Tuesday
August 14, 1979

Part III

Department of Health, Education, and Welfare

Office of the Secretary

Protection of Human Subjects of Biomedical and Behavioral Research

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Protection of Human Subjects of Biomedical and Behavioral Research

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report and Recommendations for Public Comments.

SUMMARY: The following Report and Recommendations: HEW Support of Fetoscopy was prepared by the HEW Ethics Advisory Board in response to Secretary Califano's memorandum of August 24, 1978, requesting that the Board review a grant application for support of research designed to assess the safety of fetoscopy as a technique for prenatal diagnosis. The application was submitted by the Charles R. Drew Postgraduate Medical Schoo1 (Dr. Ezra R. Davidson, Jr., principal investigator). Because the proposed research involves a possible risk to fetuses, the application may not be funded by the Department unless certain provisions of the human subject regulations are waived (part 46 of 45 CFR, Subtitle A, Subpart B). The Secretary is authorized to grant such waivers provided that the EAB has reviewed and approved the research proposal. In the attached Report and Recommendations: HEW Support of Fetoscopy, the Board has taken two actions: (l) The Ethics Advisory Board approves the requested waivers for the research application under review, and (2) The Ethics Advisory Board recommends that similar waivers be granted for subsequent applications for Departmental support of research involving fetoscopy, without review by the Board, provided that certain conditions are met.

DATES: The Secretary invites comment on the Fetoscopy Report. The comment period will close October 15, 1979.

ADDRESS: Please send comments or requests for additional information to: F. William Dommel, Jr., J.D., Assistant Director for Regulations, Office for Protection from Research Risks, National Institutes of Health, 5333 Westbard Avenue, Room 3A-17, Bethesda, Maryland 20205, telephone: (301) 496-7163, where all comments received will be available for inspection weekdays (Federal holidays excepted) between the hours of 9 a.m. and 4:30 p.m.

Dated: August 2, 1979.

Julius B. Richmond,

Assistant Secretary for Health and Surgeon General.

Approved: August 2, 1979.

Joseph A. Califano, Jr.,

Secretary.

Ethics Advisory Board

Department of Health, Education, and Welfare
Report and Recommendations: HEW Support of Fetoscopy
February 23, 1979.
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Henry W. Foster, M.D. Professor and Chairman, Department of Obstetrics and Gynecology, Meharry Medical College.
James C. Gaither, J.D., Cooley, Godward, Castro, Huddleson and Tatum, San Francisco, California.
David A. Hamburg, M.D., President, Institute of Medicine, National Academy of Sciences, Washington, D.C.
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Richard A. McCormick, S.T.D., Professor of Christian Ethics, Kennedy Institute for the Study of Reproduction and Bioethics, Georgetown University.
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Daniel C. Tosterson, M.D., Dean, Medical School, Harvard University.
Agnes N. Williams, LL.B., Potomac Maryland.
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Duane Alexander, M.D., Assistant to the Director,NICHHD.
Haig Kazazian, Jr., M.D., Professor of Pediatrics, Johns Hopkins Hospital.
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Report and Recommendations: HEW Support of Fetoscopy

Background

The Charles R. Drew Postgraduate Medical School has applied for HEW support of research designed to assess the safety of fetoscopy [1] as a technique for prenatal diagnosis. Because the investigators intend to perform fetoscopy and fetal blood sampling on fetuses whose mothers have elected to undergo abortion for reasons unrelated to the research, certain provisions of the applicable HEW regulations must be waived if the project is to receive HEW funds. Such waivers may be granted by the Secretary, on the advice of the Ethics Advisory Board, following appropriate review by the Board.

In a memorandum dated August 24, 1978, you forwarded the Drew application to the EAB for review. Two expert independent assessments of the risks and benefits of the proposed research were obtained for the Board (Tabs A and B) and a full discussion of the issues occurred at the Board's regularly scheduled meeting on November 10, 1978 in Seattle. Subsequently, the principal investigator, Dr. Ezra Davidson, was given an opportunity to respond to several questions raised during that discussion (Tab E); his letter dated January 12, 1979 (Tab F) is considered to be fully responsive. The Committee for the Protection of Human Rights at the Martin Luther King, Jr. General Hospital/Charles R. Drew Postgraduate Medical School reviewed the proposed revisions incorporated in Dr. Davidson's letter of January 12, and reaffirmed its support of the proposal on January 17, 1979. (Tab G)

For the reasons set forth below, the Ethics Advisory Board approves the necessary waivers. The Board also recommends that any subsequent applications involving fetoscopy may be approved by HEW without further review by the EAB so long as they conform to all applicable provisions of HEW regulations (45 CFR 46) with the exception of those specifically waived for the Drew proposal.

Provisions to be Waived

Approval of the Drew application requires waiver of certain provisions of sections 46.206(a), 46.207(a) and

[1] Fetoscopy provides a means of obtaining a small sample of fetal blood from the placenta through a fetoscope (a hollow tube inserted through the abdomen into the uterus, through which the fetus and placenta can be visualized). The proposed procedure would require use of a 25 to 27 gauge needle on the scope to puncture a vessel and withdraw 10 microliters of fetal blood.

46.208(a) of HEW regulations governing research on the human fetus (Subpart B of 45 CFR 46). The provisions, taken together, restrict HEW support of research on pregnant women or the fetus *in utero* to: (1) activities designed to meet the health needs of the mother or to benefit the particular fetus involved in the research, or (2) activities presenting no more than minimal risk to the fetus and designed to obtain important knowledge which cannot be obtained by other means.[2] The Drew proposal is not designed to meet the health needs of either the mothers or the fetuses participating in the research; thus, it can be approved under the regulations only if the risk to the fetus is no more than minimal or alternatively, if the Secretary, on the advice of the EAB, determines that the benefits to be derived from the research justify the risk involved.

The regulations also prohibit research personnel from taking part in decisions regarding the timing of abortions and prohibit the introduction, for research purposes, of procedural changes in the abortion process that would increase the risk to the mother or the fetus. (Sections 46.206(a)(3)(i)and(4)).

Assessment of risk

The HEW regulations do not define "minimal risk." However, since the Department's regulations implement the recommendations of the National Commission for the Protection of Human Subjects, the intent of the Commission may serve as a guide for interpretation of the regulatory provision. The Commission recognized that "minimal risk" involves a value judgment, but it offered the suggestion that no procedure be performed on a fetus-to-be-aborted unless that procedure would be acceptable for a fetus-going-to-term. The Commission's rationale was that a mother's decision for abortion does not, *per se,* change the status of the fetus for purposes of protection, and that no risk should be imposed in anticipation of abortion that would affect the mother's freedom to change her mind.

To assure that no undue risk is presented to a fetus that might be viable following abortion, the Commission recommended that no modifications of timing be made for research purposes that would result in the performance of an abortion after 20 weeks gestational age or that would impose any additional risk.[3] In this regard, it was noted that the Drew application would involve fetuses between 16 and 20 weeks gestational age and could, in the later stages of the study, delay abortion for two weeks following fetoscopy.

Applying these considerations to the application under review, it appears that since the purpose of the proposed research is to determine the risk (to both mother and fetus) from fetoscopy, the risk should be considered "undetermined" although it is expected to be no more than minimal. Nevertheless, inasmuch as fetoscopy has been applied as a diagnostic tool to fetuses going to term (see review by Dr. Alexander), the risk involved meets the Commission's criterion of acceptability as measured by willingness to perform the procedure on fetuses not intended to be aborted.

Justification of Risk

The Drew proposal had undergone reviews prior to submission to the EAB. These included scientific and technical review (by the NIH study section, NIH staff, and the site visit team) and community review (by the appropriate IRB, the Community Advisory Board for the King-Drew Sickle Cell Center, and an NIH National Advisory Council). The EAB requested two additional, independent reviews by physician investigators familiar with the problems and purposes of prenatal diagnosis; Drs. Duane Alexander and Haig Kazazian, like the preceding reviewers, both endorsed approval of the application for funding. (Tabs A and B)

The basis for the consensus in favor of the research proposal is that the benefits to be gained from the study clearly outweigh the apparent risks to mother and fetus. The most serious appear to be those of infection in mother, and of premature abortion of the fetus. The anticipated benefits are the development of a diagnostic technique that will improve the ability to detect genetic abnormalities prenatally and may also lead to methods for prenatal treatment of certain disorders. The result will be a saving of fetuses that might otherwise be aborted (because parents may choose to terminate a pregnancy unless they can be assured that a particular fetus is not affected by a disorder for which it is at risk). Improvement of techniques for prenatal diagnosis will broaden the opportunity for informed choice by parents as to whether or not to continue a pregnancy to term.

After Drs. Alexander and Kazazian had submitted their evaluations of the fetoscopy proposal, an article appeared in the *Washington Post* indicating that Yuet Wai Kan and Andree M. Dozy at the University of California had reported, in *Lancet,* a new method for detecting sickle cell disease through amniocentesis. The *Lancet* article (Tab C) was unavailable at the time of the Board's November meeting; however, the information that was available raised new questions regarding the Drew application, since amniocentesis carries less risk than does fetoscopy. Specifically, the Board wondered:

1. Whether fetoscopy should still be developed as a method of diagnosing sickle cell disease prenatally, for patients to whom the amniocentesis method is not applicable; or

2. Whether fetoscopy should be developed primarily as a method of prenatal diagnosis for disorders other than sickle cell disease; and

3. If so, whether the Drew Center, with its predominantly black subject population, is still an appropriate place to conduct such research.

Following the November meetings, Drs. Alexander and Kazanzian were asked to comment on the effect of the amniocentesis work on their risk/benefit assessments of the Drew proposal. Both concluded that the fetoscopy research continues to be important to develop a diagnostic technique for the 30-40% of black fetuses at risk for sickle cell disease for whom the amniocentesis method would not be useful. (Tab D) Further, they noted that the amniocentesis approach is still in the early stages of development; the effectiveness of this new diagnostic tool has not yet been established.

Dr. Davidson, the principal investigator at Drew Medical School, was invited to respond to a series of questions raised by the EAB in their discussion. (Tab E) In addition to the issues discussed above regarding the effect of Kan and Dozy's amniocentesis work, the questions included:

1. Uncertainty regarding the current capability of diagnosing sickle cell disease prior to 30 gestational weeks;

2. Concern about the possibility of delaying abortions past 20 gestational weeks for purposes of the research;

3. Lack of clarity in the consent forms regarding the risk of fetoscopy (which it is the purpose of the research to establish); and

4. Uncertainty regarding the length of time it is planned to leave a catheter in the mothers following fetoscopy.

[2] Other provisions within the designated sections require paternal consent, in addition to consent of the mother, unless: (a) the father's identity is unknown, (b) he is incompetent or not reasonably available, or (c) the pregnancy resulted from rape. The investigators have not requested a waiver of this requirement.

[3] See National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research on the Fetus,* May 21, 1975. Deliberations and Conclusions, sections C(4) and (H), and Recommendation 6.

Dr. Davidson provided satisfactory responses to all issues raised by the Board. (Tab F) He provided: (1) documentation for the assertion that sickle cell disease can be diagnosed in fetuses as early as 9 weeks: (2) assurance that no abortions will be performed on any fetus beyond 20 weeks gestational age; (3) assurance that no catheter will be left in place longer than 24 hours following fetoscopy: and (4) a revised consent form that reflects the Board's concern that the risks be characterized as "undetermined."

The Committee for the Protection of Human Rights at the Drew Postgraduate Medical School subsequently reviewed Dr. Davidson's reponses to the Board's concerns and reaffirmed its support of the research application. (Tab G)

Based on the foregoing considerations, the Ethics Advisory Board: 1. Approves the waiver of §§ 46.206(a)(2), (3)(i), 46.207(a) and 46.208(a) of HEW regulations governing research involving the human fetus (Subpart B of 45 CFR 46) for the fetoscopy research proposed by the Charles. R. Drew Postgraduate Medical School (Application No. 1 P60 HL 23282-01; and

2. Recommends that fetoscopy, as an experimental diagnostic procedure, be deemed acceptable for HEW support and conduct so long as the research in which it is contained meets all regulatory requirements (*e.g.*, completion of animal work, risks justified by benefits, appropriate selection of subjects, fulfillment of consent provisions, and no changes in the abortion timing or procedures that would increase risk to mother or fetus beyond the risk associated with fetoscopy and fetal blood sampling). Special precautions should be taken to assure that prospective subjects understand that the provision of health services to which they are entitled will in no way be affected by their decision regarding participation in the research. Moreover, no women should be asked to participate as subjects if participation would require that their abortion be delayed more than a few days (*e.g.*, if they present themselves for abortion at 12-14 weeks gestation, and fetoscopy cannot be performed safely until the 16th-18th week). Such delays are likely to impose psychological or social stress, if not additional medical risk. In no event should abortions be performed in such research later than the 20th gestational week.

[FR Doc. 79-24977 Filed 8-13-79; 8:45 am]

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Protection of Human Subjects of Biomedical and Behavioral Research

AGENCY: Department of Health, Education, and Welfare,

ACTION: Notice of waiver granted for HEW support of fetoscopy.

SUMMARY: On August 24, 1978, Secretary Califano requested that the HEW Ethics Advisory Board (EAB) review a grant application for support of research designed to assess the safety of fetoscopy as a technique for prenatal diagnosis. The application was submitted by the Charles R. Drew Postgraduate Medical School. Because the proposed research involves a possible risk to fetuses, the application may not be funded by the Department unless certain provisions of the human subject regulations are waived (Part 46 of 45 CFR, Subtitle A, Subpart B). The Secretary is authorized to grant such waivers provided that the EAB has reviewed and approved the research proposal. In the EAB *Report and Recommendations: HEW Support of Fetoscopy,* which is published separately in this issue of the Federal Register, the Board approved the waiver for the research application under review. As authorized by the regulations, this waiver is hereby published as a notice in the **Federal Register.**

ACTION: On August 2, 1979, the Secretary took the following action:

I hereby waive §§ 46.206(a)(2), 46.206(a)(3)(i), 46.207(a) and 46.208(a) of the HEW regulations governing research involving the human fetus (Subpart B of 45 CFR 46) for the fetoscopy research proposed by the Charles R. Drew Postgraduate Medical School (Application No. lP60 HL 23282-01).

Effective date: August 2, 1979.

FOR FURTHER INFORMATION CONTACT: F. William Dommel, Jr., J.D., Assistant Director for Regulations, Office for Protection from Research Risks, National Institutes of Health, 5333 Westbard Avenue, Room 3A17, Bethesda, Maryland 20205, telephone: (301) 496-7005

Dated August 2, 1979.

Joseph A. Califano, Jr.,

Secretary of Health, Education, and Welfare.

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