Juvenile Diabetes Foundation International

Greater Pittsburgh Chapter

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October 9, 1989

Mr. David Krantz
Executive Director
House Judiciary Committee
214 S. Office Building
Harrisburg, PA 17120

Dear Mr. Krantz:

Today we learned of House Bill 1979 which provides under ¶3216 (b) that "Any person who knowingly procures, sells or uses any tissue or organ of the remains of any aborted child for animal or human transplant, research or experimentation commits a misdemeanor of the first degree."

Extremely important research is making progress toward a cure for diabetes. This cure is based on transplanting islet cells obtained from the pancreas of dead fetuses. Only fetal cells have proven effective. The National Institutes of Health has reviewed such use of fetal tissue for research and has advocated that such use be permitted, with certain restrictions, particularly against any financial inducements to abort.

This research is critical. Pennsylvania is a leader in diabetes care, professional education and research towards a cure. In fact, JDF, a worldwide organization funding more research than any other independent organization, was started in Philadelphia nineteen years ago.

This provision of ¶ 3216 (b) can set back Pennsylvania, and its work to fight this disease, immensely.

We are not taking a position on the subject of abortion. However, on behalf of the Juvenile Diabetes Foundation of Pittsburgh, and as a Director of the Pennsylvania Diabetes Academy, I implore you to consider this matter and review the position of the NIH, providing for controlled use of fetal tissue in research. It's continuance is critical.

Very truly yours,
JUVENILE DIABETES FOUNDATION OF GREATER PITTSBURGH

Jerome N. Lehman

JDF International

The Diabetes Research Foundation

Position on Subsection 3216(b) of H.B. 1979

The Juvenile Diabetes Foundation ("JDF"), a voluntary health organization of over 160 chapters dedicated to furthering research towards a cure for diabetes and to improving the quality of life of the diabetic, vehemently opposes subsection 3216(b) of H.B. 1979 which would prohibit researchers' ability to use fetal tissue in a wide variety of critical research efforts and would subject such researchers to criminal penalties. JDF concurs with a recent report of an expert National Institutes of Health ("NIH") panel in supporting transplantation research involving the use of fetal tissue, provided that safeguards are instituted which protect against potential abuses.

Subsection 3216(b) threatens not only transplantation research but all research using fetal tissue. This would have a dramatic negative impact on the progress of promising research which may lead to cures for cancer, diabetes, Parkinson's disease, and numerous other afflictions.

Diabetes is a chronic, complex metabolic disease, which results in the inability of the body to properly maintain and use carbohydrates, fats, and proteins. It results from the interaction of various hereditary and environmental factors and is characterized by high blood glucose levels caused by a deficiency in insulin production or an impairment of its utilization. Approximately 12 million people in the United States have diabetes; each year, more than 500,000 new cases of diabetes are identified.

In recent years, the possibility that insulin-dependent diabetes can be cured by the implantation of normal insulin producing cells has excited the diabetes research world. These cells are called beta cells and are contained in islets located within the pancreas. Research utilizing normal insulin-producing cells for transplantation is being performed in a number of centers in the United States. Until March, 1988, when the Department of Health and Human Services ("DHHS") issued a moratorium on federal sponsorship of this research, NIH was funding a major research effort in this field. The research which has taken place thus far has yielded significant progress, and the diabetes community believes that beta cell transplantation holds great promise for improving diabetic therapies.

World Headquarters

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Some transplantation research has concentrated on isolating the insulin producing cells from islets within pancreases taken from adult cadavers. Numerous problems, however, are associated with the use of such cells. For instance, it is difficult to isolate the insulin producing cells, and typically many impurities exist in the product that is transplanted which may interfere with the success of the transplant. Further, these cells often do not function normally when isolated from the other cells within the islets. Researchers thus have experimented with transplantation of whole adult islets; however, it is difficult to fully isolate whole adult islets from other pancreatic cells. A final complication with adult transplants is that the host often rejects transplanted adult pancreatic tissue.

In light of these problems, many researchers have turned to fetal tissue as an alternate source for insulin producing cells. These researchers have discovered that transplantation of fetal pancreatic tissue (intact pancreatic tissue from dead 16-20 week-old fetuses -- incapable of sustaining life) does not result in the above-described problems associated with adult pancreatic tissue. When transplanting fetal pancreatic tissue, researchers do not need to isolate the insulin producing cells in order to avoid interference by other pancreatic cells. For unknown reasons only the islets grow and activate in the transplanted environment; the part of the pancreas which produces destructive digestive products does not develop. Further, since insulin producing cells function best when juxtaposed to other pancreatic cells, it is significant that researchers can transplant intact pancreatic tissue without jeopardizing the performance of the insulin producing cells. Moreover, some researchers assert that hosts are less likely to reject fetal tissue than adult tissue.

Currently, at least 30 people in the U.S. are living with fetal pancreatic transplants. Researchers are optimistic that many of these patients will experience a reduction in insulin requirements.

A national debate on the scientific, legal, and ethical issues associated with the use of fetal tissue derived from induced abortions surfaced last year when DHHS responded to an NIH proposal to conduct an on-site transplantation research project on a Parkinson's patient by issuing the aforementioned moratorium. In response to a DHHS request, the NIH convened an Advisory Panel to comprehensively deliberate these issues. By a vote of 19-2, the Panel of scientific, legal and ethical experts concluded that federal sponsorship of this research should resume, provided that certain safeguards are instituted. These safeguards include:

1. The decision to terminate a pregnancy and the procedures of abortion (including timing and method) should be kept independent from the retrieval and use of fetal tissue.

2. Proper and informed consent should be obtained from the pregnant woman. Further, the process of obtaining informed consent from the woman should be deferred until after the decision to abort has been made.

3. Payments and other forms of remuneration and compensation associated with the procurement of fetal tissue should be prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation and transportation of the tissues.

4. Potential recipients of fetal tissue, as well as any and all other participants, including researchers, hospital personnel and other service-providers, should be properly informed as to the source of the tissue in question.

5. Procedures must be adopted that accord human fetal tissue the same respect accorded other cadavers.

6. The pregnant woman should be prohibited from designating the recipient of the fetal tissue.

While in office, former Director of NIH, Dr. James Wyngaarden, endorsed these recommendations and forwarded them to DHHS, where they are undergoing review. NIH's comprehensive deliberations and recommendations demonstrate its responsible and thoughtful approach to the issues implicated by fetal tissue research.

JDF and the nation's diabetic population look to transplantation research as a major step towards discovering a cure for diabetes. Such a therapy could ameliorate not only the most severe form of diabetes, but would reduce the incidence of the numerous acute and chronic complications associated with diabetes, including blindness, end-stage renal disease, heart disease and amputations. Considering the fact that diabetes drains the American economy of over $20 billion each year, research progress embodies the potential to improve the quality of life of the diabetic and to conserve billions of dollars in scarce fiscal resources. It is imperative that policy-makers recognize the great advancements in care -- today and tomorrow -- resulting from use of fetal tissue in

biomedical research and ensure that such tissue will be readily available to clinical investigators, subject to reasonable restrictions which protect the fetus and mother.

2525h

Report of the Human Fetal Tissue Transplantation Research Panel

December 1988

Consultants to the Advisory Committee to the Director, National Institutes of Health

Volume I

Arlin M. Adams
1600 Market Street
Philadelphia, Pennsylvania 19103

December 12, 1988

James B. Wyngaarden, M.D.
Director
National Institutes of Health
Shannon Building, Room 124
Bethesda, MD 20892

Dear Dr. Wyngaarden:

The Assistant Secretary for Health, Dr. Robert Windom, posed a series of questions concerning the use of fetal tissue in medical research. You convened a panel to assist you in answering these questions. I am pleased to forward to you the answers to the questions as formulated by the panel; the considerations underlying the answers; and a number of dissenting and concurring opinions regarding the work of the panel.

Many members of the panel hold deep reservations about abortion. Yet, the United States Supreme Court has declared that a woman has a constitutional right in the first and second trimester of pregnancy to proceed with an abortion. Whatever doubt any of the panel members may have regarding the Supreme Court opinion, it still constitutes the law of the land. Thus, until the Supreme Court decision is reversed, all citizens are bound by it. Nonetheless, any activity which would serve as an inducement to women to have abortions must be dealt with extremely carefully and circumscribed to the extent possible.

Counterbalancing these concerns is the evidence brought to the panel's attention that a series of maladies might be substantially ameliorated by the prudent use of fetal tissue. Although complete proof that fetal tissue will be clinically useful has not been obtained, current evidence indicates that the use of such tissue might be beneficial in treating Parkinson's disease, childhood diabetes, Huntington's disease, and perhaps Alzheimer's disease.

The panel has carefully weighed concerns over abortion against concerns for medical research that could improve the lot of thousands of Americans. Certain precautions are paramount if such research is to be permitted. Prevention of any commercialization in obtaining the fetal tissue would seem an absolute requirement. Also, the need to separate completely the abortion procedure and the use of fetal tissue seems essential. Furthermore, Federal funding should be limited to situations that employ the most careful scientific approaches and the highest professional standards. As an additional condition for approval of this research, it is recommended that the NIH conduct periodic reviews to ensure that the concerns expressed in this report, as well as other concerns that arise as research progresses, are carefully safeguarded.

Without Federal funding, other efforts to continue research with human fetal tissue would undoubtedly proceed without Federal supervision. Thus, if the NIH proceeds cautiously, and with carefully articulated safeguards, and a program of periodic review, there would be much greater assurance that the research will be undertaken with adherence to carefully crafted guidelines. Such an arrangement would protect pregnant women and fetuses in a far more thoughtful and intelligent manner than if the NIH did not participate. Based on available evidence, various safeguards can be instituted.

It has been a high honor to serve the National Institutes of Health and the Department of Health and Human Services, and I am confident that the members of the panel stand ready to continue to assist in any way that is deemed appropriate.

Respectfully yours,

Arlin M. Adams
Chairman, Human Fetal Tissue
Transplantation Research Panel

HUMAN FETAL TISSUE TRANSPLANTATION RESEARCH PANEL

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RESPONSE OF THE PANEL TO QUESTIONS POSED

BY THE ASSISTANT SECRETARY FOR HEALTH

On the morality of research use of fetal tissue from induced abortion, three positions were discussed during the panel's deliberations.

1. Abortion is morally acceptable, and thus the research and therapeutic use of fetal tissue derived from induced abortion is also morally acceptable.

2. Abortion is immoral and so is the use of fetal tissue obtained thereby. No amount of good achieved in research or therapy could erase institutional complicity in the immorality of abortion itself or in encouragement of future abortions. No efforts at separating the procurement and use of fetal tissue from the abortion decision and procedure could make the use of fetal tissue from induced abortion morally acceptable.

3. Abortion is immoral or undesirable, but as abortion is a legal procedure in our society and with appropriate safeguards can be separated from the subsequent research use of tissue derived therefrom, the use of fetal tissue in research and therapy is not seen as complicitous with the immorality of abortion.

A decisive majority of the panel found that it was acceptable public policy to support transplant research with fetal tissue either because the source of the tissue posed no moral problem or because the immorality of its source could be ethically isolated from the morality of its use in research. Considerations supporting this decision were the fact that these abortions would occur regardless of their use in research, that neither the researcher nor the recipient would have any role in inducing or performing the abortion, and that a woman's abortion decision would be insulated from inducements to abort to provide tissue for transplant research and therapy. Accordingly, the panel found it essential that abortion decisions and procedures be kept separate from considerations of fetal tissue procurement and use in research and therapy. In keeping with that separation, it is essential that there be no offer of financial incentives or personal gain to encourage abortion or donation of fetal tissue.

Because some persons opposed to abortion would not accept the use of fetal tissue from induced abortions regardless of these insulating measures, the interests of those persons in neither participating in the research nor in receiving fetal tissue transplants should be protected by informing them of the source of such tissue.

The majority's approval of the research use of tissue from elective abortions is not to be construed as a majority vote for the moral acceptability of elective abortion.

QUESTION 1. Is an induced abortion of moral relevance to the decision to use human fetal tissue for research? Would the answer to this question provide any insight on whether and how this research should proceed?

RESPONSE TO QUESTION 1

It is of moral relevance that human fetal tissue for research has been obtained from induced abortions. However, in light of the fact that abortion is legal and that the research in question is intended to achieve significant medical goals, the panel concludes that the use of such tissue is acceptable public policy.

This position must not obscure the profound moral dimensions of the issue of abortion, nor the principled positions that divide scholars, scientists, and the public at large. It is not the charge of this panel to attempt to settle the issue of abortion or to weigh the worthiness of competing principled perspectives on abortion itself. The panel notes that induced abortion creates a set of morally relevant considerations, but notes further that the possibility of relieving suffering and saving life cannot be a matter of moral indifference to those who shape and guide public policy.

Recognizing the moral convictions deeply held in our society, the panel concludes that appropriate guidelines are required even as the research proceeds. Accordingly, the following points are noted:

1. The decision to terminate a pregnancy and the procedures of abortion should be kept independent from the retrieval and use of fetal tissue.

2. Payments and other forms of remuneration and compensation associated with the procurement of fetal tissue should be prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissues.

3. Potential recipients of such tissues, as well as research and health care participants, should be properly informed as to the source of the tissues in question.

4. Procedures must be adopted that accord human fetal tissue the same respect accorded other cadaveric human tissues entitled to respect.

[Panel Vote: 18 Yes, 3 No, 0 Abstain]

CONSIDERATIONS FOR QUESTION 1

In reaching its answer to the first question, the panel weighed the proposition that the morality of abortion could be separated in principle from the morality of the uses to which fetal tissue from induced abortions might be put. It was noted that fetal tissue would be obtained as a result of lawful, constitutionally protected decisions and actions to terminate unwanted pregnancy, and that use of cadaveric fetal tissue from induced abortions for research or therapy was generally legal. But it was also noted that the lawfulness of decisions and actions can be distinguished from their morality.

FUTURE REVIEW OF PANEL RECOMMENDATIONS

These recommendations should be reviewed
at appropriate intervals
by the Secretary of Health and Human Services.

QUESTION 2. Does the use of the fetal tissue in research encourage women to have an abortion that they might otherwise not undertake? If so, are there ways to minimize such encouragement?

RESPONSE TO QUESTION 2

Research using fetal tissue has been conducted and publicized for over 30 years. There is no evidence that this use of fetal tissue for research has had a material effect on the reasons for seeking an abortion in the past. Some panel members were concerned that a more publicized and promising research program might have such an effect in the future. To minimize any encouragement for abortion as might arise from the use of fetal tissue in research, we recommend that the measures outlined above under Question 1 be implemented, as well as the following:

- The decision and consent to abort must precede discussion of the possible use of the fetal tissue and any request for such consent as might be required for that use.

- The pregnant woman should be prohibited from designating the transplant-recipient of the fetal tissue.

The foregoing recommendations are not to be construed as denying or in any way impeding a pregnant woman's access to information regarding the use of fetal tissue in research should she request this information.

[Panel Vote: 19 Yes, 1 No, 1 Abstain]

CONSIDERATIONS FOR QUESTION 2

The panel noted that the reasons for terminating a pregnancy are complex, varied, and deeply personal. The panel regarded it highly unlikely that a woman would be encouraged to make this decision because of the knowledge that the fetal remains might be used in research.

The panel concluded further that it was sound public policy to separate as much as possible the deliberations and decisions about the abortion from any discussion of the disposition of the fetal remains.

QUESTION 3. As a legal matter, does the very process of obtaining informed consent from the pregnant woman constitute a prohibited "inducement" to terminate the pregnancy for the purposes of the research--thus precluding research of this sort, under HHS regulations?

RESPONSE TO QUESTION 3

The panel agrees that a pregnant woman should not be induced to terminate pregnancy in order to furnish fetal tissue for transplantation or medical research.

The process for obtaining informed consent from a pregnant woman for fetal tissue research does not by itself constitute a prohibited inducement to terminate the pregnancy for the purposes of research. However, knowledge of the possibility for using fetal tissue in research and transplantation might constitute motivation, reason, or incentive for a pregnant woman to have an abortion. This would not constitute a prohibited "inducement," since it is not a promise of financial reward or personal gain, nor is it coercive.

However, because the panel believes strongly that we should keep transplantation and research on fetal tissue from encouraging abortion, the panel recommends that informed consent for an abortion should precede informed consent or even the provision of preliminary information for tissue donation.

Moreover, anonymity between donor and recipient shall be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team.

Further, the timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research.

In the long term, the problem alluded to by this question may be able to be addressed by deferring the discussion of possible tissue donation until after the abortion procedure has been performed. The feasibility of this approach to fetal tissue procurement should be reviewed on a regular basis by the Department.

[Panel Vote: 20 Yes, 0 No, 1 Abstain]

CONSIDERATIONS FOR QUESTION 3

As a preliminary matter, we assume that the informed consent mentioned in the question refers to the consent sought for the purpose of using the fetal tissue in research--as distinguished from the informed consent for the abortion itself. As we have emphasized in several places, in the consent process for termination of pregnancy, we believe there should be no mention at all of the possibility of fetal tissue use in transplantation and research. The one exception might be if the pregnant woman were to ask a direct question. And even then only general information should be given; there should be no promise that her fetal tissue either could or would be so used. Panel members individually take this stand either because they do not want to do anything that might encourage abortion or as a concession to those who do not want to risk encouraging abortion.

The heart of the question pivots on the meaning of "prohibited 'inducement.'" It is not clear which inducements are in fact prohibited by Department of Health and Human Services (HHS) regulations nor is it clear exactly what an inducement is. Therefore, some clarifications are in order to determine what would be a reasonable and defensible position in the matter.

An inducement could be a coercion, an incentive, or a reason. (1) Coercion is in any case unacceptable and would surely be prohibited. In order for consent to be valid it must at least be free, voluntary, and informed. (2) We would also find incentives to be unacceptable inasmuch as our panel recommends at every turn that we should (for reasons articulated elsewhere) keep fetal tissue transplantation and research from encouraging abortion. Also, incentives to terminate a pregnancy would probably be prohibited under HHS regulations, though it might turn on how strong, i.e., how irresistible, the incentive was. (3) However, with respect to reasons, it would be unrealistic not to consider the possibility that transplantation and research with fetal tissue may enter the balance of considerations of a pregnant woman in deciding whether to have an abortion. It would be unrealistic because transplantation and research with fetal tissue will become general knowledge; it will not be possible to keep the populace from knowing about it.

By no reasonable interpretation can sheer information constitute a "prohibited 'inducement.'" The point of labeling some inducements as prohibited is to avoid manipulation of persons by coercion (a threat of harm) or by incentives (the promise of personal gain) unrelated to the risks, harms, and benefits of the act itself. Thus, that fetal tissue could benefit others might be one of many reasons to be weighed in deciding whether to terminate a pregnancy. We clearly would be unable to keep such knowledge from functioning as a reason, and in any case it does not and should not be construed to constitute a "prohibited 'inducement.'"

QUESTION 4. Is maternal consent a sufficient condition for the use of the tissue, or should additional consent be obtained? If so, what should be the substance and who should be the source(s) of the consent, and what procedures should be implemented to obtain it?

RESPONSE TO QUESTION 4

Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman. Her decision to donate fetal remains is sufficient for the use of tissue, unless the father objects (except in cases of incest or rape).

The consent should be obtained in compliance with State law and with the Uniform Anatomical Gift Act.

Customary review procedures should apply to research involving transplantation of tissue from induced abortions.

[Panel Vote: 17 Yes, 3 No, 1 Abstain]

CONSIDERATIONS FOR QUESTION 4

There are several possible ways to transfer or acquire any human tissue: donation (express or presumed), abandonment, sales, and expropriation. Although each method of transfer has been used for some human biological materials in some contexts in the United States, our society has largely adopted express donation--by the decedent while alive or by the next of kin after his or her death--as the method of transfer of cadaver organs and tissues. In cases where the decedent while alive could not or did not express his or her wishes about donation, the Uniform Anatomical Gift Act (UAGA) allows express donation by the next of kin. Presumed donation (or presumed consent) is used in 12 States for the removal of corneas; the donation of corneas by the decedent and next of kin is presumed to have been made if there is no express objection. The panel believes that express donation by the pregnant woman after the abortion decision is the most appropriate mode of transfer of fetal tissues because it is the most congruent with our society's traditions, laws, policies, and practices, including the Uniform Anatomical Gift Act and current Federal research regulations.

When a woman chooses a legal abortion for her own reasons, that act does not legally disqualify her--and should not disqualify her--as the primary decisionmaker about the disposition of fetal remains, including the donation of fetal tissue for research. Objections to this conclusion are grounded in the assumption that the decision to abort severs kinship in any but the biological sense. Nonetheless, the panel concludes that disputes about the morality of her decision to have an abortion should not deprive the woman of the legal authority to dispose of fetal remains. She still has a special connection with the fetus, and she has a legitimate interest in its disposition and use. Furthermore, the dead fetus has no interests that the pregnant woman's donation would violate. In the final analysis, any mode of transfer of fetal tissue other than maternal donation appears to raise more serious ethical problems. For all these reasons, the pregnant woman's consent, or decision to donate, should be sufficient (within the limits identified below). The panel heard no compelling reasons why federally funded transplantation research should depart from ordinary and legal

practice in the disposition and use of cadaver tissues, including fetal cadaver tissues.

However, questions have been raised about whether additional consent is needed from other parties, such as the father or a hospital ethics committee or an institutional review board. We believe that the structure provided by the UAGA (revised 1987) is generally adequate but that a modification in policy is needed for the donation of fetal tissue. Where the decedent did not express his or her wishes, the UAGA authorizes "either parent of the decedent" to make a donation, unless there is a known objection to such a donation from the other parent (or from the decedent's spouse or adult children). As applied to the donation of fetal tissue, the UAGA provides that either parent may donate unless there is a known objection by the other parent. In the panel's view, the pregnant woman's consent should be necessary for donation--that is, the father should not be able to authorize the donation by himself, and the mother should always be asked before the fetal tissue is used. In addition, her consent or donation should be sufficient, except where the procurement team knows of the father's objection to such donation. There is no legal or ethical obligation to seek the father's permission, but there is a legal and ethical obligation not to use the tissue if it is known that he objects (unless the pregnancy resulted from rape or incest).

Review procedures have been developed for federally funded research involving human subjects. These review procedures would also apply to fetal tissue transplantation research, which must be reviewed and approved by Institutional Review Boards (IRBs) before it can proceed. Such research would fall under the purview of IRBs because human subjects would receive experimental transplants of fetal tissue in a research protocol. In addition, IRBs will need to consider the adequacy of the information disclosed to the pregnant woman who is considering whether to consent to tests (e.g., for antibody to the human immunodeficiency virus) to determine the acceptability of the fetal tissue for transplantation research. Nevertheless, the pregnant woman's consent to donate the tissue is legally sufficient and should be sufficient in federally funded transplantation research, as long as there is no known objection from the father (except in cases of rape or incest).

QUESTION 5. Should there be and could there be a prohibition on the donation of fetal tissue between family members, or friends and acquaintances? Would a prohibition on donation between family members jeopardize the likelihood of clinical success?

RESPONSE TO QUESTION 5

There should be no Federal funding of experimental transplants performed with fetal tissue from induced abortions provided by a family member, friend, or acquaintance. Absent such prohibition, the potential benefits to friends and family members might encourage abortion or encourage pregnancy for the purpose of abortion--encouragements that the panel strongly opposed.

Concerns regarding maternal welfare as well as the moral status of the human fetus and, therefore, the morality of abortion itself, militate against Federal practices or policies that could have the effect of in any way encouraging abortions for the purpose of benefiting family members or acquaintances.

There is no evidence now that a prohibition against the intrafamilial use of fetal tissue would affect the attainment of valid clinical objectives. Given the current state of scientific knowledge, the treatment of diabetes with intrafamilial transplants would be contraindicated. For other conditions that are considered to be candidates for fetal tissue transplantation, currently available scientific evidence allows no definitive conclusions to be drawn with respect to this question.

[Panel Vote: 19 Yes, 0 No, 1 Abstain (Note: One panel member was out of the room when this vote was taken.)]

CONSIDERATIONS FOR QUESTION 5

There was no plea from the scientists for doing intrafamilial transplantation. In fact, the experts gave testimony that there ought to be a prohibition. If circumstances change, however, there may be reasons to modify the prohibition.

The panel did not hear any compelling evidence that suggests that a relationship between the donor and the fetus would improve the likelihood of success. Repeatedly, testimony of the experts emphasized the lack of scientific justification for intrafamilial donation by reason of current state of knowledge of immunology and disease pathophysiology. In fact, some argued that relatedness may induce the potential for disease recurrence, e.g., diabetes mellitus. It was strongly urged that the Secretary for Health and Human Services review these recommendations at regular intervals.

QUESTION 6. If transplantation using fetal tissue from induced abortions becomes more common, what impact is likely to occur on activities and procedures employed by abortion clinics? In particular, is the optimal or safest way to perform an abortion likely to be in conflict with preservation of the fetal tissue? Is there any way to ensure that induced abortions are not intentionally delayed in order to have a second trimester fetus for research and transplantation?

RESPONSE TO QUESTION 6

If fetal tissue transplants become more common, the impact on the activities and procedures of abortion clinics will depend upon the demand for tissue and the regulations and safeguards that restrict tissue procurement. To minimize this impact, it is essential that requests to donate tissue be separated from consent to the abortion, and that no fees be paid to the woman to donate, or to the clinic for its efforts in procuring fetal tissue (other than expenses incurred in retrieving fetal tissue).

The most certain impact if fetal tissue transplants become more common is that abortion facilities will more frequently--perhaps even routinely--ask women to donate fetal remains for research and therapy after they have decided to abort the fetus. The abortion clinic will also coordinate retrieval and temporary storage of fetal remains with tissue procurement organizations, either retrieving the tissue themselves or permitting procurement agency personnel to do so.

The greatest pressure for change in abortion clinic practices beyond requesting women to donate fetal tissue would occur if abortion clinics and women could profit financially from procuring fetal tissue. Current Federal law and the law of many States prohibit the buying and selling of fetal tissue, though they do permit payment of expenses incurred in procuring tissue for transplantation. Enforcement of these laws, including clear guidelines about what constitutes procurement expenses, is essential to prevent pressure to abort and to donate fetal tissue.

One could contemplate a scenario in which demand outstripped the supply of fetal tissue from abortions to end unwanted pregnancies. More effective contraception, greater acceptance of pharmacologically induced abortions, and great success in treating major diseases (such as Parkinson's and diabetes) could make the demand greater than the supply. To accommodate this scarcity, mechanisms for distributing fetal tissue to the larger number of patients demanding it would have to be devised, such as now exist for distributing the scarce supply of hearts, livers, and kidneys to patients on waiting lists for transplants.

However, this situation alone would not change the activities and practices of abortion clinics. Pressures to conceive and abort for transplantation purposes would arise outside of or apart from the activities of such clinics. Adherence to rules that specify when the request to donate tissue is made and that ban sales of fetal tissue would also limit the impact of such demand on abortion clinics.

The future medical possibilities cannot be foreseen with clarity. If, however, presently unexpected conflicts arise in the future, the choice of the abortion procedure should always be dictated by the health considerations of the woman.

[Panel Vote: 19 Yes, 2 No, 0 Abstain]

CONSIDERATIONS FOR QUESTION 6

Predicting the impact on abortion clinics of a greater frequency of fetal tissue transplants is difficult and necessarily speculative at this time. The impact will depend upon many factors, including the extent of the demand for tissue, the number of abortions, the time at which viable fetal tissue may be obtained, the rules for obtaining consent, and rules against buying and selling fetal tissue. History, of course, will supply the most accurate answers, for no one can tell just how successful the research under consideration will be.

Ideally, permission to use tissues from the aborted fetus would not even be sought until the abortion itself had been performed. The timing of and the procedures associated with the abortion would be set and the abortion would be performed before the question of tissue donation was even raised. However, post mortem tissue quickly deteriorates, and, in most instances, (e.g., transplantation of neural tissue) cryogenic storage is not a scientifically effective alternative. Thus, the pregnant woman must be consulted before the abortion is actually performed. In such instances, it is always possible for the woman herself to consider procedural options that might render the fetal tissue more useful for research or therapy; possible, but, according to experienced persons, entirely unlikely.

It was the judgment of the panel that the concerns behind Question 6 are best addressed by strict adoption of a number of safeguards; safeguards that would eliminate or at least radically reduce profit motives and tendencies toward commercialization, and safeguards that would ensure the greatest possible separation between abortion procedures, facilities, and personnel on the one hand, and fetal-tissue research procedures, facilities and personnel on the other.

Where the panel was divided was on the question of which "scenario" to adopt in framing recommendations; a so-called "worst-case" situation in which demand so outstrips supply as to exert great financial and altruistic pressures, or a so-called "reasonable-case" situation in which modest medical objectives are met only over a long period. The energetic support of research by the NIH would, of course, affect the rate of progress in this area. The strictest principles of separation would be necessary in the "worst case" and would not be untoward in their effects even under current conditions.

QUESTION 7. What actual steps are involved in procuring the tissue from the source to the researcher? Are there any payments involved? What types of payments in this situation, if any, would fall inside or outside the scope of the Hyde Amendment?

RESPONSE TO QUESTION 7

Past experience with fetal tissue research usually has had the medical researcher directly requesting fetal remains for research from physicians performing abortions, usually in the same institution. Occasionally, medical researchers have requested fetal tissue from freestanding abortion clinics in the same city.

In these instances, it is assumed that the woman aborting has consented to donation of fetal remains, though it is possible that in some instances the tissue, which would otherwise be discarded, has been treated as abandoned and used without maternal consent. If consent was obtained, it would ordinarily have been obtained before the abortion occurred but after the decision to abort had been made.

More recently, agencies or organizations have developed to provide tissue, including fetal tissue, to researchers. These have been nonprofit agencies that have solicited fetal tissue from abortion facilities and paid them a small fee for each fetal tissue retrieved to cover the costs of retrieval, including time of staff and rental of space. They have then distributed the tissue to previously identified and approved researchers conducting legitimate medical research. These agencies have usually charged the researchers the cost they have incurred in procuring the tissue.

There sometimes have been payments made to abortion facilities and physicians who have provided fetal tissue for research. These payments are intended to cover the costs to the abortion facility of providing access to the procurement agency, including staff time in requesting consent and retrieving tissue, and use of the clinic space by employees of the procurement agency.

If Federal research funds were used to pay the cost of the abortion procedure that makes fetal tissue available for research, such payment would violate the Hyde Amendment. On the other hand, the use of Federal research funds to pay tissue retrieval agencies for the costs of retrieving fetal tissue after the abortion has occurred would not violate the Amendment. Those funds would not be used "to perform abortions," but to obtain fetal tissue from abortions that would otherwise be occurring. Similarly, Federal support of fetal tissue research activities other than the cost of fetal tissue retrieval would also not violate the Hyde Amendment.

[Panel Vote: 19 Yes, 2 No, 0 Abstain]

CONSIDERATIONS FOR QUESTION 7

The description of fetal tissue procurement procedures described here is based on information presented to the panel concerning past experience in obtaining fetal tissue and on information about new organizations that have arisen to provide fetal tissue for research and therapy. Some further development along these lines may be expected, with a strong emphasis on

nonprofit retrieval agencies and no payments for tissue procurement beyond expenses.

There is no evidence that women who abort are paid money or other consideration to donate fetal tissue. Payments to abortion facilities have purported to cover expenses involved in collecting tissue and making it available. To prevent abortion clinics from making profits from fetal tissue donation, specific rules for what counts as a reasonable payment for retrieval expenses may be required.

The Hyde Amendment prohibits the use of designated Federal funds "to perform abortions except where the life of the pregnant woman would be endangered if the fetus were carried to term." It would appear, therefore, that the Hyde Amendment is not violated by support of research with fetal tissue or payment of costs incurred in retrieving that tissue because those funds would not be paid "to perform abortions."

QUESTION 8. According to HHS regulations, research on dead fetuses must be conducted in compliance with State and local laws. A few States' enacted version of the Uniform Anatomical Gift Act contains restrictions on the research applications of dead fetal tissue after an induced abortion. In those States, do these restrictions apply to therapeutic transplantation of dead fetal tissue after an induced abortion? If so, what are the consequences for NIH-funded researchers in those States?

RESPONSE TO QUESTION 8

While the Uniform Anatomical Gift Act in every State permits donations of fetal remains with maternal consent (as long as the father does not object), the panel is aware of eight States (Arkansas, Arizona, Illinois, Indiana, Ohio, Louisiana, New Mexico, and Oklahoma) that have statutes that prohibit the experimental use of cadaveric fetal tissue from induced abortions. Provisions of one statute (that in Louisiana) have been struck down on constitutional grounds.

Six of the eight States prohibit experimentation on fetuses from induced abortion. By their terms, these statutes do not apply to nonexperimental therapeutic transplants, but arguably would apply only to experimental therapeutic transplants. However, if the subject of the research is deemed to be the recipient of the fetal tissue transplant, then it may be that these statutes do not apply to experimental therapeutic transplants because they are experiments on the recipient and not on the aborted fetus.

Two of the six States would ban any use of fetal tissue from induced abortions, whether experimental or not.

Several States also have laws requiring that maternal consent be obtained before fetal tissue may be used, and ban payments for fetal tissue or providing the abortion free as an inducement to obtain fetal tissue for research.

The consequences for NIH researchers in those States depend upon the meaning of the term "experimentation" in the statutes at issue. In at least two of the States no use could be made of aborted fetal tissue. In the other six they could be used for nonexperimental therapeutic transplants or for experimental therapeutic transplants that are reasonably viewed as experiments on the recipient of the transplant and not on the fetal tissue itself.

Researchers in States with statutes appearing to ban fetal tissue transplants may seek clarification of the law.

[Panel Vote: 20 Yes, 0 No, 1 Abstain]

CONSIDERATIONS FOR QUESTION 8

Research using tissue from dead fetuses is permitted in most States, because these States have statutes modeled on the Uniform Anatomical Gift Act, which treats fetal tissue like other cadaveric remains. The panel knows of only two States that prohibit all use of fetal remains from induced abortion. In six other States known to the panel, whether tissue from induced abortions may be used is dependent upon clarification of the statutory meaning of the term "experimental."

QUESTION 9. For those diseases for which transplantation using fetal tissue has been proposed, have enough animal studies been performed to justify proceeding to human transplants? Because induced abortions during the first trimester are less risky to the woman, have there been enough animal studies for each of those diseases to justify the reliance on the equivalent of the second trimester human fetus?

RESPONSE TO QUESTION 9

There is sufficient evidence from animal experimentation to justify proceeding with human clinical trials in Parkinson's disease and juvenile diabetes. Although fetal tissue of diverse ages may be scientifically and clinically advantageous for transplantation to relieve various pathologies, no abortion should be scheduled or otherwise accommodated to suit the requirements of research.

In terms of Parkinson's disease there is a wealth of positive data on graft efficacy from animal models. Extensive research has been conducted in rodents and in non-human primates. Additional testimony from some scientists suggested that further animal studies would be helpful. It is not known, for example, if there are any long-term adverse immunological effects of the grafts. It was also pointed out that the same disease processes that caused the initial dopamine neuron degeneration could also produce degeneration of grafted neurons. Testimony stressed the need for additional research, especially in terms of developing cell lines, as discussed in Question 10, below.

In terms of diabetes, there was presented a considerable body of data with animal models of diabetes supporting the efficacy of fetal islet transplants in man and suggesting that human clinical trials were timely and appropriate. Such trials are now in progress and are currently being evaluated.

Experts testified that in other disease states, such as Alzheimer's disease, Huntington's disease, spinal cord injury, and neuroendocrine deficiencies, promising results have derived from experiments using allografts in animal disease models. In these latter diseases, experts urged further animal studies before using human fetal tissue. Acceptable preliminary data would then need to be presented to an appropriate Institutional Review Board, NIH Initial Review Group, and National Advisory Council before Public Health Service funds would be obtained.

Research in diabetes, Parkinson's disease, and neural regeneration has found that first trimester fetal tissue is not only more apt, but optimal, for transplantation, since it survives better and contains cells at a stage of differentiation which is more appropriate for the therapeutic goals. Animal studies on other disorders have not revealed a transplantation protocol that would require the use of more mature fetal tissue.

Should that possibility arise and not be restricted by law, then tissue available from abortions that have already occurred during the second trimester may be used. But, to the extent that Federal sponsorship or funding is involved, no abortion should be put off to a later date nor should any abortion be performed by an alternate method entailing greater risk to the pregnant woman in order to supply more useful fetal materials for research.

[Panel Vote: 18 Yes, 2 No, 1 Abstain]

CONSIDERATIONS FOR QUESTION 9

A summary of current literature underlying this response is to be found in the Addendum. The scientific testimony presented to the panel is provided in the appendices.

QUESTION 10. What is the likelihood that transplantation using fetal cell cultures will be successful? Will this obviate the need for fresh fetal tissue? In what time frame might this occur?

RESPONSE TO QUESTION 10

In terms of alternatives to the use of fetal tissue for transplantation, an option that was presented to the panel was the use of established lines of cells that are maintained in culture. The scientific testimony was optimistic that transplantation using cell cultures may ultimately be successful. This use of cultured cells might obviate the need for tissue directly obtained from the fetus for some purposes of research and therapy. The time frame for use of defined cell lines for transplantation is estimated to be at least 10 years, given the problems of genetic engineering to have the cells synthesize chemical messengers and differentiate after grafting.

[Panel Vote: 21 Yes, 0 No, 0 Abstain]

CONSIDERATIONS FOR QUESTION 10

The evidence in the field and expert testimony indicate that an established cell line for transplantation in diabetes must be able to synthesize, store, and release appropriate amounts of insulin when the blood sugar exceeds normal limits. At the present time, it is possible to construct cell lines by genetic engineering which synthesize insulin, but the newly formed insulin is released immediately regardless of the level of blood sugar. The genetic information for the storage and controlled release of insulin is not available at the moment and thus cannot be inserted into these cells.

A second problem may occur even if a cell line could be developed which would synthesize, store and release insulin upon demand. A normal insulin-producing cell in the pancreas is surrounded by other cells which secrete hormones that control and modulate the secretion of insulin. Thus, it may require the development of additional cell lines to release these hormones and permit the normal secretion of insulin from an insulin-producing cell line.

In regard to Parkinson's disease, it is unknown whether the transplanted neural cells will be needed only to release a specific chemical messenger or whether the transplanted cells must contact other neural cells. If both properties are required, then these two different types of genetic information would have to be inserted into the cell line.

A final problem for the development of cell lines for transplantation into patients with either diabetes or Parkinson's disease is that genetic information would have to be inserted to permit the multiplication of the cells before transplantation and then stop multiplying after transplantation. If cell multiplication could not be stopped after transplantation, the cell line would form a tumor in the patient.

ADDENDUM

SUMMARY OF CURRENT LITERATURE UNDERLYING THE RESPONSE TO QUESTION 9

Prepared by Dr. Barry J. Hoffer

In terms of Parkinson's disease (PD), there is a wealth of positive data on graft efficacy from animal models. The possible clinical application of neural grafting in patients with PD was first suggested a decade ago when it was reported that striatal implants of dopamine-(DA)-rich ventral mesencephalic tissue from rat fetuses could improve the symptoms of a 6-hydroxydopamine-induced Parkinsonian syndrome in rats (Björklund and Stenevi, 1979; Perlow et al., 1979). It has since then been convincingly demonstrated that the functional recovery is dependent on graft survival and DA fiber ingrowth into the denervated striatum (Björklund and Stenevi, 1979; Björklund et al., 1980). The growth of the grafted DA neurons exhibits a high degree of specificity and the distributional pattern of the outgrowing fibers is reminiscent of that found in the normal brain (Björklund et al., 1983). The ingrowing graft-derived DA fibers form abundant synaptic contacts with host striatal neurons (Freund et al., 1985). The grafts are metabolically, physiologically, and biochemically active (Zetterström et al., 1986; Strecker et al., 1987; Rose et al., 1985) in that they exhibit transmitter synthesis, normal firing patterns, and organotypic DA release. Successful grafting of DA-rich ventral mesencephalic tissue from fetuses to the striatum has also been reported in nonhuman primates with MPTP-induced Parkinsonism. Survival of implanted DA neurons in the caudate nucleus or the putamen has been demonstrated microscopically in rhesus monkeys (Bakay et al., 1985), african green monkeys (Redmond et al., 1986) and common marmosets. Biochemical data have indicated a near-normal ratio of homovanillic acid (a major DA metabolite) to DA in the vicinity of the grafted cells indicating that in nonhuman primates as well, grafted dopaminergic neurons are able to normalize DA turnover in DA depleted areas of CNS. Such animals have shown a permanent reduction of both drug-induced motor abnormalities and of hypokinesia, rigidity and tremor.

A key finding supporting the recent clinical trials is that human fetal DA neurons are able to survive transplantation into the DA-denervated rat striatum, reinnervate the host brain and counteract Parkinsonian symptoms (Brundin et al., 1986, 1988; Strömberg et al., 1986, 1988).

The experiments with human donor to rat host ventral mesencephalic grafts indicate that the optimal donor age is 8 to 10 weeks. About 15,000 DA cells from each human fetus were found to survive grafting to the striatum of cyclosporin A treated rats (Brundin et al., 1988). Since it has been estimated (Lindvall et al., 1987) that the human putamen is normally innervated by about 60,000 DA neurons, grafting of ventral mesencephalic tissue from one fetus into this structure should be able to restore approximately 25 percent of the normal number of cells. Further estimates, taking into account the growth capacity of each individual human DA neuron, indicate that the DA innervation provided by mesencephalic tissue from one fetus would be able to reach 40 to 80 percent of the volume of the human putamen. The symptoms of PD do not appear until more than 70 percent of the DA neurons have degenerated (Berheimer et al., 1973); until this stage is reached, DA transmission is maintained through hyperactivity of remaining neurons and postsynaptic receptor supersensitivity (Ungerstedt, 1971). It is therefore realistic to believe that tissue from human fetuses implanted into the putamen, caudate nucleus, or both, would elicit a symptomatic improvement for a patient with PD.

Transplantation has also been considered as a possible "cure" for type I diabetes. In animal models, it has been known since the early sixties that it was possible to reverse the metabolic problems of diabetes by either whole pancreas or pancreatic islet transplantation (Lacy, 1984). Islet grafting was also shown to either prevent or arrest the development of diabetic complications, seen in animals with long lasting poorly controlled diabetes (Lacy, 1984).

Animal studies show that we are now in a position to isolate islets from the rodent pancreas and transplant them to unrelated animals without the need of recipient immunosuppression (Lafferty et al., 1983). Fetal pancreas can also be used as a source of tissue for transplantation (Lafferty et al., 1983). This tissue does not contain mature islets but does contain cells which give rise to islets. Grafts of fetal pancreas are relatively slow to reverse diabetes because the islet tissue must grow and differentiate before it can function.

Fetal pancreatic tissue, with appropriate treatment, can also be grafted without the need for recipient immunosuppression (Lafferty et al., 1983). The development of technology which provides the ability to graft without the need for immunosuppressive therapy, or at least using limited immunosuppressive therapy, makes islet or fetal pancreas transplantation a potential treatment for type I diabetes.

Studies have been carried out to determine whether human fetal pancreas, obtained from cadaveric donors, has the capacity to grow, differentiate and function in animals (Hullett et al., 1987; Tuch et al., 1988). These studies have involved the grafting of human fetal pancreas to animals with no functioning immune system (i.e., "nude" mice). The fetal pancreas does grow and develop insulin containing islets. The tissue also has the capacity to reverse a diabetic condition in these animals.

Since experimental studies have reached the stage of demonstrating that human fetal pancreas can grow, differentiate, and function in animals, it now seems scientifically justified to move to experimental studies in man, while continuing with research in animals.

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JDF FETAL TISSUE TESTIMONY

My name is Carol Lurie and I am offering these remarks on behalf of the Juvenile Diabetes Foundation International, an international voluntary health organization of over 160 chapters dedicated to furthering research towards a cure for diabetes and to improving the quality of life of the diabetic.

I am a Founder and past-president of JDF. I am also the mother of a 30 -year old young man who has lived with this disease for 20 years.

I remember my first trip to Washington, 15 years ago to testify for higher appropriations for diabetes research. At that time, there was no federal diabetes initiative to speak of. With the diagnosis of diabetes, our children were afforded a slow and painful death sentence, a life awaiting the myriad of complications of diabetes -- blindness, heart disease, stroke, neurological disorder, kidney failure, to name a few. It was this fear and panic and love for our children which catalyzed the formation of JDF and our aggressive effort to see the federal government do something about diabetes.

Public policy-makers heeded our call and the federal government now spends about one-quarter of a billion dollars each year on diabetes research. The returns on this investment

have been remarkable: Researchers have identified the genetic markers of diabetes. They have developed techniques for laser photocoagulation to treat diabetic retinopathy and we can now significantly reduce the risk of blindness. They have greatly reduced the health risk to mother and child of the diabetic pregnancy. They have improved methods of insulin delivery, including the use of human insulin developed through recombinant DNA and the insulin pump.

These breakthroughs are not the result of a grand blueprint but, rather, the result of the laborious pursuit of many avenues of research inquiry. Many of these avenues lead to dead ends and a few yield the breakthroughs which improve the human condition, like kidney transplantation, the discovery of antibiotics, and the development of the polio vaccine.

As scientists have explained to you today, this nation's diabetic population awaits the results of clinical trials in which human subjects are undergoing pancreatic islet cell transplantation. I wish that I could tell you that this research will result in a cure for diabetes. That might ease this Committee's burden in evaluating the pros and cons of utilizing fetal tissue in biomedical research. However, I can offer no such guarantees. I can only plead that, as long as

there exists an iota of opportunity that disease can be eradicated through research utilizing any form of legally obtained tissue -- from adult cadaver, from fetus, or from animal -- this research must be conducted.

I am not a scientist but I think that I understand the status of diabetes-related transplantation research. You've all heard an in depth discussion of this research and it would be redundant for me to repeat its merits when time is of the essence this afternoon.

The reality of islet cell transplantation is that this tissue is often derived from aborted fetuses. We must acknowledge that the conduct of the research is not an impetus for abortion. Reasonable people can agree and disagree as to the social, economic, and moral implications of abortion, but the fact is that our legislatures and our courts have concluded that abortion is legal. And, as long as safeguards are instituted which ensure that research is ethically pursued and that the act of abortion and the conduct of research remain distinct, we believe that it is socially and morally imperative that we pursue research avenues which may lead to a cure for diabetes, Parkinson's Disease, or other devastating diseases.

JDF is terribly upset that the White House is considering promulgating an Executive Order which which prevent this research from continuing with federal support. Whether a Republican or Democrat is in the White House, it is imperative that the Executive Branch comprehend the importance of this research and that the use of fetal tissue in transplantation is not an abortion issue. Further, as we discussed earlier, safeguards can be and are imposed which prevent abuses, including:

- Animal models should be utilized before human research is initiated, as was the case with islet cell transplantation.

- Researchers should have no part in deciding the timing, methods, or procedures for terminating pregnancy.

- No inducements should be provided to encourage a mother to abort in order to obtain tissue for research purposes.

- As with all transplantation, state and local laws governing informed consent must be followed.

- Under no circumstance should a woman be permitted to abort in order to obtain tissue for a designated donee, such as her child.

With respect to the conduct of diabetes research, I have been here since the beginning. I have personally spoken with thousands of diabetics who are alive today, who can see today, who can walk today, who can bear children today, and who have dreams of a healthy tomorrow because we put fiscal resources into research and allowed the research endeavor to flourish in an administratively unfettered manner. If researchers had not been permitted to culture the diabetes virus, we could not have held out the hope for prevention of diabetes. If researchers were not permitted to utilize genetic engineering, we would not have access to pure human insulin. If researchers were not permitted to utilize animals in research, we would not have made such phenomenal progress in ameliorating diabetes' complications. Will we forego an opportunity to cure diabetes and other diseases because of our unwillingness to utilize a tissue resource -- fetal tissue -- which will otherwise be destroyed?

I appreciate that the use of fetal tissue implicates an unique array of social and ethical issues. Yet, we must resolve these issues in a way that preserves this vital avenue of biomedical research. My son's life depends upon it.

Thank you.

8290h

SUMMARY

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FETAL RESEARCH AND FETAL TISSUE RESEARCH

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Dorothy Lehrman, M.A.
Staff Associate
Division of Biomedical Research

◆

Association of
American Medical Colleges

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Robert G. Petersdorf, M.D.
President

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INTRODUCTION

Fetal research and fetal tissue research have increasingly been the subject of public debate and controversy. In participating in the debate, AAMC staff became aware of the need to set forth and understand the distinction between the two areas of research. This resulting document is an attempt to provide a clear and comprehensive description of these separate areas of research, the issues surrounding them, and a chronological perspective of their legislative/regulatory histories.

Robert G. Petersdorf, M.D., President

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Dorothy Lehrman, M.A.

EXECUTIVE SUMMARY

Fetal research and the use of fetal tissue in research are two separate issues, although the distinction is often blurred within the discussion of abortion.

Fetal research is generally performed on a living fetus *in utero*, although it is legal to perform research *ex utero*. Fetal research has been essential to the development of vaccines, fetal surgery, and prenatal diagnostic techniques.

The regulation of fetal research has a long history. Regulations for the protection of fetuses were promulgated in 1975 and, since then, there has been pressure to ban or restrict fetal research. The regulations state that a waiver must be obtained from the Secretary of the Department of Health and Human Services (DHHS) to perform fetal research that is not therapeutic and that poses greater than minimal risk to the fetus. This restriction prohibits most fetal research because the minimal risk standard only allows a researcher to observe the fetus or to perform non-invasive procedures. The regulations on fetal research have been in existence for 13 years, but the waiver provision has been functional for only two of these years. Current proposed legislation would prohibit research above the minimal risk standard for another two to three years pending a study of the issue.

Fetal tissue research, as distinct from fetal research, uses only tissue samples from deceased fetuses. For decades fetal tissue has been used in developing particular cell lines and for safety testing of vaccines. Because of the unique qualities of fetal tissue, it now is being studied for use in treatment of a wide range of conditions including Parkinson's disease, Alzheimer's disease, Huntington's chorea, diabetes, neurological diseases and injuries, blood-related diseases, cancer, AIDS, pulmonary, kidney, eye, and dental diseases.

The use of fetal tissue is regulated at the state level. All 50 states have adopted the Uniform Anatomical Gift Act, which authorizes the use of tissue obtained from dead fetuses. Federal regulations have established requirements that separate abortion procedures from the conduct of research and cover both fetal research and the use of fetal tissue in research.

Recent advances in research with fetal tissue have led to increasing public attention and legislative inquiry. DHHS has taken action to restrict the use of fetal tissue in research until the issue is studied further.

The purpose of this paper is to provide the history of the regulation of fetal research and to outline the distinction between fetal research and the use of fetal tissue in research.

FETAL RESEARCH

BENEFITS/OUTCOMES OF FETAL RESEARCH

Fetal research is performed on a living fetus *in utero*, although it is legal to perform research *ex utero*. Research may be invasive; an example is fetal surgery to save an endangered life. Other fetal research may be noninvasive as in ultrasonic detection of fetal structures and movements.

Fetal research has been instrumental in the development of vaccines. Although no pregnant women were used to develop the rubella vaccine, pregnant women were used in testing its efficacy. Fetal research has been instrumental in the diagnosis and treatment of Rh incompatibility between mother and fetus and for the detection of neural tube defects. Noninvasive or low risk procedures developed with fetal research include fetal electrocardiogram, analyses of umbilical cord blood, and observation and measurement of the fetus.

The effects of a wide range of drugs on the human fetus have been studied *in utero* including anesthetics, analgesics, cardiovascular agents, hormones, psychopharmacologic agents, diuretics, anticonvulsants, and anti-infective drugs. These efforts yielded data on which drugs cross the placenta, their relative rates of passage, and the amount of drug that reaches the fetus. Such research is no longer being conducted.

Recent advances in fetal surgery have allowed correction of urinary tract obstructions by placement of catheters in fetuses to drain fetal urine. The treatment of hydrocephalus by placement of shunts in fetal brains to drain excessive cerebrospinal fluid is an important example of therapeutic fetal research. Others include steroid therapy to accelerate lung maturation *in utero* when labor is premature and delivery is imminent and drug therapy to prevent congenital heart diseases that could later require surgery.

Now standard fetal diagnostic procedures such as amniocentesis and ultrasonography have been developed with fetal research. Diagnosis of such diseases as Tay-Sachs, cystic fibrosis, and muscular dystrophy may be made possible even earlier in pregnancy by a new, still-experimental technique called chorionic villus sampling (CVS). During the CVS procedure, a catheter, guided by ultrasound, is inserted into the uterus to withdraw a sample of chorionic villi tissue that surrounds the fetus and later becomes the placenta. CVS can be performed between the 8th and 12th week of pregnancy. (Amniocentesis is performed during the 16th week and the results take longer to obtain.)

With prenatal diagnosis, the physician may be able to plan for altered management of the newborn and therapeutic alternatives can be made available to endangered or dying fetuses, for example,

- o treating in utero anemia and nutritional deficiencies;
- o changing the time of delivery, e.g., induction of labor to treat intrauterine growth retardation;
- o changing the mode of delivery, e.g., cesarean delivery for conjoined twins;
- o instituting treatment immediately following delivery, e.g., management of cystic fibrosis or surgery for craniofacial, extremity, and chest wall deformities.

LEGISLATIVE/REGULATORY HISTORY OF FETAL RESEARCH

Since 1975 research has been conducted under carefully controlled stipulations mandated by strict Federal regulations that assure proper care and preserve respect for the fetus. While the regulations on fetal research apply only to federally-funded projects, they serve as the accepted standards for conduct of all fetal research.

In order to understand the regulation of federally-funded fetal research, it is useful to review policy concerning the involvement of human subjects in research. Policy has evolved slowly, starting with the convening of a National Institutes of Health (NIH) study group to develop guidelines for human subjects in research in the early 1960s. This was followed in 1966 by a one-page memorandum by the Surgeon General. In the late 1960s, Congress became increasingly concerned about the impact of advances in medical technology on human research subjects. In 1968, Sen. Walter Mondale (D-MN) held hearings on this issue and proposed establishment of a National Commission on Health Science and Society. Sen. Mondale intended to establish this temporary body to examine developments in medical research. However, the Senate did not approve establishment of such a commission until 1971. The companion measure in the House was not considered, and the Mondale bill died in the Senate during that session. During 1971, without publicity, NIH established a study group to examine the adequacy of Department of Health, Education, and Welfare (DHEW) guidelines for protection of human subjects and to recommend policy.

Early in the 1970s, reports of abuses in human research subjects arose. In 1972, a U.S. Public Health Service (PHS) study of 400 black men in Tuskegee, Alabama received extensive media coverage. The study, begun in the 1930s, was to determine the long-term effects of syphilis. The men had not been told if they

had syphilis and were not offered treatment. The study was not initiated under the current peer review system for research conducted with PHS funds. The exposure of this research led Sen. Jacob Javits (R-NY) to offer amendments to the Food, Drug, and Cosmetics Act on the protection of human subjects in research. He recommended that DHEW establish a panel to study the Tuskegee experiment and to examine the adequacy of DHEW guidelines for protection of human subjects. In 1972, DHEW established a group to investigate the Tuskegee experiment and report to Congress.

Increasing concern over research involving human subjects led Sen. Edward Kennedy (D-MA) in 1973 to begin a series of hearings on this issue. Fetal research was not specifically discussed. Later that year, DHEW reported to Congress on the Tuskegee research, recommending that a permanent body be established to regulate federally-supported research involving human subjects. As a result, the movement intensified to establish an independent, free-standing commission to monitor research.

Fetal research became controversial in the early 1970s. Legitimate concerns were exacerbated by lurid accounts of alleged trafficking in aborted fetuses from foreign countries. False reports were circulated that the Federal government was paying researchers to experiment on living, fully-developed fetuses obtained from women having cesarean sections.

The issues of fetal research and abortion had been linked in some state legislation, and the distinction between the two frequently was obscured within discussion of the 1973 Roe v. Wade Supreme Court decision that legalized abortion. Roe v. Wade led many states to change their abortion laws. Fetal research had been banned or regulated in some way within many state abortion statutes. Following legalization, many states proposed separate legislation to ban fetal research.

In May 1973, the House scheduled floor consideration of a bill to expand the national biomedical and behavioral research training program, which included a provision banning DHEW from conducting or supporting any research "which would violate ethical standards adopted by NIH." Rep. Angelo Roncallo (R-NY) offered an amendment prohibiting "research in the United States or abroad on a human fetus which is outside the uterus of its mother and which has a beating heart." His amendment passed by a vote of 354 to 9.

A similar Roncallo amendment was passed by both the House and Senate in the National Science Foundation (NSF) reauthorization. It prohibited live fetal research, even though NSF supports no fetal research. While this legislation had no applicable effect, it gave the fetal research issue an unforeseen boost into prominence.

Many bills regarding biomedical research were introduced in the Senate in 1973. Sen. James Buckley (R-NY) proposed a Roncallo-type amendment to a bill introduced by Sen. Kennedy. The Buckley amendment was not added to the legislation because Sen. Kennedy suggested alternative language prohibiting fetal research "before or after induced" abortion until after a proposed commission would report back to Congress. The bill was not enacted in 1973 due to House and Senate differences in language on the composition, duration, and responsibilities of this commission.

Finally, in 1974 a House/Senate compromise was reached. Among other provisions, the National Research Act (P.L. 93-348) established a National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. As part of the compromise, the same Act also placed "a prohibition, in effect until the Commission has made recommendations, on research (conducted or supported by DHEW) in the United States or abroad on a living human fetus, before or after the induced abortion of such fetus, unless such research is done for the purpose of assuring the survival of such fetus." This prohibition was to remain in effect for the four months between December 1974 and April 1975 when the Commission was to report back to Congress.

In August 1974, after passage of the National Research Act but before members were appointed to the National Commission, DHEW issued proposed guidelines based on the recommendations of the NIH study group that had been appointed in 1971. These guidelines stated that DHEW would

> permit research to be undertaken from which there will be no risk of harm to the (previable or viable) fetus if such research is conducted as part of the abortion procedure...in expectation that such research may produce new technology which will enable countless premature infants to live who now cannot.

This provision offered a safeguard to pregnant women who might change their minds about abortion by allowing research to occur only after the abortion procedure had been initiated. However, since the National Research Act prohibited DHEW research on living fetuses "before or after induced abortion" until after the Commission reported back to Congress, this proposed policy had no effect.

The Commission made its report on May 1, 1975. Based on its recommendations, DHEW issued regulations on July 29, 1975 on fetal research conducted with Federal funding, and the temporary prohibition on research "before or after induced abortion" was

lifted.[1] Current fetal research is performed under these regulations.

The regulations allow fetal research to be performed in utero or ex utero under a "minimal risk" standard or for "therapeutic" interventions. The "minimal risk" standard states that

> the risks of harm anticipated in the proposed research are not any greater, considering probability and magnitude, than those ordinarily encountered in daily life - or during the performance of routine physical or psychological examinations or tests.

This standard allows the researcher to observe, touch, or palpate the fetus external to the mother and to perform any other noninvasive procedure. Also permitted under this standard is the performance of a simple blood test. Research of indeterminate risk cannot be performed since it may exceed the "minimal risk" threshold. Any new area of fetal research will exceed the threshold because there is no research on which to make a judgment of risk. Animal studies often document risk; however, animals frequently provide insufficient models to determine risk for human experimentation. Therefore, until proven otherwise, all nontherapeutic research must be presumed to exceed the "minimal risk" standard. "Therapeutic" research can be conducted on fetuses if it will benefit the fetus directly, particularly in the case of a diseased, malformed, or near-dead fetus. Invasive procedures or other treatments that still have research status can be performed on a fetus in utero or ex utero as attempted therapy for that fetus. Currently, much research involving live fetuses in utero is performed for the therapeutic needs of the fetus. The justification for the conduct of fetal research, as specified in the regulations, is in "the development of important biomedical knowledge which cannot be obtained by other means."

The regulations legally separate abortion procedures from fetal research. They do not allow the researcher to have any

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[1] Any live birth resulting from a pregnancy is considered a child and covered under a separate set of regulations. While the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, created by the National Research Act of 1974, had established recommendations for research involving children, regulations were not finalized until 1983. These regulations affect fetal research only in that they specify that a fetus born alive following an attempted abortion is an infant. Children are covered under the same standards as fetuses. However, the regulations allow a child to be exposed to slightly more risk than allowed for fetuses under the fetal regulations if parental consent is obtained.

involvement in the timing, method, or procedure of an abortion or in determining the viability of the fetus at the termination of pregnancy. They stipulate that no monetary or other inducements are to be given to a woman to terminate pregnancy.

The regulations state that

> No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman may be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

This means that fetuses intended for abortion are not to be treated any differently from fetuses intended to be carried to term. The respect for the fetus regardless of its fate is also reflected in the fact that the regulations apply to all fetuses with no distinction between those intended to be carried to term and those intended to be aborted.

The regulations include a waiver provision. This provision permits the regulations to be "waived" for particular research projects that exceed the "minimal risk" standard and are not performed for "therapeutic" purposes. The regulatory restrictions can only be lifted on a project-by-project basis. The regulations establish an Ethical Advisory Board (EAB) of DHEW. Its functions is to review any waiver submissions and to make recommendations to the Secretary. The waiver process is lengthy; deliberations must be public, and an approval by the Secretary must be published in the Federal Register. The first EAB was chartered in 1977[2] but did not convene until 1978.

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[2] In 1977, a researcher from Vanderbilt University submitted a proposal for research on in vitro fertilization (IVF). DHEW Secretary Joseph A. Califano decided that a study of IVF research was needed before the proposal could be considered. This forced him to charter an EAB because by regulation all IVF research must be approved by an EAB. The researcher died before his proposal was considered, but a thorough analysis of IVF was published in the Federal Register, one of Secretary Califano's last efforts before leaving his position. In 1978, pressure increased for the DHEW EAB to clarify its position on IVF research. All IVF projects had to be approved by the Secretary at that time, and Secretary Patricia Harris was about to approve a carefully developed policy which would allow some IVF research to proceed without EAB clearance. IVF research that posed unusually high risk or that raised new ethical considerations would be considered by the Board on a project-by-project basis. However, Secretary Harris never approved the policy, and no Secretary since has adopted a policy on IVF. In the early (Footnote continued on page 10)

In 1980, a new DHEW policy required all Department-chartered boards to expire unless their charters were renewed. Secretary Patricia Harris, without offering any public explanation, allowed the charter of the EAB to expire without renewal. Without a Board, no waivers could be granted; so fetal research above the "minimal risk" standard was halted, unless for "therapeutic" interventions, by a de facto moratorium on the waiver.

The waiver provision functioned only between 1975 and 1980, and an EAB existed to consider a waiver only between 1978 and 1980. During that time one waiver was approved in 1979 for a project that entailed obtaining fetal blood samples for prenatal diagnosis of sickle cell anemia. The project was to determine the risk, which was presumed to be low but had not yet been determined, of obtaining fetal blood samples by a process known as fetoscopy. The study involved women who had elected to undergo abortion for reasons unrelated to the research. This waiver was approved by Secretary Joseph Califano, an outspoken opponent of abortion.

Since the EAB charter expired in 1980, there has been no vehicle to permit review of fetal research proposals that would require a waiver of the regulations, and there has been no national body to maintain the examination of ethical and scientific considerations as intended by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

In 1982, the NIH reauthorization bill passed in the House with a floor amendment by Rep. William Dannemeyer (R-CA) to "prohibit research on a living human fetus or infant, whether before or after induced abortion, unless...done for the purpose of insuring the survival of the fetus or infant." The Senate never acted upon the legislation.

In 1983, when the NIH reauthorization legislation was again introduced, Rep. Dannemeyer once more proposed his amendment, which elicited two important letters: Mortimer Lipsett, M.D., Director of the National Institute for Child Health and Human Development, responded to a request from Sen. Arlen Specter (R-PA) for an explanation of how Rep. Dannemeyer's amendment would affect fetal research. Dr. Lipsett explained that NIH supports a substantial program of research during pregnancy which has direct

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1980s, Sen. Orrin Hatch (R-UT) asked the President's Commission on Ethical Issues in Medicine and Biomedical and Behavioral Research to study IVF. The Commission declined, contending that the EAB had done a comprehensive study of IVF and that there was no need to duplicate the Board's efforts. The Federal government does not now fund any IVF research.

benefits for improving the health of the fetus and the infant. He warned that, depending on the interpretation of the Dannemeyer amendment, research could be substantially impeded. In its broadest interpretation, he wrote, the amendment could halt "all research throughout pregnancy and research on infants up to one year of age...irrespective of its relation to abortion unless undertaken to ensure the survival of that fetus or infant."

The second letter was from Sen. Jeremiah Denton (D-AL). In response, Secretary Margaret Heckler assured him of the Federal government's responsible approach to funding fetal research: no research was being undertaken on a living fetus ex utero after induced abortion, and any fetus intended for abortion was not to be treated differently from fetuses intended to be carried to term.

In 1985, the NIH reauthorization bill, the Health Research Extension Act, passed. It included a 3-year moratorium on the use of the waiver provision of the fetal research regulations and codified into Federal law a portion of the existing administrative regulations on fetal research. The moratorium on the waiver leaves current fetal research regulations intact; so fetal research can be conducted under the "minimal risk" standard and for "therapeutic" interventions. The Health Research Extension Act of 1985 created a Congressional Biomedical Ethics Board composed of members of Congress and charged with examining broad areas of protection of human subjects in biomedical research. It included studies on the application of genetic engineering and on the nature, advisability, and biomedical and ethical implications of exercising the waiver provision of the fetal research regulations.

The Congressional Board has selected twelve of its expert advisory committee members with two remaining vacancies for the public members. However, it has reached a political stalemate in appointing advisory committee members, and no staff has been hired. It is unlikely the Board will complete its studies by the time the moratorium expires on October 31, 1988. The Board will remain in place until further legislative action is taken.

The most recent proposed legislation on fetal research is contained in the upcoming 1988 NIH reauthorization bill. This legislation would prohibit research above the "minimal risk" standard for another two to three years pending a study of the issue by the National Academy of Sciences. The legislation would keep the Biomedical Ethics Board intact but not require them to do a study on fetal research.

Despite pressures for more than a decade to ban all fetal research, regulations that permit "minimal risk" and "therapeutic" fetal research have been established. The waiver provision to exempt some research proposals from the restrictions after review has remained in the regulations but has been the subject of continuing debate. Although the regulations on fetal research have existed for 13 years, the waiver provision has been

functional for only two of them. There has been a decline in researchers choosing this field of study and, given the excitement and promise in this field, fewer research proposals have been submitted than would be expected. These circumstances probably have resulted from uncertainty over the funding and conduct of fetal research. No DHHS EAB has existed since 1980, and since 1985 current law has contained a moratorium on granting waivers from the fetal research regulations.

FETAL TISSUE RESEARCH

BENEFITS/OUTCOMES OF FETAL TISSUE RESEARCH

It is important to understand the distinction between fetal research and the use of fetal tissue in research. As the name implies, fetal tissue research, unlike fetal research, uses only samples of fetal tissue. These are taken from deceased fetuses from spontaneous or induced abortions. Research utilizing fetal tissue currently has two areas of medical application: developing cell lines and transplanting tissue.

Early in its research history, fetal tissue was used in developing particular cell lines. A cell line is a sample of cells that has undergone the process of adaptation to artificial laboratory cultivation and is capable of sustaining continuous, long-term growth in culture.[3] It is a class of cells originating from the same parent cell; the cells are thus of identical nature and type. Fetal cells provide special advantages as cell lines because of their rapid growth and adaptability. The study and culture of fetal cells dates back to the 1930s.

Cell lines prepared from human tissues are essential for the reproduction of human viruses both for the diagnosis of disease and in the production of human vaccines. The discovery of the polio vaccine in the 1950s was based on cultures of human fetal kidney cells. Fetal tissues also are used extensively in the safety tests required for many vaccines.

A continuing supply of fetal tissue will be needed to prepare and test products now under license and for new products expected to be licensed. Technology is advancing rapidly so that fewer original cells from fetal tissue will be needed to develop cell lines.

Current widely publicized research with fetal tissue deals with the transplantation of such tissue into the brains or organs

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[3] Office of Technology Assessment. New Developments in Biotechnology: Ownership of Human Tissues and Cells, March, 1987.

of individuals who suffer from injuries or diseases that originate from a lack of certain cells or from the inability of certain cells to function properly. Fetal tissue has unique qualities which make it superior to adult tissue for many forms of transplantation in that it grows rapidly and is more adaptable than adult tissue. Technology has been developed that allows fetal cells to proliferate in the laboratory, which means that a small amount of fetal tissue can potentially be used to treat many patients. Such cell multiplication cannot be achieved with most adult cell types. Additionally, although both adult and fetal tissues contain cells that trigger immune responses, laboratory processes can eliminate those cells from fetal tissue. Thus, the transplantation of purified fetal cells requires neither tissue matching nor long-term immunosuppression as is the case in adult tissue transplantation.

Research with animals indicates that fetal tissue has wide treatment applications, and such animal studies have been essential to the advancement of this area of research. It is only within the last fifteen years that medical technology has made it possible to use fetal tissue for transplantation in humans, and studies with human subjects are just beginning. Research has begun with Federal and other funding in the transplantation of fetal pancreatic islet cells in patients with diabetes. Thirty patients have had fetal islet transplants in the U.S. and thirty in China. This research is still in its early stages, but patients who have undergone fetal pancreatic islet transplants have either decreased their insulin intake or have been able to live without insulin. Transplantation of fetal tissue has vast treatment potential benefiting fetuses, children, and adults.

In 1982, in Sweden, a team of surgeons unsuccessfully attempted to transplant into the brain the recipient's own adrenal tissue in four patients with Parkinson's Disease. The hypothesis was that since Parkinson's Disease is caused by a deficiency in dopamine and since the adrenal gland produces dopamine, a transfer of tissue from the adrenal gland to the brain may initiate the production of dopamine. In 1986, Mexican surgeons successfully tried a modified version of the Swedish technique, and the patients' conditions improved. The Chinese have performed successful autologous adrenal transplants in five patients. Autologous adrenal transplants in humans also have been performed in the United States.

Both the Mexican and Chinese physicians have had better results with younger patients. Animal studies in the U.S. indicate that adrenal cells are not very effective in the long run. Part of the difficulty in using adrenal tissue is that the patient must go through two surgeries, one to retrieve the adrenal tissue and a second to transplant the tissue. Animal studies have shown that tissue transplanted from the brains of animal fetuses into animals of their same species is more effective.

Researchers have been investigating fetal tissue for use in blood diseases and radiation poisoning. In 1986, Robert Gale,

M.D., of UCLA and three colleagues flew to the Soviet Union in an attempt to save radiation victims following the Chernobyl disaster. They tried to transplant liver cells from deceased fetuses to regenerate bone marrow. They used fetal liver cells because in the early human embryo the liver is the major producer of blood cells, and transplantation of fetal tissue could provide the radiation patient with the necessary blood-forming tissue. The success of the technique is not known because all the patients died from radiation-induced burns.

Such research and current animal studies provide evidence that cells taken from deceased fetuses may have applications for treating fatal blood diseases such as sickle cell anemia, thalassemia, severe combined immunodeficiency, and other inherited blood disorders. Cells from animal fetal livers have been transplanted successfully into sheep fetuses. Other applications for fetal liver cells may be in treatment of childhood and adult diseases such as aplastic anemia, leukemia, and radiation poisoning. Transplantation of fetal cells may become the preferred treatment for blood diseases because bone marrow transplants commonly engender rejection.

In current animal studies, researchers are investigating other possible uses of fetal tissue. They are studying treatment of spinal cord injuries by using fetal tissue for nerve regeneration and are attempting repair of damaged optic nerves, which normally cannot regenerate. Parkinson's disease, Alzheimer's disease, Huntington's chorea, diabetes, a wide range of neurological diseases and injuries, and blood-related diseases are the subject of fetal tissue research. Other applications for fetal tissue may be in the treatment of epilepsy, stroke, and certain learning disabilities. Fetal tissue also is being used in research on cancer, AIDS, and pulmonary, kidney, eye, and dental diseases.

LEGISLATIVE/REGULATORY HISTORY OF FETAL TISSUE RESEARCH

Federal regulations state that activities involving

> mascerated fetal material or cells, tissue or organs excised from a dead fetus shall be conducted only in accordance with any applicable state or local laws regarding such activities.

Two other stipulations from Federal regulations covering fetal research also apply to research using fetal tissue: the researcher may not be involved in the timing, method, and procedures used to terminate the pregnancy or in determining the viability of the fetus at the termination of pregnancy; and no inducements, monetary or otherwise, may be offered to the mother to terminate pregnancy for purposes of performing research. These stipulations represent the only instances in which the regulations regarding fetal research and use of fetal tissue in research overlap in these two otherwise distinct areas.

Between 1969 and 1973, all 50 states adopted the Uniform Anatomical Gift Act (UAGA) which authorizes "the gift of all or part of a human body after death for specified purposes."[4] This Act allows tissue from dead fetuses to be used for research or for therapeutic purposes. Tissue retrieved from fetuses for research is obtained from dead fetuses ex utero.

Research using fetal tissue follows the scientific tradition of medical inquiry and of the study of human pathology as in the long-standing practice of autopsy. The acceptance of this well-established practice is reflected in the adoption of the UAGA by all 50 states.

The requirement of the Federal regulations is satisfied when fetal remains are donated for research purposes in accordance with the applicable state UAGA (and when the remains are not subject to more restrictive state laws) and when the two stipulations of the Federal regulations as indicated above are fulfilled. Depending on the particular state restrictions for the disposition of fetal tissue, state UAGAs specify the requirements for maternal consent.

Many state laws on abortion were invalidated by the 1973 Roe v. Wade decision. However, those sections of state abortion laws that included language on the disposition of fetal remains were not necessarily invalidated. Although the UAGA recommended that the term "decedent" be defined to include stillborn infants and dead fetuses, this definition was omitted in the acts as passed by some states.

A number of states require that donations and transactions involving human remains be performed as "services" rather than as "sales." Furthermore, the National Organ Transplant Act (P.L. 98-507) prohibits the sale of human organs (kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, and skin). Fetal tissue and products such as blood and sperm can be sold[5] except in states that specifically have prohibited such sales.

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[4] The UAGA was revised in August 1987 by the National Commissioners on Uniform State Laws. Each state is reviewing the revised UAGA and will decide whether to adopt it. At present, no state has adopted the revised UAGA.

[5] Reimbursements ("reasonable payments") are permitted for the removal, transportation, implantation, processing, preservation, quality control, and storage of a human organ or the expenses of travel, housing, and lost wages incurred by the donor of a human organ in connection with the donation of the organ.

The use of fetal tissue in research is gaining public attention. As the media highlight ongoing advancements and ethical concerns, it is likely that debate may increase. Two proposals have emerged in 1987 on the regulation of fetal tissue: Jeremy Rifkin, Director, Foundation for Economic Trends, has petitioned the Secretary of DHHS to prohibit the sale of fetal tissue by including fetal tissue as a "human organ" under the National Organ Transplant Act. Sen. Gordon Humphrey (R-NH), along with 23 legislators, also has requested the Secretary to include fetal tissue as an organ under the Act. In another initiative, Mr. Rifkin recently filed a petition with the Secretary against the transport of dead fetal remains across state lines. DHHS has asked Mr. Rifkin to document any abuses, but he has been unable to provide any evidence of wrongdoing. Rep. Robert Dornan (R-CA) introduced legislation, also in 1987, that would authorize DHHS to regulate the interstate transport and storage of fetal tissue.

The most recent development on the use of fetal tissue has come from DHHS. On March 22, 1988, Robert Windom, M.D., DHHS Assistant Secretary for Health, prohibited NIH from conducting intramural research on the transplantation of fetal tissue from induced abortions until after a special outside advisory committee, to be appointed by NIH director, James Wyngaarden, M.D., can examine the ethical and legal issues involved. The first meeting of the committee, which has not yet been appointed, will convene in July 1988.

FETAL RESEARCH AND

FETAL TISSUE RESEARCH

QUESTIONS AND ANSWERS

This section provides answers to questions most commonly asked about fetal research and fetal tissue research.

FETAL RESEARCH

WHAT IS FETAL RESEARCH?

The term is generally used to describe research performed on a living, intact fetus inside the uterus, although it is legal to perform research outside the uterus. Fetal research is different from fetal tissue research, which is research using tissue obtained from dead fetuses. Research may invade or intrude upon the fetus as occurs in fetal surgery to save an endangered life. Other research may be external, for example, observing a fetus or performing a sonogram.

WHAT IS THE "MINIMAL RISK" STANDARD AS SPECIFIED IN THE FEDERAL REGULATIONS?

Federal regulations state that fetal research can be performed under the "minimal risk" standard or for "therapeutic" actions that directly benefit the fetus, particularly in the case of a diseased, malformed, or near dead fetus. The "minimal risk" standard states that

> the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

This standard allows the researcher to observe the fetus, to perform other noninvasive procedures, or to perform a simple blood test.

Under this standard no research of undetermined risk can be performed because it may prove to exceed the "minimal risk" threshold. Any new area of fetal research would exceed the threshold because there would be no prior research on which to make a judgment of risk. Animal studies can document risk; but, animals often provide insufficient models to determine the risk of experiments on humans. Therefore, until proven otherwise, all nontherapeutic research must be presumed to exceed the "minimal risk" standard.

WHERE ARE THE REGULATIONS GOVERNING FETAL RESEARCH CONTAINED?

The regulations can be found in the Code of Federal Regulations - 45 CFR 46 Subpart B - Sections 46.201 - 46.211. These regulations, which have been in effect since 1975, are based on the recommendations of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research established by the National Research Act of 1974 (P.L. 93-348). The legislation containing the moratorium on the waiver of the regulations can be found in the Health Research Extension Act (P.L. 99-158) of 1985, Sec. 498.

WHAT SPECIFIC AREAS OF HEALTH CARE OR TREATMENT HAVE BENEFITED FROM FETAL RESEARCH?

- Development of the rubella (German measles) vaccine;
- Development of amniocentesis, a procedure to retrieve fluid from the amniotic sac to obtain information about possible chromosomal abnormalities and about the sex of the fetus;
- Detection, management, and prevention of Rh blood group incompatibility;
- Detection of at least 30 chromosomal and metabolic disorders, and other birth defects including Down's syndrome, cystic fibrosis, and Tay-Sachs disease;
- Assessment of fetal lung maturity to understand and treat respiratory distress syndrome;
- Prevention and treatment of prematurity through fetal monitoring techniques and intensive hospital care of newborns;
- Evaluation of the health of the fetus by measurements of hormone levels in the mother's blood or urine;
- Development of new agents to prevent long and dangerous labor;
- Development of new anesthesia techniques leading to safer deliveries;
- Development of treatment advances for preeclampsia, a potentially fatal condition of late pregnancy arising from severe hypertension;
- Development of new treatments to reduce the risks of pregnancy for women with heart or metabolic disease;

- Evaluation of timing of delivery and use of antibiotics to treat premature rupture of amniotic sac membranes;

- Development of fetal surgery techniques to diagnose and treat hydrocephalus (a buildup of fluid in the brain) and urinary tract obstructions in the fetus;

- Development of chorionic villus sampling, a technique for diagnosing in the fetus a broad array of diseases and abnormalities.

WHAT ROLE HAVE ANIMAL STUDIES PLAYED IN ADVANCING FETAL RESEARCH?

Animal studies have been essential to the advancement of fetal research. Initial studies on animals have allowed risk to be determined so that procedures or treatments can be used on human beings. Drug and vaccine studies and procedures such as amniocentesis are tested on animals prior to any experiments on humans. Animal studies often have enabled researchers to comply with the "minimal risk" standard by first determining the risk through research on animals. However, animals frequently provide insufficient models to determine risk. The regulations also stipulate that appropriate studies must be conducted on animals and nonpregnant women before they are performed on pregnant women.

WHAT IS THE ADVANTAGE OF PERFORMING RESEARCH ON FETUSES?

Although animal models have been instrumental in fetal research, frequently no alternative exists to human fetal experimentation. For example, no models exist for most human genetic and metabolic disorders, and at present, research on fetuses provides the only hope of understanding both normal and abnormal development. Most diseases of the newborn, many complications of delivery, and many diseases and disorders that emerge throughout an individual's life begin during fetal development. Without fetal research, it would be impossible to develop techniques to diagnose and treat these problems prior to birth. Fetal research has produced medical benefits not only for fetuses but also for infants, children, and adults.

WHAT DO THE REGULATIONS ON FETAL RESEARCH SAY ABOUT ABORTION PROCEDURES?

Under the section on general limitations (DHHS 45 CFR 46.207), the regulations state that

> Individuals engaged in the activity (fetal research) will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy;

The regulations also state that "No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity."

These provisions are designed to legally separate fetal research and individuals who perform it from any relationship to or decisions about termination of pregnancy. These provisions respond to concerns that researchers might manipulate patient care to obtain research results. They provide appropriate protections to guard against such an occurrence.

The regulations also state that

> No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

This means that fetuses intended for abortion are not to be treated any differently from or exposed to any greater risk than fetuses intended to be carried to term. The respect for the fetus, regardless of its fate, is also reflected in the fact that the regulations apply to all fetuses with no distinctions between those intended to be carried to term and those intended to be aborted.

WHAT IS THE "WAIVER" AS IT PERTAINS TO FETAL RESEARCH?

Federal regulations state that research can be performed on fetuses only under the "minimal risk" standard or for "therapeutic" actions to help an endangered fetus.

When exercised, the waiver provision permits the regulations to be set aside or modified for particular research projects that exceed the "minimal risk" threshold and are not performed for treatment purposes. The regulatory restrictions can be lifted on a project-by-project basis after review and recommendation by an Ethical Advisory Board (EAB) of DHHS and approval by the Secretary of DHHS.

The regulations (DHHS 45 CFR 46.211) state that the Secretary may waive specific requirements of the fetal research regulations with the approval of the EAB after an opportunity for public comment. The Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a waiver and that such benefits cannot be gained except through a waiver. Any waiver will be published as a notice in the Federal Register.

The Health Research Extension Act of 1985 has placed a moratorium on use of the waiver provision. This means that no research can be conducted if it is not known to be "minimal risk" (or undetermined risk, which may exceed the "minimal risk" threshold) or intended to provide treatment until the moratorium

expires on October 31, 1988. Under the upcoming 1988 NIH reauthorization bill, further legislative action that would continue to restrict fetal research is likely.

WHAT IS THE CONGRESSIONAL BIOETHICS BOARD?

The Congressional Bioethics Board was created by the Health Research Extension Act of 1985 as a bipartisan Congressional support agency composed of 12 members of Congress. Its broad purpose is to study ethical issues arising from the delivery of health care and from biomedical and behavioral research; the protection of human subjects of such research; and developments in activities that have implications for human genetic engineering such as recombinant DNA technology.

Under this broad mandate, one study is to investigate the "nature, advisibility, and biomedical and ethical implications of exercising any waiver of the risk standard within the regulations on fetal research."

To conduct its studies, the Board is to appoint a 14-member Biomedical Ethics Advisory Committee. Twelve of this Committee's expert members have been selected, but none has been officially appointed. Two vacancies remain for representatives of the public, and no staff has been hired. It appears unlikely that the Board will report back to Congress by its deadline, October 31, 1988. The Board will remain in place until further legislative action is taken.

Pending a report to Congress by the Board, a 3-year moratorium has been placed on use of the waiver provision of the fetal research regulations. This means that no fetal research above the "minimal risk" standard can be conducted unless it is for treatment.

The 12 Congressional members of the Board are

Senate Members	House Members
Albert Gore (D-TN), Vice Chair	Willis Gradison (R-OH), Chair
Dale Bumpers (D-AK)	Thomas Bliley (R-VA)
David Durenberger (R-MN)	Thomas Luken (D-OH)
Gordon Humphrey (R-NH)	J. Roy Rowland (D-GA)
Edward Kennedy (D-MA)	Thomas Tauke (R-IA)
Lowell Weicker (R-CT)	Henry Waxman (D-CA)

FETAL TISSUE RESEARCH

WHAT IS FETAL TISSUE RESEARCH?

Research with fetal tissue uses tissue from dead fetuses obtained from spontaneous and induced abortions. This tissue is particularly useful in development of cell cultures and cell lines. A cell line is a sample of cells that can continue to grow in the laboratory. Cell lines prepared from human tissue are essential for growing human viruses in the laboratory, for the detection and study of viral diseases, and for the production of vaccines to prevent disease. Fetal cells have special advantages for developing cell lines because they grow rapidly and adapt well to artificial laboratory conditions.

Recent advances in the use of fetal tissue involve its transplantation into persons with a variety of diseases to cure or ameliorate their condition.

WHERE ARE THE REGULATIONS GOVERNING THE USE OF FETAL TISSUE IN RESEARCH?

Within the Code of Federal Regulation, under 45 CFR 46, section 46.210 - "Activities involving the dead fetus, fetal material, or the placenta" states that

> mascerated fetal material, or cells, tissues, or organs excised from a dead fetus shall be conducted only in accordance with any applicable state or local laws regarding such activities.

The legislation on fetal tissue, adopted by all 50 states, is the Uniform Anatomical Gift Act (UAGA). The UAGA reflects the well-established scientific tradition of medical inquiry and study of human pathology.

WHAT SPECIFIC AREAS OF HEALTH CARE OR TREATMENT HAVE BENEFITED FROM RESEARCH USING FETAL TISSUE?

- Development of a vaccine for polio;
- Demonstration of the relative usefulness of various drugs in the treatment of intrauterine infections, particularly syphilis;
- Detection by amniotic studies of abnormal processes during pregnancy;
- Study of certain types of cancerous cells, degenerative diseases, and birth defects;

- Study of the reasons for rejection of transplanted kidneys and livers in adults;

- Development of experimental techniques to transplant fetal tissue into the brains or other organs of fetuses, children, and adults to treat Parkinson's disease, Alzheimer's disease, Huntington's chorea, radiation poisoning, aplastic anemia, leukemia, thalassemia, combined immunodeficiency disease, epilepsy, stroke, optic nerve damage, diabetes, spinal cord nerve injuries, and a growing list of other conditions.

WHAT IS THE ADVANTAGE OF THE THERAPEUTIC USE OF FETAL TISSUE?

Fetal tissue has unique qualities which make it superior to adult tissue for many forms of transplantation in that it grows rapidly and is more adaptable than adult tissue. Technology has been developed that allows fetal cells to be proliferated in the laboratory, which means that a small amount of fetal tissue can potentially be used to treat many patients. Such cell multiplication cannot be achieved with most adult cell types. Additionally, although both adult and fetal tissues contain cells that trigger immune responses, laboratory processes can eliminate those cells from fetal tissue. Thus, the transplantation of purified fetal cells will require neither tissue matching nor long-term immunosuppression as is the case in adult tissue transplantation.

CHRONOLOGY OF FETAL RESEARCH AND FETAL TISSUE RESEARCH

Early-Mid 1960s	NIH study group issues guidelines on the protection of human subjects in research.
1968	Sen. Walter Mondale (D-MN) holds hearings on the protection of human subjects in research and proposes establishment of a National Commission on Health Science and Society.
1969 - 1973	All 50 states adopt the Uniform Anatomical Gift Act.
1971	NIH establishes study group to examine the adequacy of the DHEW guidelines for the protection of human subjects.
1972	U.S. Public Health Service study of of the long-term effects of syphilis in 400 black men in Tuskegee, Alabama, is exposed. DHEW establishes a group to investigate the experiment and report to Congress.
1973	Sen. Edward Kennedy (D-MA) begins a series of hearings on the protection of human subjects in research.
1973	Supreme Court issues Roe v. Wade decision to legalize abortion and overturns state abortion legislation that often covered fetal research. In response, many states propose legislation to ban fetal research.
1973	Many bills introduced in Congress on biomedical research. Rep. Angelo Roncallo (R-NY) and Sen. James Buckley (R-NY) offer amendments to ban research on a fetus, ex utero, with a beating heart.
1974	National Research Act (P.L. 93-348) establishes the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

December 1974 - April 1975	Fetal research is prohibited before or after induced abortion unless for the purpose of survival of the fetus.
May 1975	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research reports to Congress with recommendations on the establishment of regulations on fetal research.
July 1975	DHEW issues regulations on fetal research based on the National Commission's report.
1978	The first Ethical Advisory Board (EAB) of DHEW is convened.
1979	A waiver of the fetal research regulations is approved for a project to obtain fetal blood samples for research on sickle cell anemia.
1980	The charter of the EAB expires.
1982	Swedish team of surgeons unsuccessfully attempt transplantation of autologous adrenal tissue in patients with Parkinson's Disease.
1982	Rep. William Dannemeyer (R-CA) proposes amendment to the NIH reauthorization bill to prohibit research on a living human fetus unless for ensuring the survival of the fetus.
1983	NICHD Director Mortimer Lippsett, M.D., and DHHS Secretary Margaret Heckler respond to inquiries regarding the Dannemeyer Amendment by defending fetal research.
1983	DHHS issues regulations on the use of children in research based on the National Commission's report of 1975.

1985	NIH reauthorization bill places a 3-year moratorium on fetal research above the "minimal risk" standard and establishes the Congressional Bioethics Board to study the nature, advisability, and biomedical and ethical implications of exercising the waiver provision of the fetal research regulations.
1986	Mexican surgeons succeed with a modified version of the Swedish technique of transplanting in a recipient's brain his own adrenal tissue. U.S. follows by attempting such treatment.
1986	Robert Gale, M.D., and colleagues attempt to save radiation victims following the Chernobyl disaster by transplanting liver cells from deceased fetuses. All the patients die of radiation burns.
August 1987	National Commissioners on Uniform State Laws revise the Uniform Anatomical Gift Act. States will review and decide whether to adopt revised Act.
March 1988	NIH Director James Wyngaarden, M.D., requests approval of research calling for the implantation of human neural tissue into Parkinson's patients. DHHS Assistant Secretary for Health, Robert Windom, M.D., denies the request and asks Wyngaarden to establish an outside advisory committee to examine the desirability of the use of fetal tissue in research.
Spring 1988	Proposed legislation within the 1988 NIH reauthorization bill prohibits research above the minimal risk standard for two to three more years pending a study by the National Academy of Sciences.

GLOSSARY

"Commission" or "National Commission" - National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research

The National Research Act (P.L. 93-348) of 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and among its mandates gave the National Commission a charge to investigate and study research involving the living fetus and to recommend whether and under what circumstances such research should be conducted or supported by DHEW. Based on recommendations made by the Commission in May 1975, DHEW issued regulations on fetal research in August 1975.

"EAB" - Ethical Advisory Board

Under the fetal research regulations, one or more Ethical Advisory Boards are to be established by the Secretary of DHHS. The function of the EAB is to review any waiver submissions for fetal research proposals that may exceed the "minimal risk" standard and to make recommendations to the Secretary for the projects' approval or disapproval. An EAB was chartered in 1977, convened in 1978, and functioned only until 1980 when the charter expired. One waiver was granted in 1979.

"President's Commission" - President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

In November 1978, Congress authorized the creation of a Presidential commission with continuing responsibility to study and report on the ethical and legal implications of a number of issues in medicine and research. The Commission comprises distinguished individuals in biomedical or behavioral research, in the practice of medicine or health care, in one or more fields of ethics, theology, law, the natural sciences, the social sciences, the humanities, health administration, government, and public affairs. It expired on March 31, 1983.

The President's Commission conducted studies of health care on the definition of death, informed consent, genetic screening and counseling, differences in the availability of health care, life-sustaining treatment, and privacy and confidentiality. It conducted studies of biomedical and behavioral research on genetic engineering, compensation for injured subjects, and whistleblowing in research. Two additional studies were conducted on the adequacy, uniformity, and implementation of the Federal rules on research subjects.

"Board" - Biomedical Ethics Board

Established by statute in the Health Research Act of 1985 (P.L. 99-158), the Biomedical Ethics Board is a nonpartisan Congressional support agency consisting of six members each of the Senate and the House. Under the Board's broad mandate to study ethical issues arising from delivery of care and from biomedical and behavioral research, one study is to be on the "nature, advisability, and biomedical and ethical implications of exercising any waiver of the risk standard within the regulations on fetal research." No studies to be accomplished under the Board's charter have been initiated yet. The Board will remain in place until further legislative action is taken.

"Committee" - Biomedical Ethics Advisory Committee

The Biomedical Ethics Board is to appoint a 14-member Biomedical Ethics Advisory Committee to conduct its studies. This committee is to be composed of distinguished members in biomedical or behavioral research, in the practice of medicine or health care, in ethics, theology, law, the natural sciences, the humanities, health administration, government, or public affairs, and of the public. Twelve expert members have been selected; two vacancies remain for the public members.

REFERENCES

Fetal Research Regulations/Law

Subpart B - Additional Protections Pertaining to Research, Development, and Related Activities involving Fetuses, Pregnant Women, and Human In Vitro Fertilization, 45 C.F.R. Secs. 46.201-46.211.

National Research Act of 1974, P.L. 93-348, 88 Stat. 342.

National Research Extension Act of 1985, P.L. 99-158, 99 Stat. 820.

Waiver of Fetal Research Regulations

44 Fed. Reg. 47732 (1979).

Fetal Tissue Regulations/Law

Uniform Anatomical Gift Act - Appendix A, 57 The Georgetown Law Journal 5 (1968).

National Organ Transplant Act, P.L. 98-507, 98 Stat. 2339.

National Commission Reports

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Report and Recommendations: Research on the Fetus, 1975, U.S. Dept. of Health, Education and Welfare (DHEW Publication No. (OS) 76-127).

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Appendix: Research on the Fetus, 1975, U.S. Dept. of Health, Education and Welfare (DHEW Publication no. (OS) 76-128).

Additional copies of this report are available from the Office of Membership and Publication Orders, Association of American Medical Colleges, (202) 828-0523.

Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human in Vitro Fertilization

Source: 40 FR 33528, Aug. 8, 1975, unless otherwise noted.

§ 46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, development, and related activities involving: (1) The fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§ 46.203 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

(c) "Fetus" means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

(d) "Viable" as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.

(e) "Nonviable fetus" means a fetus *ex utero* which, although living, is not viable.

(f) "Dead fetus" means a fetus *ex utero* which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) "*In vitro* fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.204 Ethical Advisory Boards.

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health and Human Services.

(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

(d) No application or proposal involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of this subpart;

(2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) Carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in § 46.120 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

[40 FR 33528, Aug. 8, 1975, as amended at 46 FR 8386, Jan. 26, 1981]

§ 46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed;

(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

[40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975]

§ 46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§ 46.208 Activities directed toward fetuses in utero as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heart-

beat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.210 Activities involving the dead fetus, fetal material, or the placenta.

Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§ 46.211 Modification or waiver of specific requirements.

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the FEDERAL REGISTER.

APPENDIX B

UNIFORM ANATOMICAL GIFT ACT

An act authorizing the gift of all or part of a human body after death for specified purposes.

SECTION 1. (Definitions.)

(a) "Bank or storage facility" means a facility licensed, accredited or approved under the laws of any state for storage of human bodies or parts thereof.

(b) "Decedent" means a deceased individual and includes a stillborn infant or fetus.

(c) "Donor" means an individual who makes a gift of all or part of his body.

(d) "Hospital" means a hospital licensed, accredited or approved under the laws of any state and includes a hospital operated by the United States government, a state, or a subdivision thereof, although not required to be licensed under state laws.

(e) "Part" includes organs, tissues, eyes, bones, arteries, blood, other fluids and other portions of a human body, and "part" includes "parts."

(f) "Person" means an individual, corporation, government or governmental subdivision or agency, business trust, estate, trust, partnership or association or any other legal entity.

(g) "Physician" or "Surgeon" means a physician or surgeon licensed or authorized to practice under the laws of any state.

(h) "State" includes any state, district, commonwealth, territory, insular possession, and any other area subject to the legislative authority of the United States of America.

SECTION 2. (Persons Who May Execute an Anatomical Gift.)

(a) Any individual of sound mind and 18 years of age or more may give all or any part of his body for any purposes specified in Section 3, the gift to take effect upon death.

(b) Any of the following persons, in order of priority stated, when persons in prior classes are not available at the time of death, and in the absence of actual notice of contrary indications by the decedent, or actual notice of opposition by a member of the same or a prior class, may give all or any part of the decedent's body for any purposes specified in Section 3:

(1) the spouse
(2) an adult son or daughter
(3) either parent
(4) an adult brother or sister
(5) a guardian of the person of the decedent at the time of his death
(6) any other person authorized or under obligation to dispose of the body.

(c) If the donee has actual notice of contrary indications by the decedent, or that a gift by a member of a class is opposed by a member of the same or a prior class, the donee shall not accept the gift. The persons authorized by this subsection may make the gift after death or immediately before death.

(d) A gift of all or part of a body authorizes any examination necessary to assure medical acceptability of the gift for the purposes intended.

(e) The rights of the donee created by the gift are paramount to the rights of others except as provided by Section 7(d).

SECTION 3. (Persons Who May Become Donees, and Purposes for which Anatomical Gifts May be Made.) The following persons may become donees of gifts of bodies or parts thereof for the purposes stated:

(a) Any hospital, surgeon, or physician, for medical or dental education, research, advancement of medical or dental science, therapy or transplantation; or

(b) Any accredited medical or dental school, college or university for education, research, advancement of medical or dental science or therapy; or

(c) Any bank or storage facility, medical or dental education, research, advancement of medical or dental science therapy or transplantation; or

(d) Any specified individual for therapy or transplantation needed by him.

SECTION 4. (Manner of Executing Anatomical Gifts.)

(a) A gift of all or part of the body under Section 2(a) may be made by will. The gift becomes effective upon the death of the testator without waiting for probate. If the will is not probated, or if it is declared invalid for testamentary purposes, the gift, to the extent that it has been acted upon in good faith, is nevertheless valid and effective.

(b) A gift of all or part of the body under Section 2(a) may also be made by document other than a will. The gift becomes effective upon the death of the donor. The document, which may be a card designed to be carried on the person, must be signed by

the donor, in the presence of 2 witnesses who must sign the document in his presence. If the donor cannot sign, the document may be signed for him at his discretion and in the presence of 2 witnesses who must sign the document in his presence. Delivery of the document of gift during the donor's lifetime is not necessary to make the gift valid.

(c) The gift may be made to a specified donee or without specifying a donee. If the latter, the gift may be accepted by the attending physician as donee upon or following death. If the gift is made to a specified donee who is not available at the time and place of death, the attending physician upon or following death, in the absence of any expressed indication that the donor desired otherwise, may accept the gift as donee. The physician who becomes a donee under this subsection shall not participate in the procedures for removing or transplanting a part.

(d) Nothwithstanding Section 7(b), the donor may designate in his will, card or other document of gift the surgeon or physician to carry out the appropriate procedures. In the absence of a designation, or if the designee is not available, the donee or other person authorized to accept the gift may employ or authorize any surgeon or physician for the purpose.

(e) Any gift by a person designated in Section 2(b) shall be made by a document signed by him, or made by his telegraphic, recorded telephonic or other recorded message.

SECTION 5. (Delivery of Document of Gift.) If the gift is made by the donor to a specified donee, the will, card or other document, or an executed copy thereof, may be delivered to the donee to expedite the appropriate procedures immediately after death, but delivery is not necessary to the validity of the gift. The will, card or other document, or an executed copy thereof, may be deposited in any hospital, bank or storage facility or registry office that accepts them for safekeeping or for facilitation of procedures after death. On request of any interested party upon or after the donor's death, the person in possession shall produce the document for examination.

SECTION 6. (Amendment or Revocation of the Gift.)

(a) If the will, card or other document or executed copy thereof, has been delivered to a specified donee, the donor may amend or revoke the gift by:

(1) the execution and delivery to the donee of a signed statement, or

(2) an oral statement made in the presence of 2 persons and communicated to the donee, or

(3) a statement during a terminal illness or injury addressed to an attending physician and communicated to the donee, or

(4) a signed card or document found on his person or in his effects.

(b) Any document of gift which has not been delivered to the donee may be revoked by the donor in the manner set out in subsection (a) or by destruction, cancellation, or mutilation of the document and all executed copies thereof.

(c) Any gift made by a will may also be amended or revoked in the manner provided for amendment or revocation of wills, or as provided in subsection (a).

SECTION 7. (Rights and Duties at Death.)

(a) The donee may accept or reject the gift. If the donee accepts a gift of the entire body, he may, subject to the terms of the gift, authorize embalming and the use of the body in funeral services. If the gift is of a part of the body, the donee, upon the death of the donor and prior to embalming, shall cause the part to be removed without unnecessary mutilation. After removal of the part, custody of the remainder of the body vests in the surviving spouse, next of kin or other persons under obligation to dispose of the body.

(b) The time of death shall be determined by a physician who attends the donor at his death, or, if none, the physician who certifies the death. This physician shall not participate in the procedures for removing or transplanting a part.

(c) A person who acts in good faith in accord with the terms of this Act, or under the anatomical gift laws of another state (or a foreign country) is not liable for damages in any civil action or subject to prosecution in any criminal proceeding for his act.

(d) The provisions of this Act are subject to the laws of this state prescribing powers and duties with respect to autopsies.

SECTION 8. (Uniformity of Interpretation.) This Act shall be so construed as to effectuate its general purpose to make uniform the law of those states which enact it.

SECTION 9. (Short Title.) This Act may be cited as the Uniform Anatomical Gift Act.

SECTION 10. (Repeal.) The following acts and parts of acts are repealed:

(1)
(2)
(3)

SECTION 11. (Time of Taking Effect.) This Act shall take effect ...

STATEMENT

OF THE

ASSOCIATION OF AMERICAN MEDICAL COLLEGES

On

HUMAN FETAL TISSUE TRANSPLANTATION RESEARCH: THE NEED FOR FEDERAL SUPPORT

Presented to

NIH Human Fetal Tissue Transplantation Research Panel

September 14, 1988

By

Myron Genel, M.D.
Professor of Pediatrics and Associate Dean for
Government and Community Affairs
Yale University School of Medicine

Thank you, Mr. Chairman. My name is Myron Genel. I am Professor of Pediatrics and Associate Dean for Government and Community Affairs at Yale University School of Medicine. As you know from Dr. Redmond's presentation this morning, researchers at Yale have been very involved in studies of the efficacy of tissue transplantation in animals. Today, I am representing the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU). The AAMC represents the nation's 127 accredited medical schools, 435 major teaching hospitals, and 85 academic societies. The AAU represents 54 of the nation's leading research universities. Both Associations appreciate the opportunity to testify today on a topic of vital concern to biomedical research and to the health of the nation.

Introduction

Human fetal tissue transplantation has brought medicine to the threshold of important discoveries. Current research shows that such tissue transplants could mitigate the symptoms and perhaps elucidate and eliminate the causes of a number of ravaging diseases. While the decision to halt federal involvement in this research was guided by ethical concerns, equally compelling ethical concerns are raised by proposals to enjoin this research permanently and thereby to preclude the alleviation of suffering and illness in the living.

The ethical concerns which led to the convening of this Panel are understandable and important. However, many of these issues, as articulated

by Assistant Secretary for Health in his March 22, 1988 memorandum, are appropriately and adequately addressed in current laws and regulations. Other questions involving issues unique to fetal tissue transplantation, many touching on hypothetical outcomes and applications of such research, will benefit from the review and deliberation of this Panel. Ultimately, however, the need for an explication of these issues should not preclude federal support of the research. Our society is thoughtful and compassionate enough to be able to resolve the ethical dilemmas raised by fetal tissue transplantation research so that policies protecting human and fetal research subjects and those governing biomedical efforts to improve human health are not mutually or morally exclusive.

Current State of Research

Recognizing that today's presentations have provided you with a comprehensive overview of current research involving fetal tissue transplantation for therapeutic purposes, I will only briefly summarize the state of current research among AAMC and AAU institutions. No formal survey of the activities in this area has been undertaken. Much of the work conducted thus far has been in rodents and primates in whom Parkinson's disease has been induced. Few human tissue transplants have been attempted in the United States. A number of years ago, in what is believed to have been the first human tissue transplant, a fetal thymus was implanted into a child suffering from DiGeorge syndrome, a T-lymphocyte deficiency syndrome. More recent work at the University of Colorado Health Sciences Center and at the University of Wisconsin has involved the implantation of fetal pancreatic

islet cells into diabetic patients. Internationally, investigators in Mexico, Sweden, the People's Republic of China, and Great Britain have attempted fetal neural or adrenal tissue transplants to alleviate the symptoms of Parkinson's.

Fetal tissue transplantation research is in the earliest phase of exploration with many fundamental questions about its effectiveness still unanswered. The current moratorium on federal funding of research using tissue from induced abortions has brought developments in the public sector to a halt. However, work with animals continues, as does, we expect, human transplantation research supported by the private sector. Although the moratorium does not affect research which uses tissue from spontaneous abortions, concerns about the reliability and safety of the latter have made tissue from induced abortions medically preferable. In the opinion of some researcher workers, the transplantation of spontaneously aborted tissue increases the risks to the recipient. Additional difficulties involving the availability of spontaneously-aborted tissue also make it an undependable source of tissue.

While far more must be learned about fetal tissue transplantations in humans, certain aspects of the biology of fetal tissue, as reviewed earlier by Dr. Auerbach, are well known. Fetal tissue possesses unique qualities which for some forms of transplantation make it superior to adult tissue. These include rapid growth and greater adaptability. Although both adult and fetal tissues contain cells that trigger immune responses, laboratory processes can eliminate those cells from fetal tissue, and purified fetal cells can be harvested that require neither tissue matching nor long-term

immunosuppression. These qualities are believed to have contributed to the comparatively better success of fetal tissue transplants over adrenal autografts in experimental models of Parkinson's. The animal and human research conducted to date is promising and, in addition to Parkinson's disease and diabetes, other potential applications for tissue transplantation include spinal cord injuries, epilepsy, stroke, Huntington's and Alzheimer's diseases, and immunological and blood disorders.

Ethical Concerns

The concerns involved in human fetal tissue transplantation which led to the suspension of its federal support were enumerated in Assistant Secretary Windom's March memorandum. Those ten broad questions relating to the science, legality, and ethics of the therapeutic use of fetal tissue from induced abortions focused on the quality of the scientific endeavor, on whether a sufficient number of animal studies have been completed to warrant advancing to research in humans, on the mechanics of tissue acquisition, and on the effect on research of restrictive state laws. But, the most problematic questions, are those which involve the ethical issue of whether human fetal tissue transplantations from induced abortions will create direct or indirect incentives for abortion. In our view, these fundamental questions are satisfactorily answered by existing safeguards in current state and federal laws and regulations. Further, the suspension of the research raises equally important concerns about other ethical principles to which our society adheres.

The concern that success in the transplantation of fetal tissue from induced abortions will encourage abortion is addressed in current federal regulations. First, the regulations (45 CFR 46.206) require the completion of appropriate animal studies. They then erect a firm barrier between the abortion decision and the research project: contact is prohibited between the woman whose aborted tissue is to be donated, and the investigator who is explicitly banned from any involvement in the decision to terminate the pregnancy, in the timing of the abortion procedure, and in the determination of fetal death. The introduction of changes in the abortion procedure for the benefit of the research activity is also proscribed as is the proffering of inducements, monetary or otherwise, to encourage the abortion decision. These regulations also specifically address research involving dead fetal tissue by requiring the observance of relevant state and local laws, primarily the Uniform Anatomical Gift Act that governs the donation of fetal tissue and requires the informed consent of either parent and the nonobjection of the other parent. Additional restrictions on research involving nonviable fetuses and a prohibition on the sale for profit of human tissue and organs are also contained in both the regulations and in federal law (Section 498 of the Public Health Service Act and Section 301 of the National Organ Transplant Act), providing further ethical safeguards.

Actually, the use of fetal tissue in biomedical research is long established. Development of the polio vaccine in the 1950's involved cultures of human fetal kidney cells and was based on studies of human fetal cell line development which began in the 1930's. For many years, the production and testing of vaccines, the study of viral reagents, the propagation of human

viruses, and the testing of biological products have been dependent on the unique growth properties of fetal tissue. A sampling of current research using fetal tissue includes studies of oncogenesis; assessments of the effects of environmental factors on developing organisms; understanding the development of diseases; investigations of possible interactions between the AIDS virus and neural cells and examinations of the maternal-fetal transmission of AIDS; and various investigations in which human fetal tissue is a source of biological substances. All these uses are of vital importance to biomedical research and, ultimately, of course, to human health. Nevertheless, the use of fetal tissue in these cases, even though they are also of a generally therapeutic nature, has not elicited the equivalent levels of public attention and concern.

Apparently, it is the proximity of the potential benefit to a patient in fetal tissue transplantations that raises additional anxieties. The latter appear to be based on fears that the demand from potential transplant recipients, possibly numbering in the millions, will be so urgent that human fetuses will be conceived and intentionally aborted so that their organs and tissues can be harvested for transplantation. Given the safeguards just reviewed that society has already constructed regarding human and fetal research subjects, these fears are unreasoned and it is unwise and wrong to base important public policy decisions on them. Furthermore, it is also possible, and much more likely, that advancements in the immortalization of cell lines and the development of other biotechnologies will mitigate concerns about uncontrollable demand.

A more meaningful ethical concern regarding fetal tissue transplantations has to do with whether their therapeutic benefits would lend an implicit legitimacy to abortion that it does not now have. Clearly, fetal tissue transplantation is parallel in many ways to organ donation which is regarded by society as beneficent, an act of charity and selfless concern for others. But the idea that the potential medical benefits of fetal tissue will enter into a woman's decision to have an abortion completely misunderstands the complex and weighty personal factors underlying the abortion decision. It also ignores the distance the law creates between the decision and the conduct of research. Abortion would still remain a private decision on the part of a woman based on personal and medical reasons. This decision and the clinical management of the patient making it are autonomous. Federal and state law upholds this autonomy by isolating that decision from the research.

A prohibition on federal support of the research would have undesirable medical and ethical effects on our society. Suppressing the pursuit of such important knowledge--and the human compassion which motivates it--has deeply troubling implications. We must ask how such an action could in any way accord with longstanding principles which exhort us to act benevolently toward others. For physicians, this idea, articulated in the Hippocratic oath, is the essence of our work. To deny patients with fatal illnesses the possibility of lifesaving and life-extending treatments is antithetical to the values and ethical standards of medicine.

Summary: The Need for Federal Support

Biomedical research is conducted in accordance with standards, laws, and regulations which respect and protect human and fetal subjects of research. With such safeguards in place, there is no valid reason to withhold public support for human fetal tissue research. Indeed, federal support is proper and necessary. Federal funding will advance the progress of the research and ensure a more equitable distribution of its benefits.

Fetal tissue transplantation research holds tremendous promise. A federal role in the biomedical research community's effort to alleviate the suffering of so many Americans is in keeping with the fundamental principles upon which our society is based. What you decide in these deliberations will affect the progress of our research and its potential to improve human health. The AAMC and the AAU appreciate your consideration of their views on this most vital issue.

AMERICAN PARALYSIS ASSOCIATION
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SPRINGFIELD, NJ 07081

POLICY ON FETAL TISSUE RESEARCH

The American Paralysis Association believes that research using animal fetal tissue has demonstrated promise in promoting neural regeneration and neural recovery in animals. We believe that this area of study is at a seminal stage and may contribute to a cure for paralysis that is a consequence of CNS damage in humans.

We have come to this belief based on the results of researchers our organization has funded and of researchers funded by other agencies. At present the APA is funding six research teams who are using animal fetal tissue to aid in the regeneration of damaged spinal nerves; all have reported encouraging results. These researchers are among the most respected in the field of neuroscience. As further evidence of the promise within this area of research, the APA's Science Advisory Council has voted its support by recommending in 1988 the funding of four projects using fetal tissue; this funding represents one-fourth of our 1988 research grant budget.

Now that similar initial studies are being done using human fetal tissue, we believe that it is important to ensure the ready availability of such tissue for use by bona fide researchers in exploring neuronal recovery and regeneration based upon this technology. This is crucially important at this point since no known substitutes have been found for human fetal tissue in research on humans.

Consequently, the APA believes that guidelines, such as those developed by the Swedish Medical Research Council, are needed to regulate the use of human fetal tissue, to avoid practices that may lead to unnecessary restrictions on research using such tissue or on the availability of such tissue. We believe that thoughtful limits on human fetal tissue research practices that are implemented at this seminal stage will lead in the long run to fewer restrictions being placed on research in this area. Legislation or policy formulation at a national level is, thus, needed to define the conditions both for acquiring and utilizing fetal tissue. This legislation/policy must carefully balance the hope of a cure that fetal tissue research offers and the right of society to regulate actions taken toward fetuses. The net effect must be that human fetal tissue in sufficient quantity remains available to bona fide researchers, to be used under proper guidelines.

Further, the American Paralysis Association does not support the use in research of animal or human fetal tissue outside the guidelines already established by animal and human research committees at universities in which fetal tissue research is being implemented.

Finally, we believe that adequate funding support should be given to research that will (1) encourage the development of tissue "cloning" techniques that will produce fetal-like tissue, to bypass the need for fetuses per se, and (2) encourage the discovery of those factors in fetal transplants that are responsible for positive effects, so that the duplication of these factors might become possible, again bypassing the need for fetal tissue per se.

SUMMARY OF THE STATEMENT
OF THE
AMERICAN DIABETES ASSOCIATION (ADA)
ON THE
USE OF FETAL TISSUE IN TRANSPLANTATION RESEARCH

The American Diabetes Association (ADA), which represents the interests of over 11 million Americans with diabetes, believes that a permanent or extended ban on the use of human fetal tissue in transplantation research will seriously impair one of the most promising avenues of inquiry in diabetes research--the transplantation of insulin-producing pancreatic islet cells into patients with insulin-dependent diabetes mellitus (IDDM).

Researchers are currently studying the transplantation of insulin-producing pancreatic beta cells, which can be obtained from an adult or a fetus. The use of fetal beta cells offers several advantages over the transplantation of the whole pancreas or the use of adult beta cells. Fetal cells have the ability to grow and perhaps remain immunologically "naive." That is, the tissue will develop the capacity to secrete insulin in response to blood glucose levels and not be rejected by the body's immune system.

Transplanting fetal cells is easier than transplanting all or part of a pancreas, which involves difficult surgical procedures. For example, in transplanting a whole pancreas, it is necessary to drain the digestive enzymes produced in pancreatic cells; this is not necessary with transplanted fetal beta cells.

However, there are remaining difficulties with fetal beta cell transplantation and methods must be found to alleviate these difficulties. Two experimental procedures are now under study -- cryopreservation (freezing) and tissue culture. Both techniques are employed to allow clinicians the opportunity to obtain large numbers of fetal cells that are not otherwise available from one fetus. Another problem is that the fetal tissue will eventually become immunologically competent and be rejected. To avoid rejection, research has shown that fetal beta cells can be treated with high oxygen infusion, immunotoxins, or monoclonal antibodies (antibodies that attach to only one kind of molecule). These treatments mask the fetal cells from the host's immune system.

Recent clinical trials using fetal cells conducted at the University of Wisconsin and the Barbara Davis Center in Colorado have recorded some success in a small number of patients with diabetes. Further research is necessary to demonstrate the potential effectiveness of fetal beta cells as a method for insulin administration.

Fetal beta cell transplantation holds great promise as a cure for diabetes, but additional research is needed to answer the difficult questions related to rejection of the tissue and more efficient ways to obtain the needed amounts of tissue. A ban on fetal tissue transplantation research could be disastrous. We believe that while an examination of the legal, ethical and medical questions is useful, it

should not be undertaken at the expense of the research itself. Federal regulations clearly separate professionals who perform or make decisions regarding abortions from individuals who perform fetal tissue transplantation research. For these reasons, we urge the Human Fetal Tissue Transplantation Research Panel to recognize the important contributions fetal tissue transplantation research may make to the lives of millions of people with diabetes.

UNITED
PARKINSON
FOUNDATION
360 West Superior Street
Chicago, Illinois 60610
312/664-2344

The United Parkinson Foundation is an international non-profit organization chartered in the state of Illinois in 1963. The UPF is an unaffiliated, independent entity which derives its support entirely from its membership and the general public.

A major portion of operating expenses is allocated to patient services, which include background literature, exercise materials and regular newsletters sent to all members regardless of the ability of patients/spouses to contribute funds. The office in Chicago is maintained so that members may call or write for a personal response to specific questions. A highly qualified Medical Advisory Board is accessible for consultation to the staff on such matters and to supervise publication content and preparation. The office maintains an extensive referral service to guide patients to proper clinical care.

The UPF originated a unique program of educational symposia for patients and families in 1965, first in Chicago, then expanding the scope of the program to include locations in thirty states and Canada. Eight or more such meetings are presently being scheduled each year throughout the continent. The format of the symposia is two-part; the first half consisting of short talks by the host and guest speakers from the Foundation's Medical Advisory Board on such topics as differential diagnosis, past and present medications and therapies, patient and family relationships, and a realistic outlook for the future. The second half of the symposium is devoted to a question and answer session with the audience providing the questions for the panel of specialists to answer. Summaries of these symposia are published in the UPF quarterly newsletters.

These newsletters are written primarily for patient and family education; for reporting in layman's language recent advances in research, for answering questions of general interest to members, and for publishing members' suggestions. Additionally, space is offered to unaffiliated local support groups which provide emotional support and social opportunities for patients and their spouses.

Funds raised over operating costs are used to support neurologic research in the form of grants to established scientists whose primary interest is Parkinson's disease. The scope of the organization is reflected by its research support for projects in numerous locations throughout the world. Thus the UPF priorities are patient services and education, and support of research in Parkinson's disease and related afflictions. In recent years, income has been allocated as follows: patient services, 33%; research grants, 58%; administrative overhead, 9%.

Questions and requests for literature may be directed to the UPF at 360 West Superior Street, Chicago, Illinois 60610, telephone: 312/664-2344.

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FACTS ABOUT PARKINSON'S DISEASE

Parkinson's disease is a chronic, progressive, degenerative disorder of the central nervous system, named after the British physician who first described it in an essay published in 1817. There are probably four hundred thousand patients in North America, the vast majority of them over age 45. Since the disease develops slowly in a most subtle manner, it is often difficult to make a correct diagnosis early in the course of the disorder. The disease may occur and remain dormant until a period of particular stress or simply physical deterioration through aging causes the appearance of symptoms. While the extent of disability will vary from patient to patient, fortunately the disease is not fatal.

Four separate groups of symptoms can be described: tremor, rigidity, akinesia and loss of normal postural reflexes. The tremor, of hand, foot, occasionally head and/or jaw, is less evident during purposeful activity than during rest, and characteristically is absent during sleep. Psychological factors may increase tremor. Rigidity is often an early symptom, with the patient's first complaints being of stiffness or tightness as well as slowness of movement. Akinesia (also called bradykinesia) refers to slowness in the initiation and execution of voluntary movements such as rising from a low, soft chair or bed. Loss of postural reflexes may be evidenced by the patient's head falling forward as though he were sleepy, or a difficulty in maintaining an upright position. Any of these symptoms may be absent or range from mild to severe in an individual patient. Once diagnosis is suspected, drug history should be reviewed since haloperidol, reserpine, and some phenothiazines and neurotoxins have been known to produce symptoms of parkinsonism.

A large number of drugs are useful in the treatment of the symptoms of the disorder, though the disease cannot as yet be arrested or cured. The response to drugs depends on a number of factors and differs from patient to patient and may even differ in the same patient at different times during the course of the disease. In general, it is best that the patient use as few drugs as possible rather than take a number of drugs to counteract the ill effects of the initial agent. Levodopa (also known as L-dopa), usually in combination with carbidopa (Sinemet), is today considered the treatment of choice in full-blown disease, often prescribed along with other medications, and always accompanied by regular physical activity to the extent of the individual patient's ability. Medications may have limited efficacy unless the patient cooperates in a daily physical therapy routine. Side effects, which can occur with overdoses of any drug, must be treated individually, and will often be alleviated through a reduction in dosage of the offending drug. Cryosurgery, once frequently employed, had little effect on the natural course of the disease, and today is rarely considered. Transplantation procedures, which have received so much media attention of late, do seem to have efficacy; with time and more extensive experience we expect to learn duration of benefits as well as the advantages and possible disadvantages of this therapy in comparison with pharmacologic methods.

It should be noted that while levodopa and the many other antiparkinson medications developed during the last thirty years are a definite improvement over the treatments of the distant past, they, too, are merely useful in controlling disease symptoms and do not prevent the disease from progressing. A renaissance of research into Parkinson's disease has been spurred by the discovery of the effects of MPTP, a neurotoxin, and the subsequent development of an animal model of the disease. This model affords the possibility of safely and economically testing new drugs and may eventually shed light on the cause(s) of the disease, leading to prevention and cure.

# # #

UNITED PARKINSON FOUNDATION
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PUBLIC POLICY COUNCIL

of the

American Pediatric Society | Association of Medical School Pediatric Department Chairmen | Society for Pediatric Research

TRANSPLANTATION USING FETAL TISSUE

Why use fetal tissue for transplantation?

Experiments in animal models indicate that transplants of fetal tissue may prove helpful in treatment of injuries or diseases that originate from a lack of certain cells or from the inability of cells to function properly. Such treatment would benefit children with inborn-errors of metabolism, immuno-difficiencies, insulin-dependent diabetes and adults with degenerative neurological disorders such as Parkinson's, Alzheimer's, and Huntington's diseases.

Fetal tissue can be transplanted more successfully than adult tissue since it is less immunologically reactive and more adaptable, and, therefore, less prone to be rejected. Laboratory processes exist which can eliminate immune responses from fetal tissue. Fetal tissue also develops more quickly than adult tissue.

Our statement will address the need to continue exploration of the possible advances in medicine which may result from such technology. Our societies feel that judicious studies should not be unduly restricted.

How can fetal tissue become available for transplantation?

Every state has passed an anatomical gift statute allowing for a person to give all or part of his body for transplantation. Such statutes include allowing the parent or parents to act on behalf of a minor. These statutes also allow for the gift of all or part of a dead fetus for research or therapeutic purposes. Using a fetus as the donor of fetal tissue for transplantation is legally possible, usually requiring the consent of either parent as long as the other parent does not object.

Techniques for the removal of tissues and organs for transplantation into a live patient are well established. The practice is an accepted one. It is not the fetus who is the research subject and should not be considered as such.

Safeguards against abuse

Current review boards exist to monitor the use of human subjects in biomedical research situations. Together with other existing statutes and regulations, the use of fetal tissue in transplantation can be permitted, legally and ethically.

It has been suggested that successful fetal tissue transplantation therapies might lead to the demand for tissue exceeding the supply, as is the case with other organ transplantation. However, it is unlikely that demand for such therapy would develop rapidly given the existence of alternative therapies and the unknown factors yet to be discovered concerning the efficacy of this treatment. As this procedure is being studied, methods of reproducing fetal cells within the laboratory are being developed.

Conditions should be established which clearly separate the decision to abort and the decision to donate. The decision to abort is made by an individual, in consultation with the medical personnel, because that is what is right for that individual.

The decision to donate the fetus for possible use as a donor must involve different health personnel. Conflict of interest is avoided where there is a clear distinction between the two sets of health care providers.

Anonymity should exist between the donor and the recipient and between the parent(s) and the recipient. This would eliminate the possibility of a women becoming pregnant (or being paid to become pregnant) solely for the purpose of producing a fetus to be used in a transplantation procedure.

July 26, 1988

Statement by Dr. Robert E. Stevenson, Director, American Type Culture Collection; President, Tissue Culture Association; Chairman, Committee on Cells and Tumors, American Association of Tissue Banks regarding the use of human fetal tissue for research and transplantation.

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The results of using human fetal tissue in research and in the production of viral vaccines and biological products is well known and does not need to be elaborated upon here.

The benefits accruing to Society have been enormous and in our opinion far outweigh those that have accrued to date from the transplantation of whole adult organs.

It is curious that in the case of whole adult organs we have; constructed an extensive support structure of state laws for anatomical gifts, have a national Council on Transplantation, have a United Network for Organ Sharing, and have added donor consent forms to driver's licenses in many states yet have not worked out a consensus on what to do with fetal tissues whether they are available from spontaneous or induced abortions.

Isn't what really is at issue is Society's displaced anxieties about teen age mothers, unwanted pregnancies, and overly casual attitudes about the consequences of the sex act?

Scientists as scientists are not the appropriate persons to grapple with these issues, but neither should their legitimate role in helping Society be frustrated because the appropriate authorities can't or won't address them.

Responsible scientists, such as we believe ourselves to be, think that the denial of using this tissue for beneficial purposes serves no useful purpose whatsoever and in fact would be a further affront to moral sensibilities.

As scientists we believe that the issues of abortion are of a serious and difficult nature and that we should neither minimize the individuals' moral and emotional concerns nor those of Society's institutions about the outcomes. Given however that tissues are made available in a legally permissible situation and that certain professional and scientific standards are met we argue that no bar to their use be otherwise erected.

We certainly endorse and support a statement of principles or policies that could include at least the following:

Tissues that are to be collected from fetal sources for research or clinical use

1) Must be obtained under applicable regulations relating to the patient/physician/institution in the jurisdiction where the tissue is procured and with the highest professional standards

2) May not be sold or bartered for profit and should be made available with compensation for processing services only.

3) Must not be the end result of a series of actions intended to provide tissues for a related family member.

Further it is required that;

4) Physicians or personnel assisting in the termination of pregnancy not be involved with the performance or publication of research using the resulting fetal tissues or cells, nor should they be directly involved in remuneration from the use of tissues or cells in the production of any product.

5) It shall be unlawful to import or transport in interstate commerce and use fetal tissues from sources not observing comparable legal/ethical constraints to those enumerated above.

The above is proposed as a reasonable starting point for a discussion and debate on the formulation of a policy position on this issue by the Federal Government and the public, including the scientific community.

Parkinson Support Groups of America
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SUMMARY OF INTENDED PSGA TESTIMONY
HUMAN FETAL TISSUE TRANSPLANTATION RESEARCH PANEL
SEPTEMBER 14 OR 15, 1988

As the only all volunteer National Organization representing parkinsonians from across America our testimony would include the recommendation that the National Institutes of Health continue to support extramural and intramural fetal tissue transplantation research.

Our members have participated as patients in the adrenal implantation. Their emotional and physical feelings should be an integral part of the total transplantation program.

We are aware of the ethical concerns involved in any fetal tissue research and concur with the decision that established this Panel.

As the "Voice of the Parkinsonian" our recommendation is that "more not less" research be the protocol in the fetal tissue research program.

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Our organization would be represented by Ida M. Raitano, National President of the Parkinson Support Groups of America.