collegial and ongoing and less  
21 suspicious relationships between them and us?

22           Please, I'm speaking in generalities,  
23 because as several people said to me after my comment,  
24 well, well, look, the people in my university don't  
25 have any problem at all with INDs and the FDA. They  
26 do as much work that way as they do through other  
27 areas of NIH national funding and so on.

1                   So I think this varies from university to  
2 university. My own comments come from a long time  
3 involvement year after year with public -- PRIMAR,  
4 Public Responsibility for Medical and Research  
5 programs year after year. But I think that's a worthy  
6 conversation for you -- for the people in the FDA to  
7 talk through.

8                   DR. FISHMAN: We've gone through the  
9 process at Mass. General Hospital of at least thinking  
10 prospectively about how we would organize or review  
11 proposals for xenotransplantation and actually set up  
12 some in-hospital guidelines for whenever these come  
13 down the pike.

14                   One of the things that was of great  
15 interest was, first of all, as you suggested, the  
16 input of the two members, the lay members of the  
17 review committee, but also the fact that the level of  
18 sophistication of knowledge about xenotransplantation  
19 at the level of physicians was not as good as we  
20 anticipated, and the practical issues were not the  
21 ones that we expected.

22                   It came down to a very simple, very visual  
23 kind of picture, which was when the pig gets to the  
24 hospital, does he come in the front door or the back  
25 door? We began to grapple in a very concrete way with  
26 some of the questions about how do we go about doing  
27 a xenotransplant, what's involved in terms of bed

1 allocation, resource allocation.

2           Until you grapple with this, you really  
3 have no concept. I think that interacting both -- and  
4 I would hope this would be prospectively one of the  
5 roles the xeno advisory committee would play, would be  
6 to interact with those hospitals and universities that  
7 have gone through this process and would share that  
8 experience with those that have not, and to facilitate  
9 it in a variety of ways that might useful for all  
10 concerned.

11           DR. VANDERPOOL: There is just one other  
12 point on this issue. That is, one of the things that  
13 may set some researchers' attitudes more favorably  
14 toward the OPRR than the FDA in terms of the  
15 regulation of research is the discussion in Bob  
16 Levine's regulation and research book in which he  
17 contrasts the way the FDA, on the one hand, and the  
18 OPRR, on the other, does its critical review at a  
19 local level.

20           What comes across there is the FDA is more  
21 authoritarian than the OPRR, in part because the OPRR  
22 doesn't do that kind of reviewing very often and, if  
23 so, with a softer hand.

24           That's just something worth mentioning,  
25 because I think the FDA is into a very serious level  
26 of protecting the public, and that has a spinoff in  
27 terms of what you're willing to tolerate and what

1 you're willing not to tolerate, but maybe that's  
2 another parameter in terms of what some university IRB  
3 people -- what may form some of their unnecessarily  
4 unarticulated and perhaps articulated opinions.

5 MR. BENEDI: I just wanted to make a  
6 comment, and I was going to do something originally,  
7 but I'm not now. That is, everybody I've listened to,  
8 the debates yesterday and today, it's obvious to me  
9 that everyone involved is very concerned about saving  
10 lives.

11 Before we close today, what I wanted to do  
12 was to ask everyone to raise their hand if you had a  
13 donor card signed, but please sign your donor cards,  
14 and remember that it does save lives. Thank you.

15 MODERATOR PATTERSON: Dr. Coffin, would  
16 you like to say a few words?

17 DR. COFFIN: I have very little to add to  
18 what was said. Let me just say one thing very  
19 quickly, and that is from the perspective of a basic  
20 scientist who's spent a rather pleasant decade working  
21 on the very arcane subject of endogenous retroviruses.

22 It's been somewhat -- I won't say  
23 gratifying, but astonishing to see how these elements  
24 find their way -- and many other retroviral aspects  
25 besides that, in fact, find their way into the  
26 important aspects of the public arena.

27 I have been quite pleasantly surprised,

1 actually, by the openness and the willingness not only  
2 of the regulators but also of academic physicians  
3 involved more directly in these issues and the biotech  
4 companies to take these issues seriously -- as  
5 seriously as some of the virologists did initially, in  
6 fact, in some cases more seriously, at least with a  
7 more -- coming out with a stronger response.

8           I think the dialogue that has been opened  
9 up has been extraordinarily valuable for me and, I  
10 hope, for others as well. I also hope that the  
11 opportunities that become available as this process  
12 evolves -- both the dialogue and the experimentation  
13 evolve will not only open up this very promising new  
14 technology for saving lives, but also contribute  
15 greatly to our understanding of how hosts and  
16 parasites co-evolve with one another.

17           That's really what I'm looking forward to  
18 in the future.

19           MODERATOR RAUB: On that, I think we can  
20 go to the floor for comments any of you may have.

21           AUDIENCE MEMBER: Maybe I could echo  
22 John's comment as another virologist who's spent such  
23 a long time involved in this area.

24           I think everyone needs to be congratulated  
25 in putting together a framework that will almost  
26 certainly work. The question is, is it robust enough  
27 if it should fail? What happens if there's a single

1 case of infection in the first couple of years? Is  
2 there going to be a complete loss of public  
3 confidence? Will the regulatory authorities be able  
4 to deal with this situation?

5 I mean, I think it says that we've got to  
6 be very, very careful at the beginning, because if  
7 there is a single problem, everything goes. I just  
8 wonder if anyone has comments on that.

9 MODERATOR RAUB: Fritz?

10 DR. BACH: Well, actually, I wasn't going  
11 to do it, but to just comment on that, I think that is  
12 one of the reasons to involve the public before we go  
13 much further; because if the public has been involved,  
14 then it's much harder to get that kind of negative  
15 response.

16 I was going to get up to just make a 30  
17 second suggestion for the future. These conferences  
18 have clearly been exceedingly helpful, especially what  
19 we heard about the regulation, about all of the  
20 problems of infection.

21 Might I suggest that a future conference  
22 be focused on the ethical issues, so that one could  
23 have a direct focus on this and be led by some of the  
24 people whom we heard here, who have dealt with ethical  
25 issues for a very long time.

26 MODERATOR RAUB: Thank you.

27 AUDIENCE MEMBER: I don't go back quite as

1 far as you, Harold --

2 MODERATOR RAUB: Would you identify  
3 yourself, please?

4 AUDIENCE MEMBER: Yes. Ernie Prentice  
5 from University of Nebraska Medical Center.

6 I only go back to about 1980 in terms of  
7 the ethics regulation of research. When I started as  
8 a co-chair of an IRB, I had, you know, a few file  
9 folders, a couple of books on my shelf, one of which  
10 was not yours; it is now.

11 Now I've got two lateral file cabinets  
12 filled to the brim with articles on the ethics and  
13 regulation of human subject research, and I've got a  
14 bookcase filled with books dealing with those issues  
15 that are relevant to protection of human subjects.

16 My point is that we've evolved  
17 considerably in terms of our understanding of the  
18 ethical issues. We're now dealing on an IRB level  
19 with gene testing, genetic testing, tissue banking,  
20 xenotransplantation, waiver of consent in emergency  
21 research. All of these issues are extremely complex.

22 We're overloaded. OPRR knows we're  
23 overloaded. FDA knows we're overloaded. The Office  
24 of Inspector General is doing a study, and IRBs simply  
25 are inundated with work.

26 We're finding it more and more difficult  
27 to recruit members to serve on our IRBs in this

1 managed care environment. They're under pressure to  
2 publish, generate more dollars through research  
3 grants, see more patients, generate more clinical  
4 revenue, and we're finding it very tough to acquire  
5 the resources that we need to handle the additional  
6 burdens that are placed by new regulations or new  
7 areas that we have to deal with.

8           So I guess the point I want to make is a  
9 reality check. We need more resources. I don't  
10 personally know of any IRB at a major medical center  
11 that is not overloaded and at the point where they're  
12 about ready to implode.

13           So when we think about placing additional  
14 burdens on an IRB relative to xenotransplantation or  
15 any other area, we need to consider the resources as  
16 well.

17           DR. VANDERPOOL: That's excellent. I  
18 mean, at the last PRIMAR meeting in Boston, one IRB  
19 chair said, you know, I think probably the best way to  
20 get the university in the national attention is just  
21 to go on strike.

22           Of course, he knew that the university  
23 budget wouldn't be made the next month if they went on  
24 strike, but that's a tough one, and it's like we had  
25 this existing organization. You can keep piling  
26 things on and on. Most IRBs don't sponsor ethics  
27 training. They don't have time for it.



1 arrived at the mike first, you guys can duke it out.

2 Dr. Jessamine?

3 DR. JESSAMINE: I think I'd like to  
4 caution against the idea that public consultation --  
5 I think starting your public consultation with your  
6 IRBs is a start.

7 In our preliminary consultations with IRBs  
8 in New Zealand, almost -- and in my personal  
9 conversations with the heads of various IRBs, their  
10 immediate response is, you know, this is bigger than  
11 the both of us, and that you need to go, you know,  
12 beyond the IRB.

13 IRB is not a surrogate for the whole  
14 public. It's a start, and it may give you a mechanism  
15 of how you can progress, but it's not going to -- I  
16 mean, in New Zealand it's unlikely that that will be  
17 enough.

18 MODERATOR PATTERSON: Dr. Patterson.

19 DR. CHAPMAN: Just in light of the  
20 discussion about PRIMAR sponsored meetings for IRB and  
21 IACUC members, I thought it was perhaps just worth  
22 putting on the record that we're not just giving lip  
23 service to taking these issues seriously.

24 Actually, Lana Skirboll mentioned that she  
25 from NIH and Dr. Nightingale from FDA this year  
26 participated in a PRIMAR meeting about xenotransplant  
27 issues. In fact, the previous year Tom Spira, who is

1 a member of our 11-member policy group at CDC and also  
2 chairs one of our IRBs, and a representative from the  
3 FDA whose name I can't recall, and I think also  
4 someone from NIH -- at least, someone from NIH was  
5 involved in brokering it -- participated in another  
6 PRIMAR meeting specifically in a session wrestling  
7 with IRB members about issues that would be important  
8 to them when they begin to review xenotransplant  
9 clinical trials.

10 I first became familiar with PRIMAR two  
11 years ago when at their invitation I participated in  
12 a PRIMAR meeting on use of animals in research, which  
13 several people in this audience were involved in, to  
14 discuss xenotransplantation issues.

15 So there is an ongoing dialogue. It's  
16 sort of quiet and not getting a lot of public  
17 attention, but we have been intersecting with that  
18 part of the community.

19 DR. VANDERPOOL: That's absolutely  
20 correct. I just received a wonderful corrective but,  
21 nevertheless, softly worded message to the extent that  
22 IRB -- the PRIMAR meeting in San Diego did have a  
23 session on xenotransplants that FDA supported, and  
24 that's true.

25 There are continual breakout sessions on  
26 this, and I commend FDA for doing that and hope that  
27 those contributions continue with greater visibility

1 and appreciation from the research community.

2                   MODERATOR RAUB: Any other questions,  
3 comments, from the audience? Any other comments from  
4 our panelists? Oh, I'm sorry. You moved too  
5 quickly.

6                   AUDIENCE MEMBER: Maybe I'm preempting  
7 you, Dr. Patterson, but have you selected a date for  
8 your next meeting yet, and can you tell us what the  
9 title will be?

10                   MODERATOR PATTERSON: I don't want to  
11 speak out of school, but I have a long list of issues  
12 that I think need further attention based on issues  
13 raised. I think I probably envision several  
14 conferences.

15                   I think that Dr. Bach's suggestion about  
16 a conference that focuses on the ethical issues is  
17 very well taken. I think this morning's discussion on  
18 ethical frameworks could easily have assumed a life of  
19 its own, and it's incredibly important.

20                   I also think that some of the practical,  
21 everyday issues of implementing the principles  
22 outlined in the guideline also need public airing and  
23 back and forth discussion.

24                   So I think that those are at least two  
25 major areas that we need to focus on. Certainly, the  
26 proposed rule on xenotransplantation and its  
27 particular components about participating in an

1 archive, participating in a registry -- those need to  
2 be clearly delineated and discussed.

3           In addition, the proposed rules on public  
4 disclosure, how to make that really work -- that's an  
5 ideal. That's a vision. We're working very hard on  
6 that now, and we're very committed to it, but to  
7 really make it work, it's going to require some back  
8 and forth dialogue.

9           I'm an optimist. I always overestimate  
10 when we can get things accomplished and when they  
11 would be done, but I think the next year is going to  
12 be very busy.

13           AUDIENCE MEMBER: In light of the  
14 conversation that just took place on the deficiencies  
15 of local IRBs and the fact that even if a national  
16 advisory committee on xenotransplantation is created,  
17 the fact is the actual review of these protocols and  
18 clinical trials falls to the FDA, and the FDA is  
19 limited statutorily to reviewing them on the basis of  
20 safety and efficacy.

21           Much of what we've discussed here about  
22 this emerging technology is actually ethical in  
23 nature. It's my understanding there's approximately  
24 8,000 employees at the FDA, yet not one bioethicist on  
25 staff.

26           We would like to urge that the FDA  
27 consider -- because, clearly, there will be more

1 protocols coming through, whether it's gene therapy or  
2 xenotransplantation or whatever the case may be, that  
3 we believe require at least the input on a staff level  
4 of a bioethicist.

5           Otherwise, it's very difficult for the  
6 bioethics community to raise these questions and  
7 concerns when it's outside the scope of dealing with  
8 an actual concrete protocol.

9           MODERATOR PATTERSON: I think your point  
10 is very well taken. I think in the field of  
11 xenotransplantation we have been, we will continue,  
12 and we will accelerate the effort to make each  
13 protocol the subject of discussion, the relevant  
14 elements; because I think you're right.

15           It's very hard to discuss issues entirely  
16 in the abstract and in the nebulous. Specific  
17 protocol review is a key component early on,  
18 particularly when both the benefits are undefined and  
19 the risks are undefined.

20           MODERATOR RAUB: Any last words from the  
21 people on the panel?

22           If not, I'll close simply by saying thanks  
23 to all of you and those no longer here, but who  
24 contributed substantially in the last several days.

25           You've given us a lot to think about. I  
26 like to think our view of these guidelines on  
27 infectious disease and the related pieces of the

