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**MEMORANDUM
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February 9, 1995

95 FEB 9 A 7:39

To: John Podesta
From: Beth Nolan, Marvin Krislov
Re: Dr. Foster

We are leaving this for you to review. Please accept this in the spirit of the best we could do given the deadline. We know how much that excuse is worth.

There are two sets: (1) plain-language charges and responses, and (2) charges and responses with more detailed cites to articles, etc. HHS did (1) and we did (2), though we talked to each other and shared ideas. We can combine if you wish, or keep both sets for different purposes.

The most important thing is that Dr. Foster agree that his views (in both charges and responses) are not misrepresented.

It's 5 am, and we're going home. We will try to be back around 8, but feel free to start without us. Really.

THE WHITE HOUSE
WASHINGTON

95 FEB 17 P 9:14

FEBRUARY 7, 1995

MEMORANDUM FOR JOHN PODESTA

FROM: TRACEY THORNTON

SUBJECT: MEMBERS FOR FOSTER PRESS CONFERENCE

The list of Members for the Foster press conference is as follows:

Rep. Nita Lowey
Rep. Louise Slaughter
Rep. Charles Schumer
Rep. Pat Schroeder
Rep. Henry Waxman
Rep. Lloyd Doggett
Rep. Sheila Jackson Lee
Rep. Zoe Lofgren
Rep. Jerrold Nadler
Rep. Ken Bentsen
Rep. Louis Stokes
Rep. Nancy Pelosi
Rep. Cynthia McKinney
Rep. Donald Payne
Rep. Eddie Bernice Johnson



DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

The Chief of Staff

95 FEB 7 P 2:26

February 7, 1995

NOTE TO JOHN PODESTA

Attached are the relevant portions of the transcript. We have the entire day's session as well.

Kevin Thurm
Kevin Thurm

1 there is no guilt, so there is a notion of providing
2 gifts for those who suffer even without blame. But at
3 the very least what I was referring to is where you can
4 actually put your finger on the guilty party, or on
5 negligence.

6 DR. MCCARTHY: I would like to pursue that, but
7 that is another whole area.

8 MR. GAITHER: Let me pursue just one question
9 that Dr. Hamburg raised with you. As will become clear
10 shortly, the National Commission had trouble grappling
11 with risk, and deferred the issue to us. I would like
12 not to let you have that luxury.

13 When you spoke of trying to be sure that there
14 would be no additional risk before proceeding, what do you
15 do if the facts suggest that we don't know whether there
16 are additional risks, where perhaps we have no evidence
17 that there are going to be additional risks, but we are
18 not sure.

19 DR. LEIMAN: Nor is there any kind of experi-
20 mentation which would solve the issue for us. Is that
21 what you are saying?

22 MR. GAITHER: At least not in the near term.
23 Maybe five years, maybe ten years, we would know more.

24 DR. LEIMAN: Right.

25 MR. GAITHER: But if you have a situation where

1 you don't know of increased risk, does that meet your
2 standard, or do those who wish to go ahead have the
3 burden of proving that there is no increased risk?

4 DR. LEIMAN: I am trying to draw the nearest
5 analogy from cases that I know. With regard to someone
6 whose life is at stake, for example, a man dying from
7 cancer, where the physician comes in with some new
8 medication which may or may not help, it may hasten his
9 death, in fact, if it doesn't work. On the other hand
10 if it does succeed ultimately in the long run he will be
11 better off.

12 The Jewish position has always been that you
13 have a right to take that risk. That is, the patient
14 himself has a right to make a decision if it is a life
15 and death issue. So to give you the classic case very
16 quickly, a man who was dying was informed by his physicians
17 that if he did nothing he would die in six months to a year.
18 If he took a certain drug or went through a certain surgi-
19 cal procedure either he would die immediately or it would
20 be a success. What do you do in such a situation?

21 The rule was that the patient has a right to
22 make that determination for himself. He can risk immediate
23 death, that is his privilege, for long-term life.

24 The problem is complicated by what you are
25 raising, because now we are dealing not only with the patient,

1 but with the conceptus, and whereas the patient can make
2 whatever decision the patient wants to make, the risks
3 that we are not seeing here may affect the conceptus,
4 and there is no way of getting the consent of the
5 conceptus. That is why I find it problematic.

6 I would just have to say as a general rule
7 that patients have a right to take risks for good benefits.
8 And I don't think you have to prove, as you put it --
9 I don't think the burden of proof rests with the patient
10 that there is no additional risk. I don't see that at
11 all.

12 I think if we are going to fund a project for
13 any kind of research, then we have to be sure that as
14 many risks as possible are removed by animal experimenta-
15 tion and so on before we proceed and fund an experiment
16 on humans.

17 MR. HALPERN: Just one quick question to follow
18 up. I understand you say if a couple wishes to go ahead
19 with private monies with the in vitro procedure and
20 transplant, I understand you to say that it is up to this
21 woman to determine risk, and she would not --

22 DR. LEIMAN: Except I qualify that by saying
23 that there is a problem here of the conceptus, who may
24 not be --

25 MR. HALPERN: Well putting that aside, because

1 we have already discussed that enough, and in my mind I have
2 reached a conclusion. put aside the role of the couple.
3 Let's look at the role of the government, the federal
4 government in deciding to fund such research.

5 Does the government have an obligation to
6 convince itself by drawing forth evidence that there is
7 no -- whatever the standard is for the risk, coming forth
8 with evidence, finding evidence creating evidence that
9 that standard is satisfied, or is it sufficient if we
10 look to see, and well, we don't know.

11 DR. LEIMAN: It seems to me only to the extent
12 that the government will be involved in various procedures,
13 either compensation procedures, or to the extent that this
14 conceptus may one day become a responsibility of the
15 government. If you have a genetically deformed child.
16 and so on. to what extent will the government then have
17 to fund the care for that child, and so on.

18 So it seems to me that people have a right
19 to take risks so long as it does not affect other citizens,
20 and if it does affect other citizens, then the government
21 does become involved, because the government has to
22 protect its citizens.

23 MR. HALPERN: Then it would be fair to say that
24 in a particular situation it might be ethical and moral
25 for the couple to decide to go ahead, but it would not --

1 given the risk benefit ratio and whatever -- it would
2 not be ethical and moral for the government to pay for
3 that process.

4 DR. LEIMAN: So long as we are leaving the
5 conceptus out of the discussion, I think so.

6 MR. GAITHER: Dr. Henderson, one last question.

7 DR. HENDERSON: Just an observation. I wonder
8 if we are really looking at proceeding on the assumption
9 that there is no additional risk. As one looks at the
10 whole field of medicine, almost any procedure one does,
11 any drug one takes, there is some minimal additional risk.
12 Acceptable minimal additional risk I think is the way we
13 are really looking at this, and to say there is probably
14 no additional risk I think is probably not the way we
15 can look at this. I think we must say minimally acceptable
16 additional risk.

17 MR. GAITHER: I think the "acceptable" is still
18 at issue. But I think that the point is well taken.

19 Rabbi Leiman, thank you very much. We appreciate
20 it.

21 Let's take a short break and figure out how we
22 can get back to our schedule.

23 (Brief recess.)

24 MR. GAITHER: Needless to say, we have fallen a
25 bit behind schedule, and I would suggest that we postpone

100
1 for the time being the legal discussion regarding in
2 vitro fertilization, and proceed at this time to a
3 consideration of the research application involving
4 fetoscopy, submitted by the Charles Drew Postgraduate
5 Medical School.

6 I would like to note at the outset that
7 Dr. Spellman, formerly Dean at that medical school has
8 asked that he be excused from the deliberation on this
9 issue. I hope that you will stay with us and listen to
10 it, but I understand your reluctance to become involved,
11 and we will assume that you will not be involved in
12 either the discussion or the decision on this issue.

13 DR. HAMBURG: However, as a point of personal
14 privilege, you may respond to insulting remarks.

15 (Laughter.)

16 MR. GAITHER: Mrs. Mishkin, we will let you
17 describe the issue before us, and I would ask that you
18 start by describing why the application is before us and
19 what we are expected to do with it.

20 MS. MISHKIN: The HEW regulations governing
21 research involving the human fetus lay down certain
22 conditions which must be met in order for an institutional
23 review board to approve that research. If the institutional
24 review board is not able to determine that all of the
25 conditions have been met, and if it considers that the

1 research nevertheless is important, it may refer that
2 research proposal to this Board for review. And if the
3 Board determines that the research should go on, it may
4 recommend to the Secretary that he waive those parts of
5 the regulations that the research proposal cannot meet.

6 Now, the proposal before the Board at this
7 point is a proposal to perform fetoscopy on mothers who
8 have elected to have abortions for reasons totally
9 unrelated to the research, in order to discover and to
10 document what the risk to mothers and fetuses might be
11 from the procedure of fetoscopy. The purpose of develop-
12 ing the fetoscopy is to be able to diagnose prenatally
13 certain conditions for which the parents are at risk.
14 In this particular research proposal the focus is
15 primarily on prenatal diagnosis of sickle cell disease.

16 Now, the reason that this proposal is before
17 the Board is that it cannot meet or at least cannot
18 clearly meet provisions of the HEW regulations set forth
19 in sections 46.206(a), 46.207(a), and 46.208(a) which
20 briefly, taken together, require that the activities in
21 the research proposal be designed to meet the health needs
22 of either the mother or the particular fetus involved, or,
23 if that is not the case, that the procedures present no
24 more than minimal risk to the fetus.

25 Now, the problem in this proposal is that it is

1 not designed, as written, to provide therapy for the
2 mother, nor is it designed to provide therapy for the
3 fetus, because the purpose is to assess safety of a
4 technique and to do it in mothers who have already--
5 elected to undergo abortion. So there is no question
6 as to whether or not it is or not so-called therapeutic
7 research. It clearly is not. Therefore, it does not meet
8 that first condition.

9 It does not seem to meet the second condition
10 because the risks, I think, must be considered undetermined.
11 Although the HEW regulations do not define minimal risk,
12 it is possible to go and look behind those regulations
13 to the Commission's discussion of what they intended,
14 because the regulations were an attempt by the Department
15 fully to implement the Commission's recommendations on
16 research involving the fetus.

17 So I am going to offer to you for your guidance
18 what the Commission's intentions were when they made their
19 recommendations to the Secretary. That does not mean that
20 you must follow the Commission's intentions; it is only to
21 elucidate for you somewhat what the Commission had in
22 mind, because the regulations themselves give this Board
23 no guidance. The only guidance in the regulations is to
24 the institutional review boards.

25 MR. GAITHER: Let me interrupt for just one

1 second, because I think it is important that we understand
2 the standards which we are to apply. I gather what you
3 are saying is that this particular application is not
4 therapeutic and not clearly within the category or at
5 least so determined by the institutional review board,
6 as involving no more than minimal risk.

7 MS. MISHKIN: That is correct.

8 MR. GAITHER: Therefore, it can only be funded
9 if this Board determines that it is ethically acceptable?
10 Is that the standard?

11 MS. MISHKIN: Essentially, yes. If we recommend
12 to the Secretary that he waive those provisions that we
13 just mentioned because we feel the research is important
14 and justified by the benefits to be obtained from the --
15 the anticipated benefits.

16 MR. GAITHER: So there is no particular standard
17 other than for us to say to the Secretary whether or not
18 we feel that he should go ahead despite that provision in
19 the regulations?

20 MR. HALPERN: Mr. Gaither, if I could be of
21 help, if you look at subpart 5 under Tab I in our book,
22 giving us the regulation, Section 46.211 provides some
23 guidance as to the standard, at least which will guide the
24 Secretary in his decision to accept our recommendation.

25 MS. MISHKIN: At Tab I of your book, we have

and
1 reproduced the applicable provisions of 45 CFR 46,
2 and it simply says if this Board feels that the risk
3 is justified by the sum of the benefit to the subject,
4 which is not in question here, or the importance of the
5 knowledge to be gained.

6 MR. CONWAY: And you are referring us to
7 46.211?

8 MS. MISHKIN: Yes.

9 MR. HALPERN: In fact, it doesn't say that
10 the Board should be guided by the risk benefit analysis,
11 it says that the Board should consider whether waiver,
12 which is what we are talking about, is appropriate in
13 this particular instance. Then it says in making the
14 decision the Secretary will consider whether the risks
15 to the subject are so outweighed by the sum of the
16 benefit to the subject and the importance of the knowledge
17 to be gained as to warrant such a modification or a waiver.

18 MR. GAITHER: But it seems to me that it is
19 important for us to note that .211 states that the Secretary
20 can only waive, unlike the other situation before us, with
21 our approval. So that is the question, whether we would
22 approve a modification or waiver of these regulations to
23 permit this research to continue. And basically there are
24 no specific standards imposed upon us. Is that correct?

25 MS. MISHKIN: That is correct.

1 MR. GAITHER: And what you are giving us
2 is the background, now, for these particular regulations,
3 why the Commission suggested that a body such as ours be
4 involved in the deliberations.

5 MS. MISHKIN: And what the Commission coped
6 with when it discussed the problem of research on fetuses
7 to be aborted, and what standard might be appropriate in
8 considering acceptable risk to fetuses about to be aborted,
9 or whose mothers intend to go through with an abortion.
10 It was a very, very difficult problem for the Commission.
11 Any of you who followed the Commission's activities in
12 this area will know they spent a long time on this, and
13 this was one of the areas in which there was not a full
14 consensus among the Commission members.

15 First of all, let me say that this particular
16 application underwent six reviews prior to coming before
17 this Board. That included reviews by the appropriate IRB
18 at the Drew Center; a review by the community board which
19 is a separate community representative board at the Drew
20 Center; review by the appropriate study section at HEW;
21 review by a site visit team from that study section,
22 members ad hoc; review by the National Advisory Council
23 under whose auspices this particular application came --
24 if that is not six I have left one out, but they are all
25 listed there anyway.

1 The staff of the Board then shipped the whole
2 thing out to two additional people for independent reviews,
3 and those have been mailed to you and are reproduced in
4 your book. Dr. Haig Kazazian at Johns Hopkins University
5 Hospital, and Dr. Dwayne Alexander at the National
6 Institute of Child Health and Human Development.

7 Dr. Kazazian has done fetoscopy himself; he
8 no longer does so. Dr. Alexander has not done fetoscopy.
9 He was a member of the staff of the Commission and he ran
10 the amniocentesis collaborative research program, and is
11 very familiar with questions of prenatal diagnosis, and
12 the risks of various procedures associated with prenatal
13 diagnosis.

14 All of the review boards and the individual
15 reviewers have recommended approval of this research
16 application based on the importance of being able to
17 diagnose prenatally certain conditions which, up until
18 now, have not been diagnosable through amniocentesis.
19 Fetoscopy has been the only possible way to diagnose
20 sickle cell disease, among other diseases, in fetuses
21 prior to birth.

22 Now, there was one problem that we had in
23 reviewing this particular proposal, and that was it was not
24 entirely clear from the proposal, because we had conflicting
25 statements -- the site visit review said one thing, and the

1 proposal said something else -- as to whether or not
2 the investigators planned to delay abortion for more
3 than 24 hours after fetoscopy. The point of the
4 research is to do the fetoscopy, monitor the women after
5 fetoscopy, and look for complications as a result of
6 fetoscopy. Complications include possible infection
7 of the woman, possible bleeding of the fetus, and
8 subsequent abortion prior to the induced abortion which
9 is anticipated.

10 What is present in the research application is
11 a plan to perform the fetoscopy, monitor the woman for
12 24 hours, and then go ahead with the abortion as planned.
13 What is present in the site visit's review, however, is
14 a plan to continue monitoring, if they are satisfied that
15 a 24 hour delay poses no risk, to increase that delay
16 step by step, until they reach, finally, a two-week
17 delay during which they would monitor the woman for two
18 weeks following fetoscopy before going ahead with the
19 abortion.

20 I called the principal investigator to find
21 out what in fact was their intent, and he said that this
22 does seem -- that it is his intent to go incrementally if
23 they are satisfied at any one stage as to the risk to
24 mother and fetus, to go incrementally up to a two-week
25 delay. This raises a very important concern that their

1 subject population is women who are in their 16th to
2 20th week of gestation. A two-week delay in a woman who
3 presents at 20 weeks would take that woman past 20 weeks
4 gestation before her abortion, and this then would run
5 into the possibility of a viable fetus being aborted,
6 or of having a viable product of the abortion. This is
7 one problem that the Commission was very much concerned
8 about. That is why the staff recommendation on this
9 particular proposal includes the provision that no
10 abortion be postponed for reasons of this research that
11 would then have to be performed after the 20th week of
12 gestation. This is compatible with the regulations that
13 no timing or methodological change be introduced for
14 reasons of research that would add additional risk to
15 the mother or the fetus. And surely the risk of having
16 a viable product of abortion is an additional risk.

17 The current regulations note that viability
18 is possible at 20 weeks, and that is why the staff
19 recommends that no procedure be delayed beyond the 20th
20 gestational week for purposes of this research.

21 Now, the whole thing was complicated by an
22 article in the Washington Post that appeared on Saturday,
23 November 4th, while we were in the process of preparing this
24 memorandum of recommendations to you. That article
25 indicates that a physician at the University of California

1 at San Francisco believes he has developed a procedure
2 to diagnose sickle cell disease through amniocentesis,
3 thus avoiding the necessity to go to fetoscopy in order
4 to diagnose sickle cell disease. These findings are
5 supposed to have been in the most recent issue of the
6 journal Lancet. We were unable to find whatever issue
7 that was. It must not be out yet. If it is out it is
8 not available in any of the libraries we had access to
9 in Washington.

10 We tried very hard to call the investigator at
11 the University of California at San Francisco, and we
12 were unable to reach him. We do, however, have some
13 further information on that. Dr. Alexander was able to
14 reach Dr. Michael Kaback, who is Assistant Professor of
15 Pediatrics and Medical Genetics at the University of
16 California at Los Angeles, and who is familiar with the
17 work of the investigators at San Francisco.

18 What I am going to give you now is my under-
19 standing of Dr. Alexander's understanding of Dr. Kaback's
20 understanding of what they are doing in San Francisco.
21 If all of that is clear, you will know how far we are
22 removed from firsthand information. But nevertheless I
23 will give it to you, because I think it is important.

24 It goes as follows: 85 percent of sickle cell
25 carriers have an extra large piece of DNA on the gene that

1 has the sickle cell trait. Now, this condition of having
2 the extra large clump of DNA material is calling poly-
3 morphism. Thus, it is possible assuming the test-works
4 as reported, to diagnose approximately two-thirds or more
5 of sickle cell babies through amniocentesis and looking
6 for this enlarged DNA clump.

7 Now, let me break that out for you. What they
8 have to do if they identify both parents as carriers,
9 they then look for this polymorphism, in other words, the
10 extra clump of DNA in the parents. If those parents have
11 that extra clump of DNA, that is, if they fall within
12 the 85 percent of sickle cell carriers who have that
13 polymorphism, then it is possible to perform amniocentesis --
14 yes?

15 DR. FOSTER: I should clarify something at
16 this point. You are using a medical term, and I am not
17 sure -- you are saying "carriers." Do you really mean
18 carriers, or do you mean sickle cell disease?

19 MS. MISHKIN: No, I mean carriers.

20 DR. FOSTER: That is not a person with sickle
21 cell disease.

22 MS. MISHKIN: That is correct.

23 DR. FOSTER: Okay.

24 MS. MISHKIN: But again, this is my understanding
25 from Dr. Alexander through Dr. Kaback. This is the best we

1 can give you.

2 DR. FOSTER: Go ahead and let me hear you out,
3 then.

4 MS. MISHKIN: My understanding is this is
5 carriers.

6 DR. FOSTER: Okay, go ahead. I will hear you
7 out.

8 MS. MISHKIN: So if both parents are carriers,
9 either with or without the disease --

10 DR. FOSTER: It is the previous I am concerned
11 about.

12 MS. MISHKIN: Right. If both parents are
13 carriers and have this trait of the polymorphism, and it
14 is possible to be a -- 15 percent of carriers do not show
15 this trait. If they are among the 85 percent of carriers
16 who show this trait, then through amniocentesis they can
17 look for the segments in the fetus. If the fetus has
18 two segments showing the polymorphi, that is a child with
19 sickle cell disease. If the fetus has one segment that
20 child is a carrier. If the fetus has no segments, that
21 is a normal child.

22 Now, I went back and asked again whether that
23 child could be one of the 15 percent that do not show the
24 polymorphism, and the answer was that Dr. Alexander believes
25 not. The answer is if they have done this whole procedure

1 and the child does not carry that polymorphism, that
2 child is not a carrier or a diseased child with respect
3 to sickle cell.

4 Now, if either parent is not polymorphic, does
5 not have this additional clump, is within that 15 percent
6 of parents who are carriers but do not have this change
7 of the DNA, then it is impossible to diagnose the sickle
8 cell disease in the fetus through this amniocentesis
9 procedure, and that would mean that for those parents
10 the only way to diagnose the sickle cell disease in the
11 fetus would be through fetoscopy, which brings us back
12 to the Drew application.

13 Now, what all this means is there has been a
14 shift in the risk benefit analysis that all of the
15 reviewers performed on the Drew application, because
16 when they looked at the Drew application fetoscopy was
17 the only method for diagnosing sickle cell disease
18 prenatally. Now it appears, although we do not have the
19 documentation to give you, that it is possible in 85
20 percent of sickle cell carrier parents to diagnose the
21 presence or absence of sickle cell disease by amniocentesis
22 which is agreed to be a safer procedure than fetoscopy.

23 So your job is somewhat more difficult, but I
24 don't think it is impossible. One is left with the question
25 of whether it is appropriate for the investigators at Drew

1 to do the research, to assess the risks of fetoscopy
2 as a tool for prenatal diagnosis of sickle cell disease
3 in their subject population, and the reason I am
4 emphasizing this is that if it were the case that all
5 sickle cell disease could be diagnosed prenatally
6 through any other method, amniocentesis or any other,
7 then the board would have to face the question of whether
8 the subject population which the Drew Medical Center
9 serves is an appropriate population to develop the
10 methods of fetoscopy. Fetoscopy is useful for prenatal
11 diagnosis of other disorders, but not disorders which
12 are disorders of the black population, which is the
13 subject population which the Drew Center serves. So
14 then one would have to question whether the black popula-
15 tion is an appropriate subject population for developing
16 fetoscopy if they are not going to be the population which
17 will benefit from the development of that diagnostic tool.

18 In other words, one wants to have the population
19 that will benefit from the research, participate as subjects,
20 and accept the risks of that research if possible.

21 MR. HALPERN: Just related to this, are we not
22 also in the position of asking whether or not we should
23 remand this issue to Drew and the community that Drew serves
24 for them to make the risk benefit analysis again, in light
25 of this new data?

MS. MISHKIN: Absolutely. That is a very viable option, and it certainly has a great deal of merit. I think one might reasonably ask for a total reassessment, by that IRB or by any number of other people, even including the study section that reviewed it, in the light of the new information. But I think we would want to get the actual information documented before we remanded it.

I don't know if this has been clear, and if you want more elucidation of the Commission's intent or of my understanding of the regulations, I would be glad to go forward with more.

MR. GAITHER: Hank, would you say something about the science of this?

DR. FOSTER: Yes, I am going to say something about the science and the sociology, if you will indulge me.

I heard of Kan's work just a few days ago, and I knew clearly like a shock wave that it was inevitably going to affect what we have to do, or what we recommended. But I want to say some things as we go through all of this deliberation, which may take me a few moments, but I really want to run through these steps that I have written down here. Some food for thought.

I just have one question. The genetic polymorphism that is necessary in the parents -- is it required in both

1 parents? In other words, you know, both parents may be
2 carriers, but only one may show the polymorphism and the
3 other may not. Is it a requirement for both parents?
4 Do you recall?

5 MS. MISHKIN: My understanding is that it is
6 not going to be a reliable test through amniocentesis
7 unless both parents show the polymorphism.

8 DR. FOSTER: Now, the next question I have --
9 and then I will make my comments -- now, I read the research
10 proposal, and I missed this delay. That bothers me a
11 little bit, first. I have got to really clear that in my
12 mind.

13 I have done a lot of amniocentesis and therapeutic
14 abortions, probably near 700. As I read the protocol,
15 the patient would be brought in the hospital, and that would
16 be a 24 hour delay, which was not inordinate, based on the
17 information that we have. It is very reasonable. But the
18 clinical part, a catheter is introduced into the amniotic
19 cavity, and that is the time when the fetus is studied,
20 the blood vessels, and the sample is taken. Then the
21 fetoscope is withdrawn, but the catheter is left in place,
22 which is quite acceptable. In fact, this is one of the
23 techniques we use for continuous prostaglandin infusion.

24 But there gets to be a real question with regard
25 to infection after a 24 hour period with an indwelling

1 connection to the outside. I missed the entire reviewer's
2 section about some extension beyond 24 hours, and if there
3 is an extension of observation beyond 24 hours, does it
4 involve the catheter being in place? This would be
5 critical in my mind.

6 DR. MCCARTHY: Yes, it certainly does.

7 DR. FOSTER: I think that is something that
8 really needs to be addressed in terms of the details of
9 the research.

10 MS. MISHKIN: I am frankly bothered by anything
11 coming as far as to the Ethics Advisory Board through all
12 those reviews without this being quite clear. It was in
13 the site visit review, and it was because of the
14 ambiguity that I called the principal investigator.

15 Now, Dwayne Alexander was working on the
16 application in front of him, and so he really addressed
17 only the 24 hour delay. But because of the ambiguities
18 I did call, and the investigators do intend to go to two
19 weeks. I think it might not be inappropriate for the
20 Board to make some strong statement about wanting to be
21 clear on what the procedures proposed are here.

22 MR. LAZARUS: I wasn't clear either on the
23 consent procedures.

24 DR. FOSTER: That doesn't come through. But the
25 one thing I do want to say, and then I will get to the other

1 points I want to make about what all of the implications
2 of fetoscopy are as I see it. I do think a longer obser-
3 vational period is an acceptable research modality
4 provided safeguards are there. We have already talked
5 about extending beyond the 20 weeks. That can be
6 controlled for fairly well with ultrasonography for
7 establishing fetal age, and a few other things. But I
8 think you might want to consider the observation period
9 without the catheter in place, because repeated amniocen-
10 tesis has proven to be relatively safe in terms -- the
11 danger is in leaving a conduit for bacterial migration.

12 So what I am really saying is I can see the
13 investigators making a justification for an observation
14 period of longer than 24 hours, but I find it a little
15 difficult at this point to see that justification with an
16 indwelling catheter in beyond this point.

17 And now I think the things we need to be
18 concerned about irrespective of what we ultimately
19 recommend in terms of going back or whatever. There was
20 very, very strong community support for this proposal.
21 Anyone who read the type of support, and the rather
22 incisive and critical questions, I thought, that the
23 community asked in regard to many of the social and medi-
24 cal implications. I think it is keen that we remember that
25 there have been so many charges of disregard for ethic

makeups of our research, genocide and all the issues, if this is an indigenous decision by a community, I think we need to give that great respect, because it is a justification for us to say this is a decision that you made. If we say to the community no, we shouldn't do this, the community in a sense has a right to say you are willing to impose certain things on us externally that we feel are an abridgment, but here when we see something clearly directing us, you deny it. So that is something that has to be considered strongly in terms of sociology.

I think another thing that is very important from what I know about this -- Drew has been one of the few centers that had federal support prior to the moratorium in 1973, I believe, involving aborted fetal subjects on the research, has gone through the steps of animal experiments. They have used the ovine model very well with sheep and I think we certainly have to give that some accord. They have gone through all the steps prior to using humans.

Now, the implications of Kan's work I don't need to go over. You have made that very clear. So I will move on to my fourth point.

Mitch Spellman makes this point a lot, and it is a good point. There is a basis for basic research with regard to doing fetoscopy, irrespective of Kan's work.

1 There is a basic need. Now, I am going to go slowly and
2 really try to make this point.

3 Kan's approach right now is the acceptable
4 one. It is a reaction. It is an after-the-fact approach.
5 It gives us an option simply to abort a defective pregnancy.
6 Basic research will afford us a much broader and brighter
7 horizon, might I add. And that is the possibility of
8 diagnosing the defective fetus and then preventing the
9 development of sickle cell disease in that fetus.

10 Now, I will try and paint a picture. In utero,
11 for all of us normally, there is a different set of protein
12 in two of the chains of our hemoglobin in early fetal life.
13 The normal hemoglobin molecule has four chains, two upper
14 alpha chains, which are proteins in a set sequence, and
15 two lower, somewhat larger, beta chains in a set sequence.

16 The only difference between one who has sickle
17 cell hemoglobin and a normal person is out of 184 amino
18 acids in one of those chains, and that is in set sequence,
19 there is an exchange of valine for glutamic acid, in the
20 sixth position from the end. One of 184 chains. That is
21 the only difference. But because of this change in the
22 chain, certain physical and chemical defects, as you may
23 call them, are imparted into the hemoglobin. It makes it
24 less stable. Its ability to hold and release oxygen is
25 affected. The stability of the red cell membrane is affected.

It changes its pattern of migration in an electrical field. This is how we do our hemoglobin electrophoresis.

Back to in utero, none of us has these beta chains when we are developing. We have another chain called a gamma chain, and that gamma chain is provided for through a mechanism which we yet do not fully understand, and this is where our basic research should continue. There are repressor genes and activator genes. Rarely, through chance, some people who were destined to have sickle cell disease never develop it. But they continue to make the gamma chains which make fetal hemoglobin throughout life, even in the postnatal period. And these people have absolutely no trouble. That is the ideal situation for the sickle cell person, is to be able to find that mechanism that will prevent the turning on of the activator genes from going from gamma chains to defective beta chains. So there is a clear need for this kind of research in spite of the work by Kahn and his group.

It is at this basic step where not only will we be able to diagnose the child destined to have sickle cell disease, but indeed, to prevent it. So I think that alone justifies continuation of this basic research approach.

Lastly -- well, that includes -- I wanted to say something about the basic science of the molecule. So there

1 is a real horizon out there that has to be untapped,
2 and that is the ability to diagnose the abnormal hemoglobin,
3 but not by default to get rid of the fetus. That is the
4 thinking that if you want to prevent forest fires, cut
5 down all the trees. I want to take a different approach.
6 I want to see can we afford this fetus that was destined
7 to be one thing, that our basic research will continue to
8 allow us to do something about it.

9 So I just wanted these thoughts to be in the
10 back of our minds, particularly in light of Kan's recent
11 work as to the obsolescence of this continued basic research
12 approach.

13 MS. MISHKIN: Is the research to develop that
14 therapy now ready for pursuing through fetoscopy now, or
15 does one have to wait for more development in animals and
16 other methods before you actually go to fetuses in utero?

17 DR. FOSTER: I think I understand your question,
18 Barbara. Are you saying is our technique to such a point
19 that we can go ahead with just the technique of amnioscopy?

20 MS. MISHKIN: No, I am asking whether one would
21 endorse the Drew application today on the basis of the
22 need to develop the prenatal therapy, or are we not yet
23 there with respect to the therapy, with the animal work
24 and so forth?

25 DR. FOSTER: I think the animal work has been done

I think that has been satisfied.

MS. MISHKIN: There is one other thing I forgot to mention on the risk benefit analysis, and that is the concern about using fetuses to be aborted. There is not much direction in the HEW regulations on this matter, but the Commission came down to a guideline that may or may not be useful for you, but I think it has some merit. That is, they felt that it was ethically acceptable to perform procedures on a fetus to be aborted if one would feel ready to perform those procedures on a fetus intended to go to term.

In other words, if one had done all of the animal work, including primate work, which they have done in this case, and if they were unable to do it on fetuses to be aborted to further assess the risk, if they would be willing then to go forward therapeutically with it on fetuses going to term. That condition has been met in this case, because there are apparently several groups who are performing amniocentesis on fetuses intended to go to term.

FATHER MCCORMICK: Fetoscopy, you mean?

MS. MISHKIN: In fetoscopy, yes.

MR. GAITHER: In somebody's judgment.

MS. MISHKIN: I mean the condition of its being performed on fetuses going to term has been met, and the

1 question is whether or not that meets your feeling of
2 acceptability for performing the procedure on fetuses
3 to be aborted. But this procedure is being performed
4 on fetuses going to term.

5 MR. GAITHER: Can I just ask for some clari-
6 fication, first? One, what are the purposes of this
7 particular protocol? Is it particularly experience and
8 safety, or does it get into the basic research questions
9 that Dr. Foster was mentioning?

10 MS. MISHKIN: My understanding of the protocol
11 is that it is to assess the risks of infection, of bleeding,
12 of premature abortion, and so forth, that are attendant
13 with fetoscopy. Now, Dr. Alexander also sees an additional
14 benefit, which is developing the competence of the
15 investigators to perform the procedure prior to trying
16 to do it on fetuses going to term. That also is included.
17 That is not the primary purpose of the application as
18 written. The application is to determine with somewhat
19 better certainty the risks involved to mother and fetus.

20 DR. FOSTER: And a part of that is improving
21 the technique. It is not basically designed to go into a
22 specific basic research question. As I understand it, it
23 is what Barbara says, to assess the safety and to improve
24 the technique. That is going to evolve from that. And
25 that is one of the reasons I feel they are asking for a

1 somewhat longer observation period, because if you do
2 the procedure and then proceed directly to the termination,
3 you would deny some of the longer term effects, delayed
4 bleeding and the like.

5 MR. GAITHER: Two further points of clarification,
6 and then I will open the discussion. The work that
7 is presently going on at Yale and the University of
8 California, has that been subjected to these regulations
9 and approved, the distinction being that it was therapeutic,
10 that is, regarded to be of benefit to a possible
11 child, and that is why it is different, or not? Do you
12 know what the status is?

13 MS. MISHKIN: I am not entirely clear. My
14 understanding is probably not with respect to the Yale
15 group, because I do not think that is funded by HEW. I
16 believe that is the information we got from Jerry
17 Mahoney just recently. But as you know, the regulations
18 are somewhat ambiguous with respect to whether or not
19 research conducted at an institution but not funded by
20 HEW must be reviewed by the IRB, and also subject to the
21 same review standards. So it is a somewhat unclear point
22 with respect to the Yale group.

23 DR. MCCARTHY: It is perfectly clear that the
24 Yale group felt obliged under Section 474(b) of the Public
25 Health Service Act to have Dr. Mahoney's research involving

1 fetoscopy reviewed by the IRB. They also made the
2 interpretation, which I think is a reasonable one.
3 although not the only possible one -- they made the
4 interpretation that they need not review according to
5 HEW standards. And in fact, there is some question in
6 my mind as to whether Dr. Mahoney's work would have been
7 acceptable under HEW standards, because I think they
8 regard this as more than minimal risk -- not a great deal
9 more, but somewhat more than minimal risk. Therefore,
10 if they had followed our standards, his work would have
11 had to come to the Board. Because it is not funded by
12 HEW, they decided they could make that decision and they
13 have made it and are carrying out that work.

14 MR. GAITHER: There would not have been a
15 distinction based on their work being therapeutic and
16 this work not, because of the abortion?

17 DR. MCCARTHY: No. As I understand it,
18 initially they -- and I am not quite sure at what phase
19 they are in. They have planned a series of steps, the
20 later stages of which they intend to be therapeutic. As
21 I understand it, they are still in the diagnostic phase
22 of those steps, but I believe their approval goes all the
23 way to -- assuming all the other stages are carried out
24 with no untoward events -- they intend to go all the way
25 to applying fetoscopy to therapeutic interventions to try

to assist fetuses that are in one way or another abnormal.

MR. GAITHER: Mr. Lazarus?

MR. LAZARUS: I think one of the key issues in this request is the problem of risk and how it is presented to the patient. Barbara says in her note that the risk presented by research cannot be characterized as minimal. Rather, it should be considered undetermined. And yet, the patient consent states that "I have been advised that these risks are minimal to me and to my fetus."

I think that one of the items that must be clarified is the whole consent procedure, and the nature of the risk must be spelled out a lot more consistently than they are spelled out under the present consent procedure that has been presented by Drew.

MS. MISHKIN: I think one of the problems is that minimal risk, as I pointed out, is not defined in the HEW regulations, and in the Commission's report and its deliberations, that was a problem in two areas. At one point they indicate -- and they indicate more strongly in subsequent reports -- that risk which has not yet been determined should not be classified as minimal, but should remain under the categorization of undetermined.

On the other hand, there were some Commissioners, although not all of them -- there was a difference of opinion on this point, as to whether when you are talking about a

1 fetus to be aborted, one can consider risk of abortion
2 as a minimal risk to that fetus, whereas one would not
3 consider risk of abortion a minimal risk to a fetus
4 intended to go to term. This was one of the very diffi-
5 cult points where there was a lack of consensus among
6 the Commission members.

7 So I think that when the IRB and the various
8 people who reviewed the Drew application determined that
9 it was minimal risk, that was not a clearly unacceptable
10 determination. It was simply their interpretation, given
11 very little guidance from the Department as to how to
12 assess and categorize that risk.

13 MR. LAZARUS: It would seem to me, though, that
14 a patient's consent is very important with the nature of
15 the risk, which is undetermined. It should be very
16 carefully spelled out.

17 MR. GAITHER: Particularly when one is
18 conducting the research for the purpose of finding out
19 how risky the procedure is.

20 MR. LAZARUS: Right.

21 MR. HALPERN: Underlining the illogic of the
22 word "minimal" where you are saying we don't know what it
23 means, well, the problem is it is in our HEW regulations,
24 and if in fact the risk is minimal as the patient is told,
25 it wouldn't be here.

MS. MISHKIN: That is right. It would not be before this Board if the risk were minimal. Then the IRB could have approved the project by themselves, although there is another provision that would need a waiver, so it probably would come here anyway. That is, the regulations currently provide that there be no change in timing or procedure of an abortion for research purposes that would add any additional risk, and that provision does not say "that would add more than minimal risk," but that "would add any additional risk." So it might have had to come here even so.

DR. MCCARTHY: But the determination, the very point that Mr. Lazarus made, was picked up in the Office for Protection from Research Risks, which refused to -- even though it had been reviewed by all of the subsidiary bodies -- refused to go ahead and fund until and unless it had been approved by this Board.

So it is that very point: If you are doing research to assess risk, it does not seem possible then to prejudge the outcome by calling it minimal. It may turn out to be minimal, but there is no justification for the research if you already know it is minimal.

MR. LAZARUS: And you are getting your consents under a false clause.

DR. MCCARTHY: Yes, and I think the Office for

1 Protection from Research Risks was correct in making the
2 judgment that it should come before this Board to comply
3 with HEW regs.

4 MR. GAITHER: Yes, Dr. Henderson?

5 DR. HENDERSON: Let me just carry that a little
6 further. One of the important criteria here is that the
7 research is important and justified. I think this is what
8 is indicated. Clearly we have got investigators who are
9 very competent people and they have obviously proceeded
10 step by step in reaching the point they have.

11 I guess there are a couple of thing in my own
12 mind that are rather unclear. There are two centers where
13 the work is being done now, Toronto and New Haven, where
14 the risks now appear to be rather small. I think this
15 is perhaps where the statement is that it is probably a
16 minimal risk, that experienced people following along with
17 two other centers, and doing what I interpret or what I
18 understand is the same procedure that they are doing in
19 New Haven and Toronto.

20 The question I guess I have, then, is is it
21 necessary to fund yet a third center? Should HEW fund a
22 third center to be doing this? What are the advantages?

23 The initial point here, as they say, initially
24 it is limited to an assessment of the safety. I find that
25 fully justified to go -- initially one is doing a study to

1 assess the safety. But then I ask what is the ultimate
2 objective, because we want research which is important
3 and justified. What is it that it is leading to? Obviously
4 there is an objective here.

5 I believe, as I interpret it, that they would
6 hope to be defining sickle cell disease. Now, I think in
7 talking with you earlier, the question is can you identify
8 either the sickle cell trait or sickle cell disease before
9 30 weeks? Can you define it at this period in time?

10 Perhaps we are talking about, as you mentioned
11 earlier, longer term basic research, which requires this
12 technique to be used. Is it enough to say that it is
13 important that we do longer term basic research employing
14 this technique without defining what is that basic long
15 term research, and are we at the point now to approve of
16 this sort of application which is based on safety, for some
17 sort of ill-defined subsequent future, when in fact we
18 are supposed to be judging this that the research is
19 important and justified.

20 Now, it is obvious that there are a lot of
21 very good people who have looked at this, and I am asking
22 the questions, I would say, out of ignorance, because I
23 found some contradictions here which I am having trouble
24 with.

25 FATHER MCCARTHY: Do you want to respond to

1 that, because I have got a different point I want to raise.

2 DR. FOSTER: Well, yes. I tried to make some
3 of them and I will try again. I think there are quite
4 a number of justifications, Don, for continuing. One
5 of the biggest reasons -- I think the assumption is not
6 completely correct that this work is being done at the
7 other centers. I don't think there is anywhere the
8 proportionate interest in sickle cell disease at either
9 other center, nor is there the particular population
10 base in either other center to be able to address this
11 effectively.

12 Even if Kan's work proves to be what it is
13 purported to be, based on what Ms. Mishkin has said, we
14 are still left with 15 percent of a large population that
15 is at great need, as you are probably aware. About eight
16 percent of the blacks in this country harbor the sickle
17 cell trait, and that is 2.5 million people, and 15 percent
18 of that is a large part of the population.

19 So I think there is still in our current state
20 of the art to continue to try and be able to diagnose
21 sickle hemoglobinopathies prior to the 30th week. I think
22 there may be ways that we can do it. As yet we can't do
23 it very reliably.

24 So I think the justification for continuing
25 this work is clearly there. The justification may not be

1 as strong as it was, but I certainly think it is within
2 the realm of acceptability. This is what I personally
3 feel.

4 Let me say one other question while I have
5 the microphone. Let me address one other question
6 regarding therapy versus research. I have not seen the
7 research proposals that John Hobbins had at Yale, or
8 what Kan has done at USC. But I do know that a lot of
9 their fetoscopy work was therapeutic. The work on
10 thalassemia was clearly therapeutic. It was done for
11 the same reasons that we do amniocentesis, to decide
12 whether or not the pregnancy should continue, and to
13 provide a therapeutic abortion. In fact, I know much
14 of that.

15 Hobbins' most recent article, which I believe
16 was December of last year where he had, as I recall,
17 about six or seven patients with sickle cell disease
18 which he was working with. These were all therapeutic.
19 He had tried to make a determination as to what type of
20 hemoglobinopathy, whether it would be homozygous or
21 heterozygous around the 22nd week, and the results were
22 just inconclusive. His conclusion at the end of the article
23 was that at this point we still can't do it. But that was
24 clearly done to be therapeutic. Had he felt that he could
25 have made the determination, he would have offered therapeutic

1 abortion. So I do know that some of the work has been
2 therapeutic.

3 DR. MCCARTHY: That is correct. I should
4 amend what I said. I think what Mahoney is doing is
5 now tending to move into the preventive therapy and not --
6 so I would like to amend what I said before about
7 therapy, because it was clearly for the purpose of
8 giving parents the option of a therapeutic abortion.
9 But now they hope to move into preventive therapy, which
10 is the sense in which I was using "therapeutic."

11 MR. GAITHER: Is there an answer to Dr. Henderson's
12 question, though? Do we know whether this technique will
13 enable the researcher to determine the presence of the
14 sickle cell disease?

15 DR. FOSTER: We never know that until we do
16 the research. I mean, no, I don't think we know it
17 beforehand.

18 MR. GAITHER: I think that is kind of a funda-
19 mental point here, because implicit in all of these
20 papers, it seems to me, is precisely that, that this
21 technique will enable the discovery of whether or not the
22 disease is present. The question is whether it can be
23 safely done. Now, if that is wrong, my whole reading of
24 all of these papers is very much mistaken. I think it is
25 a very fundamental point.

1 Either we are dealing with something that we
2 know can help, and the question is whether it is safe, or
3 we are dealing with something that we don't know much
4 about.

5 DR. HENDERSON: I am puzzled by your statement
6 that the sickle cell trait is not identifiable before the
7 30th week. This is what is concerning me at the moment.
8 And if it isn't identifiable before the 30th week, because
9 you do have fetal hemoglobin present, I am not quite sure
10 where this technique leads. I think this is information
11 which we do have a reasonable body of knowledge on, do we
12 not?

13 DR. FOSTER: I don't know. The only thing that
14 I do know is that the struggle has been to try and be
15 able to diagnose sickle cell -- homozygous sickle cell
16 disease at a point at which therapeutic abortion could be
17 offered. Right now we don't have that capability, and it
18 was my understanding that one of the thrusts of this
19 research proposal was to help to try and find that
20 capability.

21 I would certainly think that this is an issue
22 that again could be raised with the team, the basic research
23 team who conducted the site visit. I think that these might
24 be some issues that Jim and the staff might wish to bring up.

25 MR. HALPERN: Dr. Henderson, it might be helpful

1 if you were to point Dr. Foster to the passage you were
2 referring to in our materials with respect to this precise
3 issue, as to what extent does the primary researcher here
4 feel that we are ready to use fetoscopy for genetic
5 diagnosis. My reading is that he feels that we are not
6 ready to undertake that.

7 DR. HENDERSON: I gather that this is what he
8 was looking to investigate.

9 DR. FOSTER: Where are you reading from?

10 MR. HALPERN: Page 3, Tab H.

11 MR. LAZARUS: A letter to Arthur Percy from the
12 principal investigator. A letter from Ezra Davidson to
13 Percy. It is at page 3 under item five. It is the second
14 paragraph under item five.

15 DR. HENDERSON: I have had trouble identifying
16 specifically what is the outcome above and beyond an
17 assessment of safety, which I think would not to me be
18 enough of a justification to go ahead with it. I think
19 we are looking for the further outcome, which is the
20 diagnosis of the sickle cell disease, and this is where
21 I am having a little bit of trouble.

22 MR. HALPERN: My point is that the principal
23 investigator himself, the way I read that paragraph, has
24 himself pointedly not addressed the question of whether
25 this procedure has merit as a tool for investigating genetic

1 disease. That is the way I read that.

2 DR. HENDERSON: That is the way I read it, too.
3 I assumed I was just missing something.

4 MR. GAITHER: Dr. Hamburg?

5 DR. HAMBURG: In principle, there is simply no
6 question about that at all. I mean, there is zero uncer-
7 tainty as to whether having the fetal blood available would
8 be useful in analyzing the biochemistry of this disorder.
9 The hemoglobin that is abnormal is in the blood of the
10 fetus, and if you can get the blood of the fetus the chance
11 of applying the most advanced techniques to understand the
12 nature of the disorder is, I would say, much greater than
13 anything otherwise conceivable. This in the face of the
14 fact that you can use squamous cells from the skin for
15 some things, and you can use fibroblasts for some things.
16 But by and large, having the blood available if you can
17 safely get it, it seems to me, offers opportunities and
18 analytical capabilities an order of magnitude greater than
19 anything known to me. So I don't think that is an issue.

20 You may ask can you do it now, and the answer
21 is apparently no -- that is, the early diagnosis. But if
22 you are going to get there this is clearly the royal road.

23 Therefore, the issue to me is much more the
24 safety than the potentiality for analyzing this disorder
25 and a whole bunch of other disorders as well.

20
20
1 Now, there is another question, and Hank,
2 I am sure you have a lot to clarify this, but the new
3 work -- the question about the new work in San Francisco
4 and what bearing that has on it. First of all, the other
5 centers that are active, as I understand it, have concen-
6 trated on thalassemia, they have concentrated on the
7 hemophilia. This is, I believe, the principal center
8 concerned with sickle cell disease, and it serves a
9 community in which sickle cell disease and the trait are
10 really prevalent and it is highly appropriate, therefore
11 to study it in that community. The community wants to
12 learn more about the disease. They carry the main burden
13 of it in the country.

14 Now, the new work may say that there are
15 alternatives which can do some of this. Here we are in
16 an awkward position on two or three counts. One, we don't
17 have firsthand -- although a valiant effort has been made
18 to get it -- just what their findings are. But even if
19 we knew their findings, I wouldn't be terribly impressed.
20 I mean, in the absence of replication there are so many
21 ways that even good investigators can make mistakes. The
22 history of science is so replete with sort of loose
23 assertions in the first go-round, even with the most care-
24 work, and particularly when it comes to human investigation.

25 So we need to know what they found, and we need

1 somebody else to replicate it before I would be satisfied
2 that 15 percent was accurate.

3 Now, as I think you lawyers say, arguendo, if
4 15 percent were to be replicated, then we would have
5 another decision to make. Is that enough of a problem
6 to go ahead and pursue the matter? Also, it is more than
7 the 15 percent question. It is also the question of how
8 much analytical power is there from the techniques used
9 by the investigators at the University of California as
10 compared with the analytical power made possible by
11 having the fetal blood.

12 If you made the extreme assumption, and said
13 well, most of the problem of investigating this disease
14 was taken care of by the new technique, and you don't
15 need fetal blood -- it would help, it would be nice, but
16 you can gain so much in the next few years by simply
17 amniocentesis, and you therefore say well, sickle cell
18 is therefore not the issue.

19 Then the question would become for this group
20 is there improvement in the technique -- is this to be
21 methodological research, to improve the technique of
22 fetoscopy in order to get the safety to the point at
23 which it could be useful for all sorts of other things
24 beyond hemoglobinopathies, immune system disorders, for
25 example. Then it is a somewhat different kind of

808

1 justification, but they still would be in the ballgame,
2 I would think, in view of the fact that they have already
3 done a lot of the background work in nonhuman species,
4 and have some human experience.

5 That would, however, leave us with the question,
6 is this the appropriate community. Do you need to go back
7 to the community and say to them now it is not justified
8 in terms of a disease which is highly prevalent in this
9 community, but it is justified on some other grounds. Do
10 you still want to back it?

11 DR. FOSTER: We have made a presumption -- I
12 have heard a presumption, and I am a little bit confused.
13 As I look at Ezra's letter -- Dr. Davidson's letter of
14 May 10th to his own committee, he makes a statement to
15 me that is kind of fundamental. We have assumed -- I have
16 heard two or three times today -- that the safety of the
17 technique has already been evaluated and established.
18 That is what I have heard two or three times. Did I hear
19 that?

20 MS. MISHKIN: Of which technique, fetoscopy or
21 amniocentesis? That is the point of the research, and that
22 is why we prefer to call it undetermined rather than
23 established as minimal.

24 DR. FOSTER: Well, given that --

25 DR. HENDERSON: It has been done twice.

1 DR. FOSTER: That is -- hear what I am saying,
2 then.

3 DR. HENDERSON: Talking about the experience
4 of two centers is not a large number, I agree.

5 DR. FOSTER: And I heard very clearly Dr. Henderson
6 state that at two centers they have done this and it has
7 been established. Do we need to do it again? Yet the
8 principal investigator's primary thrust is that the safety
9 has not been fully and completely evaluated. That is one
10 of the main reasons he puts forth. And of course, to
11 what degree do we make that determination, or the investi-
12 gating team who looked at it to me gets to be important.

13 DR. HAMBURG: May I put that slightly differently?
14 I think it is a question of finding ways to further reduce
15 the risk of the technique, which is, after all, still a
16 problem with amniocentesis.

17 DR. FOSTER: Even the figure they gave was very
18 high 2.4 percent.

19 DR. MCCARTHY: And we don't have all the infor-
20 mation from Yale, and very little from Toronto. But much
21 of the Yale work was observational, so that some of the
22 additional steps that are contemplated in this research
23 have not been evaluated extensively, at least, at Yale.
24 That is to say they used the scope and they took pictures
25 of the fetus in order to determine whether certain kinds of

1 observational defects, or defects that could be discerned
2 by observation could be identified. They were able to
3 look at certain positions of the hands and the fingers of
4 the fetus, and so on, and make some determinations as to
5 the likelihood of thalassemia. But the taking of fetal
6 blood and the question of the risk associated with fetal
7 bleeding, and so on, has not been carefully determined
8 by Yale.

9 So I think there are similarities, but there
10 are also differences that would justify going ahead with
11 this research.

12 MR. LAZARUS: Even on the extended basis,
13 carrying it out for 20 days?

14 DR. MCCARTHY: I think that is a separate
15 question, and at least our staff was not persuaded that
16 we should authorize going ahead with that without a good
17 deal more observation about that point.

18 DR. FOSTER: Just quickly, I just wanted to
19 restate, I was beginning to get a feeling that it was
20 being stated that the risk had been evaluated, you know,
21 it has been done, and for that reason, that should alter
22 greatly our thinking. I just kind of wanted to put that
23 in perspective. I don't know if we can make that judgment.

24 MR. GAITHER: Father McCormick.

25 FATHER MCCORMICK: I am really terribly confused

1 about the factual -- I have got two points I want to
2 make -- the factual problem of the assessment of the
3 risk. I hear the word "undetermined," and "more than
4 minimal." I hear it is being done, and yet therefore it
5 is justifiably being done, or at least that is the
6 connotation. If it is no more than minimal risk in the
7 way it is being done, then it shouldn't be before us.
8 I am confused on that. Why is it here?

9 But I have got a more basic problem I want to
10 raise and point your attention to under number (i) in
11 that 46.211, which is a matter of ethical principle which
12 is going to bother us, and we may as well call attention
13 to it right now. That is the types of cases that ought
14 to come to us. The sentence reads, "In making such
15 decisions, the Secretary will consider whether the risks
16 to the subject are so outweighed by the sum of the
17 benefits to the subject --" now, notice the next word.

18 MR. LAZARUS: Where are you reading?

19 FATHER MCCORMICK: That number we adverted to
20 before, 46.211, under (i).

21 MR. LAZARUS: Okay, 211.

22 FATHER MCCORMICK: Got it?

23 MR. LAZARUS: Yes, right.

24 FATHER MCCORMICK: Okay, about the Secretary will
25 consider.

1 MR. LAZARUS: Right.

2 FATHER MCCORMICK: Then it says, "and the
3 importance of the knowledge to be gained as to warrant
4 such modification and waiver." There are two conditions
5 there, by the word "and," unless I am misreading this. It
6 has got to be of some benefit to the subject, and the
7 importance of the knowledge to be gained. In other words,
8 the supposition of that is that the procedure, experimental
9 or investigative, is going to be of some benefit to the
10 subject.

11 DR. HAMBURG: I wouldn't interpret it that way.
12 It says the sum of benefits. It may be zero plus ten, but
13 it still comes out to ten.

14 FATHER MCCORMICK. Therefore it should be "or?"

15 DR. HAMBURG: No.

16 FATHER MCCORMICK: No, wait a minute. What I
17 have in mind is this. If the only consideration --

18 MR. GAITHER: Dick, hold on.

19 THE REPORTER: I don't know what happened,
20 because everybody talked at once. You will have to watch
21 that.

22 MR. GAITHER: Okay, I am sorry.

23 Father McCormick?

24 FATHER MCCORMICK: The point I was making is
25 this: If a fetus about to be aborted, and that is what we

1 are talking about -- is going to undergo more than minimal
2 risk, in other words, the type of risk we would not allow
3 to be visited upon one going to term, then that case comes
4 to the Secretary to see whether the knowledge outweighs the
5 risk.

6 I want to point out that there are just an awful
7 lot of people who would say that the knowledge to be gained
8 never outweighs the risk, as an ethical principle. In
9 other words, there are people who would challenge the very
10 supposition of bringing this to the Secretary. I would be
11 one of them. And I think we are going to run into that
12 all the way along the line.

13 MS. MISHKIN: There is one point here which you
14 raised, which is the point at which the regulations are
15 slightly at variance with the Commission's recommendations.
16 The Commission foresaw difficulty along these lines, and
17 its recommendation was that projects would come before
18 this Board if there was difficulty in interpreting the
19 regulations. If there was any difficulty in interpretation,
20 and this, I think, might fall well within that category,
21 whether it was disjunctive or conjunctive, and how one
22 were to interpret that.

23 That provision did not really make it clearly
24 into the regulations, but that is a point of history which
25 might help.

1 FATHER MCCORMICK: Or if the danger were minimal
2 or not. Wasn't that one of the interpretative charges?

3 MS. MISHKIN: Yes, questions of defining minimal
4 risk, questions of assessing that, or simply questions of
5 applying the regulations to a particular project at hand.

6 FATHER MCCORMICK: Right.

7 MS. WILLIAMS: I think we should bear in mind
8 that while the risk to the fetus in this case is more than
9 minimal, the chance of harm to the fetus, I think, is very,
10 very minimal indeed, because before the fetus could be
11 said to be harmed, we would have to have a conjunction of
12 two circumstances: number one, that the fetus would be
13 aborted as a result of the procedure, which is certainly
14 apparently less than five percent, a less than five percent
15 chance. Then we would have to have a second circumstance
16 coinciding, which is that the mother has changed her mind
17 about whether she wishes to abort the child. I would think
18 in a well-run protocol, this chance would probably be a
19 less than one percent chance. So mathematically, the chance
20 that the fetus would lose its life is a very minimal
21 chance indeed.

22 MS. MISHKIN: Although that chance increases as
23 the delay between fetoscopy and abortion increases, especially
24 if they develop a therapeutic technique. They may find out
25 that the baby does not seem to be affected by sickle cell,

1 and you are waiting two weeks from that period, and
2 down the foreseeable future the mother might very well
3 change her mind during those two weeks. And then your
4 risk of harm might become realized.

5 MR. HALPERN: I would only say that I think
6 Dick is in really a better position to state this,
7 but I will make the argument for him, that many would
8 quarrel with the assumption that the fetus to be aborted
9 has a diminished moral status from the fetus for whom we
10 have no intent to abort. We can't backstop it. Many
11 would say we cannot backstop what we do to a fetus by
12 saying well, five percent, it is only five percent, and
13 moreover, we plan to abort this fetus tomorrow.

14 MR. GAITHER: I don't think the point was
15 made that there is any difference in the moral status,
16 but rather when one assesses the risk of the procedure,
17 one ought to be realistic about the circumstances in
18 which you are looking at it.

19 MR. HALPERN: Well, I think once we talk about
20 risk, though, I think that -- risk to whom? Even if we are
21 going to talk in terms of risk, I still think the bottom
22 line is whether you are going to -- maybe moral status is
23 too loaded a word. But I think we are talking about moral
24 status.

25 MR. GAITHER: I think you have to separate the

1 two points. I think that Father McCormick has made the
2 point basically saying no risk is tolerable in a very
3 general sense. But when one looks at the risk to a
4 fetus about to be aborted, it seems to me difficult to
5 say that you cannot, in assessing the risk, look at
6 whether or not the fetus is going to be aborted.

7 MR. HALPERN: I understand the Commission
8 recommendations. They flat-out say no, you cannot.

9 MR. GAITHER: I understand what the Commission
10 said about a lot of things, and that was one of them,
11 like saying we can't decide what minimal is, and we will
12 give that to somebody else. I am not sure that that
13 question was really resolved. Otherwise, these regula-
14 tions would not be in existence.

15 DR. HAMBURG: Well, in considering ethical
16 options, if you are going to talk about various positions,
17 including extreme positions, there is a position extant
18 which says, in effect, no abortion without research.
19 That is if you are going to involve the loss of life
20 that is involved in abortion, and the moral distaste of
21 a considerable segment of the population that goes along
22 with that, then the outstanding compensatory feature, or
23 one of the principal compensatory features is that you
24 learn something that can be of benefit to human life in the
25 future. Therefore, any justification for abortion must be

1 linked with research. That is a position which exists.
2 I am not advocating it, but if you are talking about
3 options, that is one at the other end of the spectrum.

4 FATHER MCCORMICK: I think the Commission's
5 recommendations, though, as Phil has said, are clear on
6 this, that just because a fetus is going to be aborted
7 does not diminish the harm that can be done to it, just
8 as I can inflict harm on a condemned or dying person.
9 Therefore, just the fact of coming abortion does not
10 alter one's assessment of what is tolerable in terms of
11 harm. I think that is quite clear in the directives of
12 the Commission.

13 DR. HAMBURG: It is a question of the harm today
14 or the harm tomorrow.

15 DR. HENDERSON: Well, in this case I don't have
16 any trouble with it, because they are applying a diagnostic
17 procedure or a proposed diagnostic procedure, which they
18 are intending, hopefully, to apply broadly to many children
19 whose parents have this trait. So I think they are hoping
20 to apply a safe procedure, as they would if this child were
21 to go on to term.

22 DR. HAMBURG: Point of clarification. Did you
23 say that there would in fact be sequential decision making?
24 That is, if they were going to extend the period incrementally
25 and accumulate enough experience at each step in order to know

1 what complications might arise? They weren't going to
2 go from -- make a 20 day jump all at once, or something
3 of that sort?

4 MS. MISHKIN: No, it was to be incremental, and
5 they would not even make the incremental increases unless
6 they were satisfied with respect to risk, at whatever stage
7 they had previously completed.

8 DR. MCCARTHY: Dick, would you go back over the
9 principle you enunciated? I was first not clear whether
10 you espoused it or whether you merely cited a principle
11 held by some, and secondly, I don't think I understood
12 it regarding the sum of the benefits to the fetus or to
13 the subject, and the knowledge to be gained. And if I
14 heard you correctly, you said that unless there was some
15 benefit to the subject, no amount of knowledge would
16 justify it? Could you go over that again, because I am
17 not clear what it was you were stating.

18 FATHER MCCORMICK: Well, this 46.211 covers
19 cases that come to us, that are beyond the provisions of
20 the Commission. Therefore, the presumption is that there
21 is some difficulty with regard to the assessment of
22 minimal risk, or that there is beyond minimal risk, but
23 there is great knowledge to be gained.

24 Now, realistically, we are talking about non-
25 therapeutic interventions, because the others are not

1 problematic. If there is a risk, but it is going to be
2 therapeutic to the subject, then there is no problem.
3 So I was just pushing that "and" as a small point.

4 If a thing would come to us and there would be
5 no benefit to the fetus, the fetus to be aborted, or what-
6 ever fetus, and the risk were more than minimal, let us
7 say considerable, then there is a strong body -- I think
8 perhaps the strongest body of opinion in the ethical
9 community, would be that no amount of knowledge could
10 justify that.

11 DR. MCCARTHY: More than minimum. I think
12 I understand.

13 FATHER MCCORMICK: Because I had to fight
14 pretty hard with a whole bunch of my colleagues just to
15 get minimal risk accepted, if you remember.

16 DR. MCCARTHY: Yes. Okay, you have clarified
17 that for me. I didn't understand it the first time.

18 MR. GAITHER: Let me make a suggestion here.
19 I think that we are all grappling with some gaps in our
20 understanding, and while I am very reluctant to put this
21 over to the next meeting, I really think that we have to
22 do so. It seems to me that we need clarification in terms
23 of what has happened at the University of California. Does
24 that development have a significant impact on this applica-
25 tion in terms of its importance? I think that is a question

1 that ought to be addressed to the investigators as well
2 as to our two experts. And we do have, I think, enough
3 time for them to examine that question and get back to us
4 before our January meeting.

5 MS. MISHKIN: I might add, it might be interesting
6 to find out, as Dr. Foster suggested, what the community
7 review group would feel about the impact of that, also.

8 MR. GAITHER: Well, I would think unless there
9 is a significant change scientifically, to start the whole
10 process over would not be warranted. So it seems to me
11 it needs to be taken in steps. I would think the investi-
12 gators should make that judgment rather than for us to make
13 it absent some body of scientific knowledge.

14 DR. HAMBURG: One brief addendum, Jim. The
15 paper that they have in the Lancet at the moment, which
16 will be available, I think the investigator should be
17 contacted to see if they have other papers in press. They
18 may well. We should get everything they have.

19 MR. GAITHER: Let me try this, and then come
20 back, and please, everybody chip in what they think we
21 need. The second that I think needs clarification is
22 whether or not we can assume significance of the underlying
23 procedure here, namely that we do know today that the
24 availability of the blood sample will be of tremendous
25 importance to us, even if it may not be able to tell us

31
1 every case of the sickle cell disease. We know that it
2 will get us a lot farther along the road than anything
3 we have today.

4 The question that you raised, Dr. Henderson,
5 are we looking at safety before we know whether the
6 procedure is important, or can we really assume today
7 that indeed the procedure is very important for this and
8 other purposes. What we need to know now is whether we
9 can safely employ it. It seems to me that our experts
10 ought to be able to advise us on that question.

11 MR. LAZARUS: That is the question of whether
12 the procedure is important?

13 MR. GAITHER: Yes, right.

14 And the third is to get an answer for the
15 question raised by Mr. Lazarus, can we really -- well,
16 one should state it diplomatically, I guess. Shouldn't
17 the consent form spell out rather clearly what we know
18 not in terms of a conclusion, as to whether it is
19 minimal or great or something else, but rather whether
20 there is risk to the mother and whether there is risk to
21 the fetus. It seems to me that it certainly needs to be
22 pointed out in the consent form that the purpose is to
23 determine, perhaps within a range, what the real risk is.
24 And if you were in fact reading from the consent form, it
25 seems to me clear that this body should not approve a project

1 with that kind of consent form contained in it given
2 this purpose.

3 Are there other things that people believe
4 should be learned before we can reasonably be expected to
5 pass on this application?

6 MR. HALPERN: I am troubled by one thing. I
7 think it is unspoken or implicit in this, that by performing
8 the fetoscopies at Drew there is going to be improved
9 competence on the part of the physicians. We heard last
10 night from a witness, or perhaps it was, I think, from
11 you, Dr. Foster, about how at your institution in
12 performing laparoscopies over time, how dramatically
13 the rate of complication was reduced.

14 I think in looking at this, not at any words,
15 in looking at this I think implicit in this is saying
16 well, if we proceed at Drew, in this community, with
17 performing fetoscopies, although they are nontherapeutic,
18 we will raise the competence of physicians, and that future
19 members of the community needing therapeutic fetoscopies
20 will thereby benefit from this improved competence.

21 I would like our reviewers or even to go back
22 to the investigator, to see if this unspoken -- to me what
23 I read as this implicit justification for approving the
24 protocol has in fact been, is being taken into account.
25 And if it is being taken into account, then I would like to

715

1 see it addressed directly, because if we do address it
2 directly, it certainly raises the importance of what we
3 have been told occurred at the University of California
4 at San Francisco with respect to the ability to diagnose
5 sickle cell disease through amniocentesis, because then
6 the impulse on the part of the members of the community
7 to undergo risk now so that fetoscopy would later be
8 improved fetoscopy, or at least the procedure would
9 reduce risk because of the improved competence of the
10 physicians, would then be available to either them or
11 to members of their community for therapeutic diagnostic
12 purposes.

13 I think if that is what is powering this,
14 we ought to address it directly.

15 MR. LAZARUS: Another thing is that that has
16 to get into the consent form. It is obvious from the
17 other experiences that the first three or six that are
18 done are more dangerous than the other ones.

19 MR. HALPERN: And I fear that in the --

20 MR. GAITHER: And it is explicit here. Whether
21 they are acknowledging it in their protocol, it certainly
22 is acknowledged in the evaluation by the two people retained
23 to look at it for us.

24 DR. MCCARTHY I think in this question of risk
25 I am coming back to the consent form, and I fully agree with

1 Mr. Lazarus about the statement about minimal risk. There
2 are two factors, and this makes it so difficult to make
3 a statement about risk, and I think Mrs. Williams alluded
4 to this. One is the consequence, and in some of the
5 description contained in the consent form, the consequence
6 would be dramatic, bleeding of the mother and possible
7 very serious consequences.

8 The other is the incidence, and it looks as
9 if the chances of those drastic and dreadful consequences
10 are very remote. And so you have the question, because
11 it is unlikely to occur, does one call it a minimal risk?
12 It is the same sort of thing we face when we fly on an
13 airplane. Because the incidence is small we say it is
14 not very risky. But if the thing crashes it is almost
15 certain to be dreadful, and therefore terrible. That is
16 a terrible risk, but we think it may be still acceptable
17 or minimal because it is so infrequent. So I think there
18 are two aspects here to what we call minimal, and I daresay
19 the Commission left those things unresolved for us, and
20 perhaps we need to move toward a definition of minimal
21 risk in this context.

22 MR. GAITHER: I think that if the --

23 MR. LAZARUS: I think the point is that if this
24 were minimal risk by somebody's interpretation it wouldn't
25 be before this committee.

1 MR. GAITHER: I think it points out the
2 difficulty of putting labels. It may be that the focus
3 is entirely wrong, that what needs to be expressed are
4 the underlying facts that you just talked about. Namely,
5 it may not happen to you, the chances are only one in
6 500 that it will happen, but if it does, we won't see you
7 tomorrow. Now, that is a lot more meaningful than a
8 conclusion that says the risk is minimal. I think that
9 is something we really need to focus on, and I would
10 hope that as this comes back to us at the next meeting,
11 that somebody talk to the investigators about that kind
12 of approach.

13 MS. MISHKIN: The Commission did address that
14 later in subsequent reports, and stressed what Charlie
15 was just mentioning, that risk includes both probability
16 and severity of the thing happening. But I think what
17 Mr. Lazarus has pointed out very dramatically, and
18 Charlie's analogy would hold, it may be that the probability
19 of an airplane crash is very low, but we sure would want
20 to know if we were on the test flight. That is not coming
21 through very clearly. This thing is to determine the
22 probability, and that is not on that consent form.

23 MR. HALPERN: Also, I think the way one measures
24 the risk, or measures these two factors -- I think if it
25 is therapeutic, if I am to be helped, I will be much more



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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The Chief of Staff

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NOTE TO JOHN PODESTA

Attached are the relevant portions of the transcript. We have the entire day's session as well.

Kevin Thurm
Kevin Thurm

1 there is no guilt, so there is a notion of providing
2 gifts for those who suffer even without blame. But at
3 the very least what I was referring to is where you can
4 actually put your finger on the guilty party, or on
5 negligence.

6 DR. MCCARTHY: I would like to pursue that, but
7 that is another whole area.

8 MR. GAITHER: Let me pursue just one question
9 that Dr. Hamburg raised with you. As will become clear
10 shortly, the National Commission had trouble grappling
11 with risk, and deferred the issue to us. I would like
12 not to let you have that luxury.

13 When you spoke of trying to be sure that there
14 would be no additional risk before proceeding, what do you
15 do if the facts suggest that we don't know whether there
16 are additional risks, where perhaps we have no evidence
17 that there are going to be additional risks, but we are
18 not sure.

19 DR. LEIMAN: Nor is there any kind of experi-
20 mentation which would solve the issue for us. Is that
21 what you are saying?

22 MR. GAITHER: At least not in the near term.
23 Maybe five years, maybe ten years, we would know more.

24 DR. LEIMAN: Right.

25 MR. GAITHER: But if you have a situation where

160 161
1 you don't know of increased risk, does that meet your
2 standard, or do those who wish to go ahead have the
3 burden of proving that there is no increased risk?

4 DR. LEIMAN: I am trying to draw the nearest
5 analogy from cases that I know. With regard to someone
6 whose life is at stake, for example, a man dying from
7 cancer, where the physician comes in with some new
8 medication which may or may not help, it may hasten his
9 death, in fact, if it doesn't work. On the other hand
10 if it does succeed ultimately in the long run he will be
11 better off.

12 The Jewish position has always been that you
13 have a right to take that risk. That is, the patient
14 himself has a right to make a decision if it is a life
15 and death issue. So to give you the classic case very
16 quickly, a man who was dying was informed by his physicians
17 that if he did nothing he would die in six months to a year.
18 If he took a certain drug or went through a certain surgi-
19 cal procedure either he would die immediately or it would
20 be a success. What do you do in such a situation?

21 The rule was that the patient has a right to
22 make that determination for himself. He can risk immediate
23 death, that is his privilege, for long-term life.

24 The problem is complicated by what you are
25 raising, because now we are dealing not only with the patient,

1 but with the conceptus, and whereas the patient can make
2 whatever decision the patient wants to make, the risks
3 that we are not seeing here may affect the conceptus,
4 and there is no way of getting the consent of the
5 conceptus. That is why I find it problematic.

6 I would just have to say as a general rule
7 that patients have a right to take risks for good benefits.
8 And I don't think you have to prove, as you put it --
9 I don't think the burden of proof rests with the patient
10 that there is no additional risk. I don't see that at
11 all.

12 I think if we are going to fund a project or
13 any kind of research, then we have to be sure that as
14 many risks as possible are removed by animal experimenta-
15 tion and so on before we proceed and fund an experiment
16 on humans.

17 MR. HALPERN: Just one quick question to follow
18 up. I understand you say if a couple wishes to go ahead
19 with private monies with the in vitro procedure and
20 transplant, I understand you to say that it is up to this
21 woman to determine risk, and she would not --

22 DR. LEIMAN: Except I qualify that by saying
23 that there is a problem here of the conceptus, who may
24 not be --

25 MR. HALPERN: Well putting that aside, because

1 we have already discussed that enough, and in my mind I have
2 reached a conclusion. put aside the role of the couple.
3 Let's look at the role of the government, the federal
4 government in deciding to fund such research.

5 Does the government have an obligation to
6 convince itself by drawing forth evidence that there is
7 no -- whatever the standard is for the risk, coming forth
8 with evidence, finding evidence creating evidence that
9 that standard is satisfied, or is it sufficient if we
10 look to see, and well, we don't know.

11 DR. LEIMAN: It seems to me only to the extent
12 that the government will be involved in various procedures,
13 either compensation procedures, or to the extent that this
14 conceptus may one day become a responsibility of the
15 government. If you have a genetically deformed child,
16 and so on, to what extent will the government then have
17 to fund the care for that child, and so on.

18 So it seems to me that people have a right
19 to take risks so long as it does not affect other citizens,
20 and if it does affect other citizens, then the government
21 does become involved, because the government has to
22 protect its citizens.

23 MR. HALPERN: Then it would be fair to say that
24 in a particular situation it might be ethical and moral
25 for the couple to decide to go ahead, but it would not --

164
1 given the risk benefit ratio and whatever -- it would
2 not be ethical and moral for the government to pay for
3 that process.

4 DR. LEIMAN: So long as we are leaving the
5 conceptus out of the discussion, I think so.

6 MR. GAITHER: Dr. Henderson, one last question.

7 DR. HENDERSON: Just an observation. I wonder
8 if we are really looking at proceeding on the assumption
9 that there is no additional risk. As one looks at the
10 whole field of medicine, almost any procedure one does,
11 any drug one takes, there is some minimal additional risk.
12 Acceptable minimal additional risk I think is the way we
13 are really looking at this, and to say there is probably
14 no additional risk I think is probably not the way we
15 can look at this. I think we must say minimally acceptable
16 additional risk.

17 MR. GAITHER: I think the "acceptable" is still
18 at issue. But I think that the point is well taken.

19 Rabbi Leiman, thank you very much. We appreciate
20 it.

21 Let's take a short break and figure out how we
22 can get back to our schedule.

23 (Brief recess.)

24 MR. GAITHER: Needless to say, we have fallen a
25 bit behind schedule, and I would suggest that we postpone

1 for the time being the legal discussion regarding in
2 vitro fertilization, and proceed at this time to a
3 consideration of the research application involving
4 fetoscopy, submitted by the Charles Drew Postgraduate
5 Medical School.

6 I would like to note at the outset that
7 Dr. Spellman, formerly Dean at that medical school has
8 asked that he be excused from the deliberation on this
9 issue. I hope that you will stay with us and listen to
10 it, but I understand your reluctance to become involved,
11 and we will assume that you will not be involved in
12 either the discussion or the decision on this issue.

13 DR. HAMBURG: However, as a point of personal
14 privilege, you may respond to insulting remarks.

15 (Laughter.)

16 MR. GAITHER: Mrs. Mishkin, we will let you
17 describe the issue before us, and I would ask that you
18 start by describing why the application is before us and
19 what we are expected to do with it.

20 MS. MISHKIN: The HEW regulations governing
21 research involving the human fetus lay down certain
22 conditions which must be met in order for an institutional
23 review board to approve that research. If the institutional
24 review board is not able to determine that all of the
25 conditions have been met, and if it considers that the

1 research nevertheless is important, it may refer that
2 research proposal to this Board for review. And if the
3 Board determines that the research should go on, it may
4 recommend to the Secretary that he waive those parts of
5 the regulations that the research proposal cannot meet.

6 Now, the proposal before the Board at this
7 point is a proposal to perform fetoscopy on mothers who
8 have elected to have abortions for reasons totally
9 unrelated to the research, in order to discover and to
10 document what the risk to mothers and fetuses might be
11 from the procedure of fetoscopy. The purpose of develop-
12 ing the fetoscopy is to be able to diagnose prenatally
13 certain conditions for which the parents are at risk.
14 In this particular research proposal the focus is
15 primarily on prenatal diagnosis of sickle cell disease.

16 Now, the reason that this proposal is before
17 the Board is that it cannot meet or at least cannot
18 clearly meet provisions of the HEW regulations set forth
19 in sections 46.206(a), 46.207(a), and 46.208(a) which
20 briefly, taken together, require that the activities in
21 the research proposal be designed to meet the health needs
22 of either the mother or the particular fetus involved, or,
23 if that is not the case, that the procedures present no
24 more than minimal risk to the fetus.

25 Now, the problem in this proposal is that it is

1 not designed, as written, to provide therapy for the
2 mother, nor is it designed to provide therapy for the
3 fetus, because the purpose is to assess safety of a
4 technique and to do it in mothers who have already
5 elected to undergo abortion. So there is no question
6 as to whether or not it is or not so-called therapeutic
7 research. It clearly is not. Therefore, it does not meet
8 that first condition.

9 It does not seem to meet the second condition
10 because the risks, I think, must be considered undetermined.
11 Although the HEW regulations do not define minimal risk,
12 it is possible to go and look behind those regulations
13 to the Commission's discussion of what they intended,
14 because the regulations were an attempt by the Department
15 fully to implement the Commission's recommendations on
16 research involving the fetus.

17 So I am going to offer to you for your guidance
18 what the Commission's intentions were when they made their
19 recommendations to the Secretary. That does not mean that
20 you must follow the Commission's intentions; it is only to
21 elucidate for you somewhat what the Commission had in
22 mind, because the regulations themselves give this Board
23 no guidance. The only guidance in the regulations is to
24 the institutional review boards.

25 MR. GAITHER: Let me interrupt for just one

1 second, because I think it is important that we understand
2 the standards which we are to apply. I gather what you
3 are saying is that this particular application is not
4 therapeutic and not clearly within the category or at
5 least so determined by the institutional review board,
6 as involving no more than minimal risk.

7 MS. MISHKIN: That is correct.

8 MR. GAITHER: Therefore, it can only be funded
9 if this Board determines that it is ethically acceptable?
10 Is that the standard?

11 MS. MISHKIN: Essentially, yes. If we recommend
12 to the Secretary that he waive those provisions that we
13 just mentioned because we feel the research is important
14 and justified by the benefits to be obtained from the --
15 the anticipated benefits.

16 MR. GAITHER: So there is no particular standard
17 other than for us to say to the Secretary whether or not
18 we feel that he should go ahead despite that provision in
19 the regulations?

20 MR. HALPERN: Mr. Gaither, if I could be of
21 help, if you look at subpart 5 under Tab I in our book,
22 giving us the regulation, Section 46.211 provides some
23 guidance as to the standard, at least which will guide the
24 Secretary in his decision to accept our recommendation.

25 MS. MISHKIN: At Tab I of your book, we have

1 reproduced the applicable provisions of 45 CFR 46,
2 and it simply says if this Board feels that the risk
3 is justified by the sum of the benefit to the subject,
4 which is not in question here, or the importance of the
5 knowledge to be gained.

6 MR. CONWAY: And you are referring us to
7 46.211?

8 MS. MISHKIN: Yes.

9 MR. HALPERN: In fact, it doesn't say that
10 the Board should be guided by the risk benefit analysis,
11 it says that the Board should consider whether waiver,
12 which is what we are talking about, is appropriate in
13 this particular instance. Then it says in making the
14 decision the Secretary will consider whether the risks
15 to the subject are so outweighed by the sum of the
16 benefit to the subject and the importance of the knowledge
17 to be gained as to warrant such a modification or a waiver.

18 MR. GAITHER: But it seems to me that it is
19 important for us to note that .211 states that the Secretary
20 can only waive, unlike the other situation before us, with
21 our approval. So that is the question, whether we would
22 approve a modification or waiver of these regulations to
23 permit this research to continue. And basically there are
24 no specific standards imposed upon us. Is that correct?

25 MS. MISHKIN: That is correct.

1 MR. GAITHER: And what you are giving us
2 is the background, now, for these particular regulations,
3 why the Commission suggested that a body such as ours be
4 involved in the deliberations.

5 MS. MISHKIN: And what the Commission coped
6 with when it discussed the problem of research on fetuses
7 to be aborted, and what standard might be appropriate in
8 considering acceptable risk to fetuses about to be aborted,
9 or whose mothers intend to go through with an abortion.
10 It was a very, very difficult problem for the Commission.
11 Any of you who followed the Commission's activities in
12 this area will know they spent a long time on this, and
13 this was one of the areas in which there was not a full
14 consensus among the Commission members.

15 First of all, let me say that this particular
16 application underwent six reviews prior to coming before
17 this Board. That included reviews by the appropriate IRB
18 at the Drew Center; a review by the community board which
19 is a separate community representative board at the Drew
20 Center; review by the appropriate study section at HEW;
21 review by a site visit team from that study section,
22 members ad hoc; review by the National Advisory Council
23 under whose auspices this particular application came --
24 if that is not six I have left one out, but they are all
25 listed there anyway.

1 The staff of the Board then shipped the whole
2 thing out to two additional people for independent reviews,
3 and those have been mailed to you and are reproduced in
4 your book. Dr. Haig Kazazian at Johns Hopkins University
5 Hospital, and Dr. Dwayne Alexander at the National
6 Institute of Child Health and Human Development.

7 Dr. Kazazian has done fetoscopy himself; he
8 no longer does so. Dr. Alexander has not done fetoscopy.
9 He was a member of the staff of the Commission and he ran
10 the amniocentesis collaborative research program, and is
11 very familiar with questions of prenatal diagnosis, and
12 the risks of various procedures associated with prenatal
13 diagnosis.

14 All of the review boards and the individual
15 reviewers have recommended approval of this research
16 application based on the importance of being able to
17 diagnose prenatally certain conditions which, up until
18 now, have not been diagnosable through amniocentesis.
19 Fetoscopy has been the only possible way to diagnose
20 sickle cell disease, among other diseases, in fetuses
21 prior to birth.

22 Now, there was one problem that we had in
23 reviewing this particular proposal, and that was it was not
24 entirely clear from the proposal, because we had conflicting
25 statements -- the site visit review said one thing, and the

1 proposal said something else -- as to whether or not
2 the investigators planned to delay abortion for more
3 than 24 hours after fetoscopy. The point of the
4 research is to do the fetoscopy, monitor the women after
5 fetoscopy, and look for complications as a result of
6 fetoscopy. Complications include possible infection
7 of the woman, possible bleeding of the fetus, and
8 subsequent abortion prior to the induced abortion which
9 is anticipated.

10 What is present in the research application is
11 a plan to perform the fetoscopy, monitor the woman for
12 24 hours, and then go ahead with the abortion as planned.
13 What is present in the site visit's review, however, is
14 a plan to continue monitoring, if they are satisfied that
15 a 24 hour delay poses no risk, to increase that delay
16 step by step, until they reach, finally, a two-week
17 delay during which they would monitor the woman for two
18 weeks following fetoscopy before going ahead with the
19 abortion.

20 I called the principal investigator to find
21 out what in fact was their intent, and he said that this
22 does seem -- that it is his intent to go incrementally if
23 they are satisfied at any one stage as to the risk to
24 mother and fetus, to go incrementally up to a two-week
25 delay. This raises a very important concern that their

1 subject population is women who are in their 16th to
2 20th week of gestation. A two-week delay in a woman who
3 presents at 20 weeks would take that woman past 20 weeks
4 gestation before her abortion, and this then would run
5 into the possibility of a viable fetus being aborted,
6 or of having a viable product of the abortion. This is
7 one problem that the Commission was very much concerned
8 about. That is why the staff recommendation on this
9 particular proposal includes the provision that no
10 abortion be postponed for reasons of this research that
11 would then have to be performed after the 20th week of
12 gestation. This is compatible with the regulations that
13 no timing or methodological change be introduced for
14 reasons of research that would add additional risk to
15 the mother or the fetus. And surely the risk of having
16 a viable product of abortion is an additional risk.

17 The current regulations note that viability
18 is possible at 20 weeks, and that is why the staff
19 recommends that no procedure be delayed beyond the 20th
20 gestational week for purposes of this research.

21 Now, the whole thing was complicated by an
22 article in the Washington Post that appeared on Saturday,
23 November 4th, while we were in the process of preparing this
24 memorandum of recommendations to you. That article
25 indicates that a physician at the University of California

1 at San Francisco believes he has developed a procedure
2 to diagnose sickle cell disease through amniocentesis,
3 thus avoiding the necessity to go to fetoscopy in order
4 to diagnose sickle cell disease. These findings are
5 supposed to have been in the most recent issue of the
6 journal Lancet. We were unable to find whatever issue
7 that was. It must not be out yet. If it is out it is
8 not available in any of the libraries we had access to
9 in Washington.

10 We tried very hard to call the investigator at
11 the University of California at San Francisco, and we
12 were unable to reach him. We do, however, have some
13 further information on that. Dr. Alexander was able to
14 reach Dr. Michael Kaback, who is Assistant Professor of
15 Pediatrics and Medical Genetics at the University of
16 California at Los Angeles, and who is familiar with the
17 work of the investigators at San Francisco.

18 What I am going to give you now is my under-
19 standing of Dr. Alexander's understanding of Dr. Kaback's
20 understanding of what they are doing in San Francisco.
21 If all of that is clear, you will know how far we are
22 removed from firsthand information. But nevertheless I
23 will give it to you, because I think it is important.

24 It goes as follows: 85 percent of sickle cell
25 carriers have an extra large piece of DNA on the gene that

1 has the sickle cell trait. Now, this condition of having
2 the extra large clump of DNA material is calling poly-
3 morphism. Thus, it is possible assuming the test works
4 as reported, to diagnose approximately two-thirds or more
5 of sickle cell babies through amniocentesis and looking
6 for this enlarged DNA clump.

7 Now, let me break that out for you. What they
8 have to do if they identify both parents as carriers,
9 they then look for this polymorphism, in other words, the
10 extra clump of DNA in the parents. If those parents have
11 that extra clump of DNA, that is, if they fall within
12 the 85 percent of sickle cell carriers who have that
13 polymorphism, then it is possible to perform amniocentesis --
14 yes?

15 DR. FOSTER: I should clarify something at
16 this point. You are using a medical term, and I am not
17 sure -- you are saying "carriers." Do you really mean
18 carriers, or do you mean sickle cell disease?

19 MS. MISHKIN: No, I mean carriers.

20 DR. FOSTER: That is not a person with sickle
21 cell disease.

22 MS. MISHKIN: That is correct.

23 DR. FOSTER: Okay.

24 MS. MISHKIN: But again, this is my understanding
25 from Dr. Alexander through Dr. Kaback. This is the best we

1 can give you.

2 DR. FOSTER: Go ahead and let me hear you out,
3 then.

4 MS. MISHKIN: My understanding is this is
5 carriers.

6 DR. FOSTER: Okay, go ahead. I will hear you
7 out.

8 MS. MISHKIN: So if both parents are carriers,
9 either with or without the disease --

10 DR. FOSTER: It is the previous I am concerned
11 about.

12 MS. MISHKIN: Right. If both parents are
13 carriers and have this trait of the polymorphism, and it
14 is possible to be a -- 15 percent of carriers do not show
15 this trait. If they are among the 85 percent of carriers
16 who show this trait, then through amniocentesis they can
17 look for the segments in the fetus. If the fetus has
18 two segments showing the polymorphi, that is a child with
19 sickle cell disease. If the fetus has one segment that
20 child is a carrier. If the fetus has no segments, that
21 is a normal child.

22 Now, I went back and asked again whether that
23 child could be one of the 15 percent that do not show the
24 polymorphism, and the answer was that Dr. Alexander believes
25 not. The answer is if they have done this whole procedure

1 and the child does not carry that polymorphism, that
2 child is not a carrier or a diseased child with respect
3 to sickle cell.

4 Now, if either parent is not polymorphic, does
5 not have this additional clump, is within that 15 percent
6 of parents who are carriers but do not have this change
7 of the DNA, then it is impossible to diagnose the sickle
8 cell disease in the fetus through this amniocentesis
9 procedure, and that would mean that for those parents
10 the only way to diagnose the sickle cell disease in the
11 fetus would be through fetoscopy, which brings us back
12 to the Drew application.

13 Now, what all this means is there has been a
14 shift in the risk benefit analysis that all of the
15 reviewers performed on the Drew application, because
16 when they looked at the Drew application fetoscopy was
17 the only method for diagnosing sickle cell disease
18 prenatally. Now it appears, although we do not have the
19 documentation to give you, that it is possible in 85
20 percent of sickle cell carrier parents to diagnose the
21 presence or absence of sickle cell disease by amniocentesis
22 which is agreed to be a safer procedure than fetoscopy.

23 So your job is somewhat more difficult, but I
24 don't think it is impossible. One is left with the question
25 of whether it is appropriate for the investigators at Drew

1 to do the research, to assess the risks of fetoscopy
2 as a tool for prenatal diagnosis of sickle cell disease
3 in their subject population, and the reason I am
4 emphasizing this is that if it were the case that all
5 sickle cell disease could be diagnosed prenatally
6 through any other method, amniocentesis or any other,
7 then the board would have to face the question of whether
8 the subject population which the Drew Medical Center
9 serves is an appropriate population to develop the
10 methods of fetoscopy. Fetoscopy is useful for prenatal
11 diagnosis of other disorders, but not disorders which
12 are disorders of the black population, which is the
13 subject population which the Drew Center serves. So
14 then one would have to question whether the black popula-
15 tion is an appropriate subject population for developing
16 fetoscopy if they are not going to be the population which
17 will benefit from the development of that diagnostic tool.

18 In other words, one wants to have the population
19 that will benefit from the research, participate as subjects
20 and accept the risks of that research if possible.

21 MR. HALPERN: Just related to this, are we not
22 also in the position of asking whether or not we should
23 remand this issue to Drew and the community that Drew serves
24 for them to make the risk benefit analysis again, in light
25 of this new data?

MS. MISHKIN: Absolutely. That is a very viable option, and it certainly has a great deal of merit. I think one might reasonably ask for a total reassessment, by that IRB or by any number of other people, even including the study section that reviewed it, in the light of the new information. But I think we would want to get the actual information documented before we remanded it.

I don't know if this has been clear, and if you want more elucidation of the Commission's intent or of my understanding of the regulations, I would be glad to go forward with more.

MR. GAITHER: Hank, would you say something about the science of this?

DR. FOSTER: Yes, I am going to say something about the science and the sociology, if you will indulge me.

I heard of Kan's work just a few days ago, and I knew clearly like a shock wave that it was inevitably going to affect what we have to do, or what we recommended. But I want to say some things as we go through all of this deliberation, which may take me a few moments, but I really want to run through these steps that I have written down here. Some food for thought.

I just have one question. The genetic polymorphism that is necessary in the parents -- is it required in both

1 parents? In other words, you know, both parents may be
2 carriers, but only one may show the polymorphism and the
3 other may not. Is it a requirement for both parents?
4 Do you recall?

5 MS. MISHKIN: My understanding is that it is
6 not going to be a reliable test through amniocentesis
7 unless both parents show the polymorphism.

8 DR. FOSTER: Now, the next question I have --
9 and then I will make my comments -- now, I read the research
10 proposal, and I missed this delay. That bothers me a
11 little bit, first. I have got to really clear that in my
12 mind.

13 I have done a lot of amniocentesis and therapeutic
14 abortions, probably near 700. As I read the protocol,
15 the patient would be brought in the hospital, and that would
16 be a 24 hour delay, which was not inordinate, based on the
17 information that we have. It is very reasonable. But the
18 clinical part, a catheter is introduced into the amniotic
19 cavity, and that is the time when the fetus is studied,
20 the blood vessels, and the sample is taken. Then the
21 fetoscope is withdrawn, but the catheter is left in place,
22 which is quite acceptable. In fact, this is one of the
23 techniques we use for continuous prostaglandin infusion.

24 But there gets to be a real question with regard
25 to infection after a 24 hour period with an indwelling

1 connection to the outside. I missed the entire reviewer's
2 section about some extension beyond 24 hours, and if there
3 is an extension of observation beyond 24 hours, does it
4 involve the catheter being in place? This would be
5 critical in my mind.

6 DR. MCCARTHY: Yes, it certainly does.

7 DR. FOSTER: I think that is something that
8 really needs to be addressed in terms of the details of
9 the research.

10 MS. MISHKIN: I am frankly bothered by anything
11 coming as far as to the Ethics Advisory Board through all
12 those reviews without this being quite clear. It was in
13 the site visit review, and it was because of the
14 ambiguity that I called the principal investigator.

15 Now, Dwayne Alexander was working on the
16 application in front of him, and so he really addressed
17 only the 24 hour delay. But because of the ambiguities
18 I did call, and the investigators do intend to go to two
19 weeks. I think it might not be inappropriate for the
20 Board to make some strong statement about wanting to be
21 clear on what the procedures proposed are here.

22 MR. LAZARUS: I wasn't clear either on the
23 consent procedures.

24 DR. FOSTER: That doesn't come through. But the
25 one thing I do want to say, and then I will get to the other

1 points I want to make about what all of the implications
2 of fetoscopy are as I see it. I do think a longer obser-
3 vational period is an acceptable research modality
4 provided safeguards are there. We have already talked
5 about extending beyond the 20 weeks. That can be
6 controlled for fairly well with ultrasonography for
7 establishing fetal age, and a few other things. But I
8 think you might want to consider the observation period
9 without the catheter in place, because repeated amniocen-
10 tesis has proven to be relatively safe in terms -- the
11 danger is in leaving a conduit for bacterial migration.

12 So what I am really saying is I can see the
13 investigators making a justification for an observation
14 period of longer than 24 hours, but I find it a little
15 difficult at this point to see that justification with an
16 indwelling catheter in beyond this point.

17 And now I think the things we need to be
18 concerned about irrespective of what we ultimately
19 recommend in terms of going back or whatever. There was
20 very, very strong community support for this proposal.
21 Anyone who read the type of support, and the rather
22 incisive and critical questions, I thought, that the
23 community asked in regard to many of the social and medi-
24 cal implications. I think it is keen that we remember that
25 there have been so many charges of disregard for ethic

makeups of our research, genocide and all the issues, if this is an indigenous decision by a community, I think we need to give that great respect, because it is a justification for us to say this is a decision that you made. If we say to the community no, we shouldn't do this, the community in a sense has a right to say you are willing to impose certain things on us externally that we feel are an abridgment, but here when we see something clearly directing us, you deny it. So that is something that has to be considered strongly in terms of sociology.

I think another thing that is very important from what I know about this -- Drew has been one of the few centers that had federal support prior to the moratorium in 1973, I believe, involving aborted fetal subjects on the research, has gone through the steps of animal experiments. They have used the ovine model very well with sheep and I think we certainly have to give that some accord. They have gone through all the steps prior to using humans.

Now, the implications of Kan's work I don't need to go over. You have made that very clear. So I will move on to my fourth point.

Mitch Spellman makes this point a lot, and it is a good point. There is a basis for basic research with regard to doing fetoscopy, irrespective of Kan's work.

1 There is a basic need. Now, I am going to go slowly and
2 really try to make this point.

3 Kan's approach right now is the acceptable
4 one. It is a reaction. It is an after-the-fact approach.
5 It gives us an option simply to abort a defective pregnancy.
6 Basic research will afford us a much broader and brighter
7 horizon, might I add. And that is the possibility of
8 diagnosing the defective fetus and then preventing the
9 development of sickle cell disease in that fetus.

10 Now, I will try and paint a picture. In utero,
11 for all of us normally, there is a different set of protein
12 in two of the chains of our hemoglobin in early fetal life.
13 The normal hemoglobin molecule has four chains, two upper
14 alpha chains, which are proteins in a set sequence, and
15 two lower, somewhat larger, beta chains in a set sequence.

16 The only difference between one who has sickle
17 cell hemoglobin and a normal person is out of 184 amino
18 acids in one of those chains, and that is in set sequence,
19 there is an exchange of valine for glutamic acid, in the
20 sixth position from the end. One of 184 chains. That is
21 the only difference. But because of this change in the
22 chain, certain physical and chemical defects, as you may
23 call them, are imparted into the hemoglobin. It makes it
24 less stable. Its ability to hold and release oxygen is
25 affected. The stability of the red cell membrane is affected.

1 It changes its pattern of migration in an electrical
2 field. This is how we do our hemoglobin electrophoresis.

3 Back to in utero, none of us has these beta
4 chains when we are developing. We have another chain
5 called a gamma chain, and that gamma chain is provided
6 for through a mechanism which we yet do not fully under-
7 stand, and this is where our basic research should
8 continue. There are repressor genes and activator genes.
9 Rarely, through chance, some people who were destined to
0 have sickle cell disease never develop it. But they
1 continue to make the gamma chains which make fetal
2 hemoglobin throughout life, even in the postnatal period.
3 And these people have absolutely no trouble. That is
4 the ideal situation for the sickle cell person, is to
5 be able to find that mechanism that will prevent the
6 turning on of the activator genes from going from gamma
7 chains to defective beta chains. So there is a clear
8 need for this kind of research in spite of the work by
9 Kahn and his group.

20 It is at this basic step where not only will we
21 be able to diagnose the child destined to have sickle cell
22 disease, but indeed, to prevent it. So I think that alone
23 justifies continuation of this basic research approach.

24 Lastly -- well, that includes -- I wanted to say
25 something about the basic science of the molecule. So there

1 is a real horizon out there that has to be untapped,
2 and that is the ability to diagnose the abnormal hemoglobin,
3 but not by default to get rid of the fetus. That is the
4 thinking that if you want to prevent forest fires, cut
5 down all the trees. I want to take a different approach.
6 I want to see can we afford this fetus that was destined
7 to be one thing, that our basic research will continue to
8 allow us to do something about it.

9 So I just wanted these thoughts to be in the
10 back of our minds, particularly in light of Kan's recent
11 work as to the obsolescence of this continued basic research
12 approach.

13 MS. MISHKIN: Is the research to develop that
14 therapy now ready for pursuing through fetoscopy now, or
15 does one have to wait for more development in animals and
16 other methods before you actually go to fetuses in utero?

17 DR. FOSTER: I think I understand your question,
18 Barbara. Are you saying is our technique to such a point
19 that we can go ahead with just the technique of amnioscopy?

20 MS. MISHKIN: No, I am asking whether one would
21 endorse the Drew application today on the basis of the
22 need to develop the prenatal therapy, or are we not yet
23 there with respect to the therapy, with the animal work
24 and so forth?

25 DR. FOSTER: I think the animal work has been done

I think that has been satisfied.

MS. MISHKIN: There is one other thing I forgot to mention on the risk benefit analysis, and that is the concern about using fetuses to be aborted. There is not much direction in the HEW regulations on this matter, but the Commission came down to a guideline that may or may not be useful for you, but I think it has some merit. That is, they felt that it was ethically acceptable to perform procedures on a fetus to be aborted if one would feel ready to perform those procedures on a fetus intended to go to term.

In other words, if one had done all of the animal work, including primate work, which they have done in this case, and if they were unable to do it on fetuses to be aborted to further assess the risk, if they would be willing then to go forward therapeutically with it on fetuses going to term. That condition has been met in this case, because there are apparently several groups who are performing amniocentesis on fetuses intended to go to term.

FATHER MCCORMICK: Fetoscopy, you mean?

MS. MISHKIN: In fetoscopy, yes.

MR. GAITHER: In somebody's judgment.

MS. MISHKIN: I mean the condition of its being performed on fetuses going to term has been met, and the

1 question is whether or not that meets your feeling of
2 acceptability for performing the procedure on fetuses
3 to be aborted. But this procedure is being performed
4 on fetuses going to term.

5 MR. GAITHER: Can I just ask for some clari-
6 fication, first? One, what are the purposes of this
7 particular protocol? Is it particularly experience and
8 safety, or does it get into the basic research questions
9 that Dr. Foster was mentioning?

10 MS. MISHKIN: My understanding of the protocol
11 is that it is to assess the risks of infection, of bleeding,
12 of premature abortion, and so forth, that are attendant
13 with fetoscopy. Now, Dr. Alexander also sees an additional
14 benefit, which is developing the competence of the
15 investigators to perform the procedure prior to trying
16 to do it on fetuses going to term. That also is included.
17 That is not the primary purpose of the application as
18 written. The application is to determine with somewhat
19 better certainty the risks involved to mother and fetus.

20 DR. FOSTER: And a part of that is improving
21 the technique. It is not basically designed to go into a
22 specific basic research question. As I understand it, it
23 is what Barbara says, to assess the safety and to improve
24 the technique. That is going to evolve from that. And
25 that is one of the reasons I feel they are asking for a

1 somewhat longer observation period, because if you do
2 the procedure and then proceed directly to the termination,
3 you would deny some of the longer term effects, delayed
4 bleeding and the like.

5 MR. GAITHER: Two further points of clarification,
6 and then I will open the discussion. The work that
7 is presently going on at Yale and the University of
8 California, has that been subjected to these regulations
9 and approved, the distinction being that it was therapeutic,
10 that is, regarded to be of benefit to a possible
11 child, and that is why it is different, or not? Do you
12 know what the status is?

13 MS. MISHKIN: I am not entirely clear. My
14 understanding is probably not with respect to the Yale
15 group, because I do not think that is funded by HEW. I
16 believe that is the information we got from Jerry
17 Mahoney just recently. But as you know, the regulations
18 are somewhat ambiguous with respect to whether or not
19 research conducted at an institution but not funded by
20 HEW must be reviewed by the IRB, and also subject to the
21 same review standards. So it is a somewhat unclear point
22 with respect to the Yale group.

23 DR. MCCARTHY: It is perfectly clear that the
24 Yale group felt obliged under Section 474(b) of the Public
25 Health Service Act to have Dr. Mahoney's research involving

1 fetoscopy reviewed by the IRB. They also made the
2 interpretation, which I think is a reasonable one,
3 although not the only possible one -- they made the
4 interpretation that they need not review according to
5 HEW standards. And in fact, there is some question in
6 my mind as to whether Dr. Mahoney's work would have been
7 acceptable under HEW standards, because I think they
8 regard this as more than minimal risk -- not a great deal
9 more, but somewhat more than minimal risk. Therefore,
10 if they had followed our standards, his work would have
11 had to come to the Board. Because it is not funded by
12 HEW, they decided they could make that decision and they
13 have made it and are carrying out that work.

14 MR. GAITHER: There would not have been a
15 distinction based on their work being therapeutic and
16 this work not, because of the abortion?

17 DR. MCCARTHY: No. As I understand it,
18 initially they -- and I am not quite sure at what phase
19 they are in. They have planned a series of steps, the
20 later stages of which they intend to be therapeutic. As
21 I understand it, they are still in the diagnostic phase
22 of those steps, but I believe their approval goes all the
23 way to -- assuming all the other stages are carried out
24 with no untoward events -- they intend to go all the way
25 to applying fetoscopy to therapeutic interventions to try

to assist fetuses that are in one way or another abnormal.

MR. GAITHER: Mr. Lazarus?

MR. LAZARUS: I think one of the key issues in this request is the problem of risk and how it is presented to the patient. Barbara says in her note that the risk presented by research cannot be characterized as minimal. Rather, it should be considered undetermined. And yet, the patient consent states that "I have been advised that these risks are minimal to me and to my fetus."

I think that one of the items that must be clarified is the whole consent procedure, and the nature of the risk must be spelled out a lot more consistently than they are spelled out under the present consent procedure that has been presented by Drew.

MS. MISHKIN: I think one of the problems is that minimal risk, as I pointed out, is not defined in the HEW regulations, and in the Commission's report and its deliberations, that was a problem in two areas. At one point they indicate -- and they indicate more strongly in subsequent reports -- that risk which has not yet been determined should not be classified as minimal, but should remain under the categorization of undetermined.

On the other hand, there were some Commissioners, although not all of them -- there was a difference of opinion on this point, as to whether when you are talking about a

1 fetus to be aborted, one can consider risk of abortion
2 as a minimal risk to that fetus, whereas one would not
3 consider risk of abortion a minimal risk to a fetus
4 intended to go to term. This was one of the very diffi-
5 cult points where there was a lack of consensus among
6 the Commission members.

7 So I think that when the IRB and the various
8 people who reviewed the Drew application determined that
9 it was minimal risk, that was not a clearly unacceptable
10 determination. It was simply their interpretation, given
11 very little guidance from the Department as to how to
12 assess and categorize that risk.

13 MR. LAZARUS: It would seem to me, though, that
14 a patient's consent is very important with the nature of
15 the risk, which is undetermined. It should be very
16 carefully spelled out.

17 MR. GAITHER: Particularly when one is
18 conducting the research for the purpose of finding out
19 how risky the procedure is.

20 MR. LAZARUS: Right.

21 MR. HALPERN: Underlining the illogic of the
22 word "minimal" where you are saying we don't know what it
23 means, well, the problem is it is in our HEW regulations,
24 and if in fact the risk is minimal as the patient is told,
25 it wouldn't be here.

MS. MISHKIN: That is right. It would not be before this Board if the risk were minimal. Then the IRB could have approved the project by themselves, although there is another provision that would need a waiver, so it probably would come here anyway. That is, the regulations currently provide that there be no change in timing or procedure of an abortion for research purposes that would add any additional risk, and that provision does not say "that would add more than minimal risk," but that "would add any additional risk." So it might have had to come here even so.

DR. MCCARTHY: But the determination, the very point that Mr. Lazarus made, was picked up in the Office for Protection from Research Risks, which refused to -- even though it had been reviewed by all of the subsidiary bodies -- refused to go ahead and fund until and unless it had been approved by this Board.

So it is that very point: If you are doing research to assess risk, it does not seem possible then to prejudge the outcome by calling it minimal. It may turn out to be minimal, but there is no justification for the research if you already know it is minimal.

MR. LAZARUS: And you are getting your consents under a false clause.

DR. MCCARTHY Yes, and I think the Office for

1 Protection from Research Risks was correct in making the
2 judgment that it should come before this Board to comply
3 with HEW regs.

4 MR. GAITHER: Yes, Dr. Henderson?

5 DR. HENDERSON: Let me just carry that a little
6 further. One of the important criteria here is that the
7 research is important and justified. I think this is what
8 is indicated. Clearly we have got investigators who are
9 very competent people and they have obviously proceeded
10 step by step in reaching the point they have.

11 I guess there are a couple of thing in my own
12 mind that are rather unclear. There are two centers where
13 the work is being done now, Toronto and New Haven, where
14 the risks now appear to be rather small. I think this
15 is perhaps where the statement is that it is probably a
16 minimal risk, that experienced people following along with
17 two other centers, and doing what I interpret or what I
18 understand is the same procedure that they are doing in
19 New Haven and Toronto.

20 The question I guess I have, then, is is it
21 necessary to fund yet a third center? Should HEW fund a
22 third center to be doing this? What are the advantages?

23 The initial point here, as they say, initially
24 it is limited to an assessment of the safety. I find that
25 fully justified to go -- initially one is doing a study to

1 assess the safety. But then I ask what is the ultimate
2 objective, because we want research which is important
3 and justified. What is it that it is leading to? Obviously
4 there is an objective here.

5 I believe, as I interpret it, that they would
6 hope to be defining sickle cell disease. Now, I think in
7 talking with you earlier, the question is can you identify
8 either the sickle cell trait or sickle cell disease before
9 30 weeks? Can you define it at this period in time?

10 Perhaps we are talking about, as you mentioned
11 earlier, longer term basic research, which requires this
12 technique to be used. Is it enough to say that it is
13 important that we do longer term basic research employing
14 this technique without defining what is that basic long
15 term research, and are we at the point now to approve of
16 this sort of application which is based on safety, for some
17 sort of ill-defined subsequent future, when in fact we
18 are supposed to be judging this that the research is
19 important and justified.

20 Now, it is obvious that there are a lot of
21 very good people who have looked at this, and I am asking
22 the questions, I would say, out of ignorance, because I
23 found some contradictions here which I am having trouble
24 with.

25 FATHER MCCARTHY: Do you want to respond to

1 that, because I have got a different point I want to raise.

2 DR. FOSTER: Well, yes. I tried to make some
3 of them and I will try again. I think there are quite
4 a number of justifications, Don, for continuing. One
5 of the biggest reasons -- I think the assumption is not
6 completely correct that this work is being done at the
7 other centers. I don't think there is anywhere the
8 proportionate interest in sickle cell disease at either
9 other center, nor is there the particular population
10 base in either other center to be able to address this
11 effectively.

12 Even if Kan's work proves to be what it is
13 purported to be, based on what Ms. Mishkin has said, we
14 are still left with 15 percent of a large population that
15 is at great need, as you are probably aware. About eight
16 percent of the blacks in this country harbor the sickle
17 cell trait, and that is 2.5 million people, and 15 percent
18 of that is a large part of the population.

19 So I think there is still in our current state
20 of the art to continue to try and be able to diagnose
21 sickle hemoglobinopathies prior to the 30th week. I think
22 there may be ways that we can do it. As yet we can't do
23 it very reliably.

24 So I think the justification for continuing
25 this work is clearly there. The justification may not be

1 as strong as it was, but I certainly think it is within
2 the realm of acceptability. This is what I personally
3 feel.

4 Let me say one other question while I have
5 the microphone. Let me address one other question
6 regarding therapy versus research. I have not seen the
7 research proposals that John Hobbins had at Yale, or
8 what Kan has done at USC. But I do know that a lot of
9 their fetoscopy work was therapeutic. The work on
10 thalassemia was clearly therapeutic. It was done for
11 the same reasons that we do amniocentesis, to decide
12 whether or not the pregnancy should continue, and to
13 provide a therapeutic abortion. In fact, I know much
14 of that.

15 Hobbins' most recent article, which I believe
16 was December of last year where he had, as I recall,
17 about six or seven patients with sickle cell disease
18 which he was working with. These were all therapeutic.
19 He had tried to make a determination as to what type of
20 hemoglobinopathy, whether it would be homozygous or
21 heterozygous around the 22nd week, and the results were
22 just inconclusive. His conclusion at the end of the article
23 was that at this point we still can't do it. But that was
24 clearly done to be therapeutic. Had he felt that he could
25 have made the determination, he would have offered therapeutic

1 abortion. So I do know that some of the work has been
2 therapeutic.

3 DR. MCCARTHY: That is correct. I should
4 amend what I said. I think what Mahoney is doing is
5 now tending to move into the preventive therapy and not --
6 so I would like to amend what I said before about
7 therapy, because it was clearly for the purpose of
8 giving parents the option of a therapeutic abortion.
9 But now they hope to move into preventive therapy, which
10 is the sense in which I was using "therapeutic."

11 MR. GAITHER: Is there an answer to Dr. Henderson's
12 question, though? Do we know whether this technique will
13 enable the researcher to determine the presence of the
14 sickle cell disease?

15 DR. FOSTER: We never know that until we do
16 the research. I mean, no, I don't think we know it
17 beforehand.

18 MR. GAITHER: I think that is kind of a funda-
19 mental point here, because implicit in all of these
20 papers, it seems to me, is precisely that, that this
21 technique will enable the discovery of whether or not the
22 disease is present. The question is whether it can be
23 safely done. Now, if that is wrong, my whole reading of
24 all of these papers is very much mistaken. I think it is
25 a very fundamental point.

1 Either we are dealing with something that we
2 know can help, and the question is whether it is safe, or
3 we are dealing with something that we don't know much
4 about.

5 DR. HENDERSON: I am puzzled by your statement
6 that the sickle cell trait is not identifiable before the
7 30th week. This is what is concerning me at the moment.
8 And if it isn't identifiable before the 30th week, because
9 you do have fetal hemoglobin present, I am not quite sure
10 where this technique leads. I think this is information
11 which we do have a reasonable body of knowledge on, do we
12 not?

13 DR. FOSTER: I don't know. The only thing that
14 I do know is that the struggle has been to try and be
15 able to diagnose sickle cell -- homozygous sickle cell
16 disease at a point at which therapeutic abortion could be
17 offered. Right now we don't have that capability, and it
18 was my understanding that one of the thrusts of this
19 research proposal was to help to try and find that
20 capability.

21 I would certainly think that this is an issue
22 that again could be raised with the team, the basic research
23 team who conducted the site visit. I think that these might
24 be some issues that Jim and the staff might wish to bring up.

25 MR. HALPERN: Dr. Henderson, it might be helpful

1 if you were to point Dr. Foster to the passage you were
2 referring to in our materials with respect to this precise
3 issue, as to what extent does the primary researcher here
4 feel that we are ready to use fetoscopy for genetic
5 diagnosis. My reading is that he feels that we are not
6 ready to undertake that.

7 DR. HENDERSON: I gather that this is what he
8 was looking to investigate.

9 DR. FOSTER: Where are you reading from?

10 MR. HALPERN: Page 3, Tab H.

11 MR. LAZARUS: A letter to Arthur Percy from the
12 principal investigator. A letter from Ezra Davidson to
13 Percy. It is at page 3 under item five. It is the second
14 paragraph under item five.

15 DR. HENDERSON: I have had trouble identifying
16 specifically what is the outcome above and beyond an
17 assessment of safety, which I think would not to me be
18 enough of a justification to go ahead with it. I think
19 we are looking for the further outcome, which is the
20 diagnosis of the sickle cell disease, and this is where
21 I am having a little bit of trouble.

22 MR. HALPERN: My point is that the principal
23 investigator himself, the way I read that paragraph, has
24 himself pointedly not addressed the question of whether
25 this procedure has merit as a tool for investigating genetic

1 disease. That is the way I read that.

2 DR. HENDERSON: That is the way I read it, too.

3 I assumed I was just missing something.

4 MR. GAITHER: Dr. Hamburg?

5 DR. HAMBURG: In principle, there is simply no
6 question about that at all. I mean, there is zero uncer-
7 tainty as to whether having the fetal blood available would
8 be useful in analyzing the biochemistry of this disorder.
9 The hemoglobin that is abnormal is in the blood of the
10 fetus, and if you can get the blood of the fetus the chance
11 of applying the most advanced techniques to understand the
12 nature of the disorder is, I would say, much greater than
13 anything otherwise conceivable. This in the face of the
14 fact that you can use squamous cells from the skin for
15 some things, and you can use fibroblasts for some things.
16 But by and large, having the blood available if you can
17 safely get it, it seems to me, offers opportunities and
18 analytical capabilities an order of magnitude greater than
19 anything known to me. So I don't think that is an issue.

20 You may ask can you do it now, and the answer
21 is apparently no -- that is, the early diagnosis. But if
22 you are going to get there this is clearly the royal road.

23 Therefore, the issue to me is much more the
24 safety than the potentiality for analyzing this disorder
25 and a whole bunch of other disorders as well.

200
202

1 Now, there is another question, and Hank,
2 I am sure you have a lot to clarify this, but the new
3 work -- the question about the new work in San Francisco
4 and what bearing that has on it. First of all, the other
5 centers that are active, as I understand it, have concen-
6 trated on thalassemia, they have concentrated on the
7 hemophilia. This is, I believe, the principal center
8 concerned with sickle cell disease, and it serves a
9 community in which sickle cell disease and the trait are
10 really prevalent and it is highly appropriate, therefore,
11 to study it in that community. The community wants to
12 learn more about the disease. They carry the main burden
13 of it in the country.

14 Now, the new work may say that there are
15 alternatives which can do some of this. Here we are in
16 an awkward position on two or three counts. One, we don't
17 have firsthand -- although a valiant effort has been made
18 to get it -- just what their findings are. But even if
19 we knew their findings, I wouldn't be terribly impressed.
20 I mean, in the absence of replication there are so many
21 ways that even good investigators can make mistakes. The
22 history of science is so replete with sort of loose
23 assertions in the first go-round, even with the most careful
24 work, and particularly when it comes to human investigation

25 So we need to know what they found, and we need

1 somebody else to replicate it before I would be satisfied
2 that 15 percent was accurate.

3 Now, as I think you lawyers say, arguendo, if
4 15 percent were to be replicated, then we would have
5 another decision to make. Is that enough of a problem
6 to go ahead and pursue the matter? Also, it is more than
7 the 15 percent question. It is also the question of how
8 much analytical power is there from the techniques used
9 by the investigators at the University of California as
10 compared with the analytical power made possible by
11 having the fetal blood.

12 If you made the extreme assumption, and said
13 well, most of the problem of investigating this disease
14 was taken care of by the new technique, and you don't
15 need fetal blood -- it would help, it would be nice, but
16 you can gain so much in the next few years by simply
17 amniocentesis, and you therefore say well, sickle cell
18 is therefore not the issue.

19 Then the question would become for this group
20 is there improvement in the technique -- is this to be
21 methodological research, to improve the technique of
22 fetoscopy in order to get the safety to the point at
23 which it could be useful for all sorts of other things
24 beyond hemoglobinopathies, immune system disorders, for
25 example. Then it is a somewhat different kind of

1 justification, but they still would be in the ballgame,
2 I would think, in view of the fact that they have already
3 done a lot of the background work in nonhuman species,
4 and have some human experience.

5 That would, however, leave us with the question,
6 is this the appropriate community. Do you need to go back
7 to the community and say to them now it is not justified
8 in terms of a disease which is highly prevalent in this
9 community, but it is justified on some other grounds. Do
10 you still want to back it?

11 DR. FOSTER: We have made a presumption -- I
12 have heard a presumption, and I am a little bit confused.
13 As I look at Ezra's letter -- Dr. Davidson's letter of
14 May 10th to his own committee, he makes a statement to
15 me that is kind of fundamental. We have assumed -- I have
16 heard two or three times today -- that the safety of the
17 technique has already been evaluated and established.
18 That is what I have heard two or three times. Did I hear
19 that?

20 MS. MISHKIN: Of which technique, fetoscopy or
21 amniocentesis? That is the point of the research, and that
22 is why we prefer to call it undetermined rather than
23 established as minimal.

24 DR. FOSTER: Well, given that --

25 DR. HENDERSON: It has been done twice.

1 DR. FOSTER: That is -- hear what I am saying,
2 then.

3 DR. HENDERSON: Talking about the experience
4 of two centers is not a large number, I agree.

5 DR. FOSTER: And I heard very clearly Dr. Henderson
6 state that at two centers they have done this and it has
7 been established. Do we need to do it again? Yet the
8 principal investigator's primary thrust is that the safety
9 has not been fully and completely evaluated. That is one
10 of the main reasons he puts forth. And of course, to
11 what degree do we make that determination, or the investi-
12 gating team who looked at it to me gets to be important.

13 DR. HAMBURG: May I put that slightly differently?
14 I think it is a question of finding ways to further reduce
15 the risk of the technique, which is, after all, still a
16 problem with amniocentesis.

17 DR. FOSTER: Even the figure they gave was very
18 high 2.4 percent.

19 DR. MCCARTHY: And we don't have all the infor-
20 mation from Yale, and very little from Toronto. But much
21 of the Yale work was observational, so that some of the
22 additional steps that are contemplated in this research
23 have not been evaluated extensively, at least, at Yale.
24 That is to say they used the scope and they took pictures
25 of the fetus in order to determine whether certain kinds of

1 observational defects, or defects that could be discerned
2 by observation could be identified. They were able to
3 look at certain positions of the hands and the fingers of
4 the fetus, and so on, and make some determinations as to
5 the likelihood of thalassemia. But the taking of fetal
6 blood and the question of the risk associated with fetal
7 bleeding, and so on, has not been carefully determined
8 by Yale.

9 So I think there are similarities, but there
10 are also differences that would justify going ahead with
11 this research.

12 MR. LAZARUS: Even on the extended basis,
13 carrying it out for 20 days?

14 DR. MCCARTHY: I think that is a separate
15 question, and at least our staff was not persuaded that
16 we should authorize going ahead with that without a good
17 deal more observation about that point.

18 DR. FOSTER: Just quickly, I just wanted to
19 restate, I was beginning to get a feeling that it was
20 being stated that the risk had been evaluated, you know,
21 it has been done, and for that reason, that should alter
22 greatly our thinking. I just kind of wanted to put that
23 in perspective. I don't know if we can make that judgment.

24 MR. GAITHER: Father McCormick.

25 FATHER MCCORMICK: I am really terribly confused

1 about the factual -- I have got two points I want to
2 make -- the factual problem of the assessment of the
3 risk. I hear the word "undetermined," and "more than
4 minimal." I hear it is being done, and yet therefore it
5 is justifiably being done, or at least that is the
6 connotation. If it is no more than minimal risk in the
7 way it is being done, then it shouldn't be before us.
8 I am confused on that. Why is it here?

9 But I have got a more basic problem I want to
10 raise and point your attention to under number (i) in
11 that 46.211, which is a matter of ethical principle which
12 is going to bother us, and we may as well call attention
13 to it right now. That is the types of cases that ought
14 to come to us. The sentence reads, "In making such
15 decisions, the Secretary will consider whether the risks
16 to the subject are so outweighed by the sum of the
17 benefits to the subject --" now, notice the next word.

18 MR. LAZARUS: Where are you reading?

19 FATHER MCCORMICK: That number we adverted to
20 before, 46.211, under (i).

21 MR. LAZARUS: Okay, 211.

22 FATHER MCCORMICK: Got it?

23 MR. LAZARUS: Yes, right.

24 FATHER MCCORMICK: Okay, about the Secretary will
25 consider.

1 MR. LAZARUS: Right.

2 FATHER MCCORMICK: Then it says, "and the
3 importance of the knowledge to be gained as to warrant
4 such modification and waiver." There are two conditions
5 there, by the word "and," unless I am misreading this. It
6 has got to be of some benefit to the subject, and the
7 importance of the knowledge to be gained. In other words,
8 the supposition of that is that the procedure, experimental
9 or investigative, is going to be of some benefit to the
10 subject.

11 DR. HAMBURG: I wouldn't interpret it that way.
12 It says the sum of benefits. It may be zero plus ten, but
13 it still comes out to ten.

14 FATHER MCCORMICK. Therefore it should be "or?"

15 DR. HAMBURG: No.

16 FATHER MCCORMICK: No, wait a minute. What I
17 have in mind is this. If the only consideration --

18 MR. GAITHER: Dick, hold on.

19 THE REPORTER: I don't know what happened,
20 because everybody talked at once. You will have to watch
21 that.

22 MR. GAITHER: Okay, I am sorry.

23 Father McCormick?

24 FATHER MCCORMICK: The point I was making is
25 this: If a fetus about to be aborted, and that is what we

1 are talking about -- is going to undergo more than minimal
2 risk, in other words, the type of risk we would not allow
3 to be visited upon one going to term, then that case comes
4 to the Secretary to see whether the knowledge outweighs the
5 risk.

6 I want to point out that there are just an awful
7 lot of people who would say that the knowledge to be gained
8 never outweighs the risk, as an ethical principle. In
9 other words, there are people who would challenge the very
10 supposition of bringing this to the Secretary. I would be
11 one of them. And I think we are going to run into that
12 all the way along the line.

13 MS. MISHKIN: There is one point here which you
14 raised, which is the point at which the regulations are
15 slightly at variance with the Commission's recommendations.
16 The Commission foresaw difficulty along these lines, and
17 its recommendation was that projects would come before
18 this Board if there was difficulty in interpreting the
19 regulations. If there was any difficulty in interpretation,
20 and this, I think, might fall well within that category,
21 whether it was disjunctive or conjunctive, and how one
22 were to interpret that.

23 That provision did not really make it clearly
24 into the regulations, but that is a point of history which
25 might help.

1 FATHER MCCORMICK: Or if the danger were minimal
2 or not. Wasn't that one of the interpretative charges?

3 MS. MISHKIN: Yes, questions of defining minimal
4 risk, questions of assessing that, or simply questions of
5 applying the regulations to a particular project at hand.

6 FATHER MCCORMICK: Right.

7 MS. WILLIAMS: I think we should bear in mind
8 that while the risk to the fetus in this case is more than
9 minimal, the chance of harm to the fetus, I think, is very,
10 very minimal indeed, because before the fetus could be
11 said to be harmed, we would have to have a conjunction of
12 two circumstances: number one, that the fetus would be
13 aborted as a result of the procedure, which is certainly
14 apparently less than five percent, a less than five percent
15 chance. Then we would have to have a second circumstance
16 coinciding, which is that the mother has changed her mind
17 about whether she wishes to abort the child. I would think
18 in a well-run protocol, this chance would probably be a
19 less than one percent chance. So mathematically, the chance
20 that the fetus would lose its life is a very minimal
21 chance indeed.

22 MS. MISHKIN: Although that chance increases as
23 the delay between fetoscopy and abortion increases, especially
24 if they develop a therapeutic technique. They may find out
25 that the baby does not seem to be affected by sickle cell,

1 and you are waiting two weeks from that period, and
2 down the foreseeable future the mother might very well
3 change her mind during those two weeks. And then your
4 risk of harm might become realized.

5 MR. HALPERN: I would only say that I think
6 Dick is in really a better position to state this,
7 but I will make the argument for him, that many would
8 quarrel with the assumption that the fetus to be aborted
9 has a diminished moral status from the fetus for whom we
10 have no intent to abort. We can't backstop it. Many
11 would say we cannot backstop what we do to a fetus by
12 saying well, five percent, it is only five percent, and
13 moreover, we plan to abort this fetus tomorrow.

14 MR. GAITHER: I don't think the point was
15 made that there is any difference in the moral status,
16 but rather when one assesses the risk of the procedure,
17 one ought to be realistic about the circumstances in
18 which you are looking at it.

19 MR. HALPERN: Well, I think once we talk about
20 risk, though, I think that -- risk to whom? Even if we are
21 going to talk in terms of risk, I still think the bottom
22 line is whether you are going to -- maybe moral status is
23 too loaded a word. But I think we are talking about moral
24 status.

25 MR. GAITHER: I think you have to separate the

1 two points. I think that Father McCormick has made the
2 point basically saying no risk is tolerable in a very
3 general sense. But when one looks at the risk to a
4 fetus about to be aborted, it seems to me difficult to
5 say that you cannot, in assessing the risk, look at
6 whether or not the fetus is going to be aborted.

7 MR. HALPERN: I understand the Commission
8 recommendations. They flat-out say no, you cannot.

9 MR. GAITHER: I understand what the Commission
10 said about a lot of things, and that was one of them,
11 like saying we can't decide what minimal is, and we will
12 give that to somebody else. I am not sure that that
13 question was really resolved. Otherwise, these regula-
14 tions would not be in existence.

15 DR. HAMBURG: Well, in considering ethical
16 options, if you are going to talk about various positions,
17 including extreme positions, there is a position extant
18 which says, in effect, no abortion without research.
19 That is if you are going to involve the loss of life
20 that is involved in abortion, and the moral distaste of
21 a considerable segment of the population that goes along
22 with that, then the outstanding compensatory feature, or
23 one of the principal compensatory features is that you
24 learn something that can be of benefit to human life in the
25 future. Therefore, any justification for abortion must be

1 linked with research. That is a position which exists.

2 I am not advocating it, but if you are talking about
3 options, that is one at the other end of the spectrum.

4 FATHER MCCORMICK: I think the Commission's
5 recommendations, though, as Phil has said, are clear on
6 this, that just because a fetus is going to be aborted
7 does not diminish the harm that can be done to it, just
8 as I can inflict harm on a condemned or dying person.
9 Therefore, just the fact of coming abortion does not
10 alter one's assessment of what is tolerable in terms of
11 harm. I think that is quite clear in the directives of
12 the Commission.

13 DR. HAMBURG: It is a question of the harm today
14 or the harm tomorrow.

15 DR. HENDERSON: Well, in this case I don't have
16 any trouble with it, because they are applying a diagnostic
17 procedure or a proposed diagnostic procedure, which they
18 are intending, hopefully, to apply broadly to many children
19 whose parents have this trait. So I think they are hoping
20 to apply a safe procedure, as they would if this child were
21 to go on to term.

22 DR. HAMBURG: Point of clarification. Did you
23 say that there would in fact be sequential decision making?
24 That is, if they were going to extend the period incrementally
25 and accumulate enough experience at each step in order to know

1 what complications might arise? They weren't going to
2 go from -- make a 20 day jump all at once, or something
3 of that sort?

4 MS. MISHKIN: No, it was to be incremental, and
5 they would not even make the incremental increases unless
6 they were satisfied with respect to risk, at whatever stage
7 they had previously completed.

8 DR. MCCARTHY: Dick, would you go back over the
9 principle you enunciated? I was first not clear whether
10 you espoused it or whether you merely cited a principle
11 held by some, and secondly, I don't think I understood
12 it regarding the sum of the benefits to the fetus or to
13 the subject, and the knowledge to be gained. And if I
14 heard you correctly, you said that unless there was some
15 benefit to the subject, no amount of knowledge would
16 justify it? Could you go over that again, because I am
17 not clear what it was you were stating.

18 FATHER MCCORMICK: Well, this 46.211 covers
19 cases that come to us, that are beyond the provisions of
20 the Commission. Therefore, the presumption is that there
21 is some difficulty with regard to the assessment of
22 minimal risk, or that there is beyond minimal risk, but
23 there is great knowledge to be gained.

24 Now, realistically, we are talking about non-
25 therapeutic interventions, because the others are not

1 problematic. If there is a risk, but it is going to be
2 therapeutic to the subject, then there is no problem.
3 So I was just pushing that "and" as a small point.

4 If a thing would come to us and there would be
5 no benefit to the fetus, the fetus to be aborted, or what-
6 ever fetus, and the risk were more than minimal, let us
7 say considerable, then there is a strong body -- I think
8 perhaps the strongest body of opinion in the ethical
9 community, would be that no amount of knowledge could
10 justify that.

11 DR. MCCARTHY: More than minimum. I think
12 I understand.

13 FATHER MCCORMICK: Because I had to fight
14 pretty hard with a whole bunch of my colleagues just to
15 get minimal risk accepted, if you remember.

16 DR. MCCARTHY: Yes. Okay, you have clarified
17 that for me. I didn't understand it the first time.

18 MR. GAITHER: Let me make a suggestion here.
19 I think that we are all grappling with some gaps in our
20 understanding, and while I am very reluctant to put this
21 over to the next meeting, I really think that we have to
22 do so. It seems to me that we need clarification in terms
23 of what has happened at the University of California. Does
24 that development have a significant impact on this applica-
25 tion in terms of its importance? I think that is a question

1 that ought to be addressed to the investigators as well
2 as to our two experts. And we do have, I think, enough
3 time for them to examine that question and get back to us
4 before our January meeting.

5 MS. MISHKIN: I might add, it might be interesting
6 to find out, as Dr. Foster suggested, what the community
7 review group would feel about the impact of that, also.

8 MR. GAITHER: Well, I would think unless there
9 is a significant change scientifically, to start the whole
10 process over would not be warranted. So it seems to me
11 it needs to be taken in steps. I would think the investi-
12 gators should make that judgment rather than for us to make
13 it absent some body of scientific knowledge.

14 DR. HAMBURG: One brief addendum, Jim. The
15 paper that they have in the Lancet at the moment, which
16 will be available, I think the investigator should be
17 contacted to see if they have other papers in press. They
18 may well. We should get everything they have.

19 MR. GAITHER: Let me try this, and then come
20 back, and please, everybody chip in what they think we
21 need. The second that I think needs clarification is
22 whether or not we can assume significance of the underlying
23 procedure here, namely that we do know today that the
24 availability of the blood sample will be of tremendous
25 importance to us, even if it may not be able to tell us

31
1 every case of the sickle cell disease. We know that it
2 will get us a lot farther along the road than anything
3 we have today.

4 The question that you raised, Dr. Henderson,
5 are we looking at safety before we know whether the
6 procedure is important, or can we really assume today
7 that indeed the procedure is very important for this and
8 other purposes. What we need to know now is whether we
9 can safely employ it. It seems to me that our experts
10 ought to be able to advise us on that question.

11 MR. LAZARUS: That is the question of whether
12 the procedure is important?

13 MR. GAITHER: Yes, right.

14 And the third is to get an answer for the
15 question raised by Mr. Lazarus, can we really -- well,
16 one should state it diplomatically, I guess. Shouldn't
17 the consent form spell out rather clearly what we know
18 not in terms of a conclusion, as to whether it is
19 minimal or great or something else, but rather whether
20 there is risk to the mother and whether there is risk to
21 the fetus. It seems to me that it certainly needs to be
22 pointed out in the consent form that the purpose is to
23 determine, perhaps within a range, what the real risk is.
24 And if you were in fact reading from the consent form, it
25 seems to me clear that this body should not approve a project

1 with that kind of consent form contained in it given
2 this purpose.

3 Are there other things that people believe
4 should be learned before we can reasonably be expected to
5 pass on this application?

6 MR. HALPERN: I am troubled by one thing. I
7 think it is unspoken or implicit in this, that by performing
8 the fetoscopies at Drew there is going to be improved
9 competence on the part of the physicians. We heard last
10 night from a witness, or perhaps it was, I think, from
11 you, Dr. Foster, about how at your institution in
12 performing laparoscopies over time, how dramatically
13 the rate of complication was reduced.

14 I think in looking at this, not at any words,
15 in looking at this I think implicit in this is saying
16 well, if we proceed at Drew, in this community, with
17 performing fetoscopies, although they are nontherapeutic,
18 we will raise the competence of physicians, and that future
19 members of the community needing therapeutic fetoscopies
20 will thereby benefit from this improved competence.

21 I would like our reviewers or even to go back
22 to the investigator, to see if this unspoken -- to me what
23 I read as this implicit justification for approving the
24 protocol has in fact been, is being taken into account.
25 And if it is being taken into account, then I would like to

1 see it addressed directly, because if we do address it
2 directly, it certainly raises the importance of what we
3 have been told occurred at the University of California
4 at San Francisco with respect to the ability to diagnose
5 sickle cell disease through amniocentesis, because then
6 the impulse on the part of the members of the community
7 to undergo risk now so that fetoscopy would later be
8 improved fetoscopy, or at least the procedure would
9 reduce risk because of the improved competence of the
10 physicians, would then be available to either them or
11 to members of their community for therapeutic diagnostic
12 purposes.

13 I think if that is what is powering this,
14 we ought to address it directly.

15 MR. LAZARUS: Another thing is that that has
16 to get into the consent form. It is obvious from the
17 other experiences that the first three or six that are
18 done are more dangerous than the other ones.

19 MR. HALPERN: And I fear that in the --

20 MR. GAITHER: And it is explicit here. Whether
21 they are acknowledging it in their protocol, it certainly
22 is acknowledged in the evaluation by the two people retained
23 to look at it for us.

24 DR. MCCARTHY I think in this question of risk --
25 I am coming back to the consent form, and I fully agree with

1 Mr. Lazarus about the statement about minimal risk. There
2 are two factors, and this makes it so difficult to make
3 a statement about risk, and I think Mrs. Williams alluded
4 to this. One is the consequence, and in some of the
5 description contained in the consent form, the consequence
6 would be dramatic, bleeding of the mother and possible
7 very serious consequences.

8 The other is the incidence, and it looks as
9 if the chances of those drastic and dreadful consequences
10 are very remote. And so you have the question, because
11 it is unlikely to occur, does one call it a minimal risk?
12 It is the same sort of thing we face when we fly on an
13 airplane. Because the incidence is small we say it is
14 not very risky. But if the thing crashes it is almost
15 certain to be dreadful, and therefore terrible. That is
16 a terrible risk, but we think it may be still acceptable
17 or minimal because it is so infrequent. So I think there
18 are two aspects here to what we call minimal, and I daresay
19 the Commission left those things unresolved for us, and
20 perhaps we need to move toward a definition of minimal
21 risk in this context.

22 MR. GAITHER. I think that if the --

23 MR. LAZARUS: I think the point is that if this
24 were minimal risk by somebody's interpretation it wouldn't
25 be before this committee.

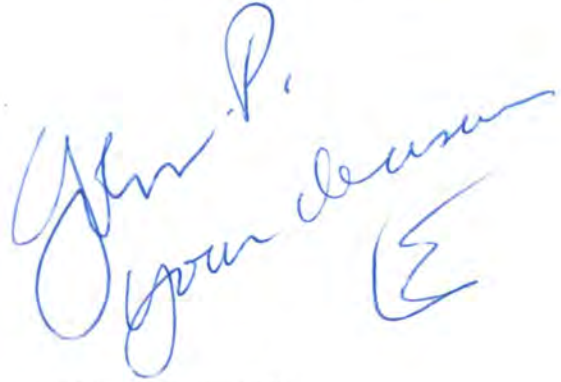
1 MR. GAITHER: I think it points out the
2 difficulty of putting labels. It may be that the focus
3 is entirely wrong, that what needs to be expressed are
4 the underlying facts that you just talked about. Namely,
5 it may not happen to you, the chances are only one in
6 500 that it will happen, but if it does, we won't see you
7 tomorrow. Now, that is a lot more meaningful than a
8 conclusion that says the risk is minimal. I think that
9 is something we really need to focus on, and I would
10 hope that as this comes back to us at the next meeting,
11 that somebody talk to the investigators about that kind
12 of approach.

13 MS. MISHKIN: The Commission did address that
14 later in subsequent reports, and stressed what Charlie
15 was just mentioning, that risk includes both probability
16 and severity of the thing happening. But I think what
17 Mr. Lazarus has pointed out very dramatically, and
18 Charlie's analogy would hold, it may be that the probability
19 of an airplane crash is very low, but we sure would want
20 to know if we were on the test flight. That is not coming
21 through very clearly. This thing is to determine the
22 probability, and that is not on that consent form.

23 MR. HALPERN: Also, I think the way one measures
24 the risk, or measures these two factors -- I think if it
25 is therapeutic, if I am to be helped, I will be much more

Fax Cover Sheet

===== 95 FEB 10 A10:26 =====

Please Deliver to:**Erskine Bowles****Fax #: 94566703**
Company: White House**From:****Robert L. Shiffer****Fax #: (202)205-9918**
Phone: (202)619-5326**Pages:**
=====**Message:****This fax was sent using Castelle's FaxPress network fax server.**

February 9, 1995

TO: Erskine Bowles
FROM: Bob Schiffer
SUBJECT: Dr. Henry W. Foster Jr.

I would like to offer you my help in the confirmation of Dr. Henry W. Foster Jr.

During the 1970's before going to Wall Street I worked for Governor Hugh Carey (NY) and coordinated health policy for his administration. I coordinated a number of confirmation battles that related to abortion. I worked closely with lay Catholic groups, and other grassroot organizations that could be very useful during the coming days.

Erskine-- I feel strongly this fight can be won and end up being a plus for the administration. You know you can count on me helping you. I can be reached at 619-5348.