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Fetal Tissue Research: The Cutting Edge?

by

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A recent series of reports in the *New England Journal of Medicine*¹⁻³ have been interpreted as providing support for the use of fetal brain tissue transplantation as a treatment for Parkinson's disease.⁴ The publication of these studies also provided impetus for President Clinton to repeal the administrative ban on the use of federal funds for transplanting aborted human fetal tissue into patients. Although this decision may be viewed by some as the end to a long political battle between "pro-choice" and "pro-life" factions, such an assessment underestimates the depth of the issues involved. The questions that have been raised on many occasions regarding the ethical issues surrounding the use of tissue obtained from the intentionally-aborted human fetus remain largely unanswered.⁵⁻¹¹ The purpose of this article is to review such questions and to emphasize the unfinished nature of the debate. There are three major ethical questions relating specifically to the question of using fetal brain tissue for treating Parkinson's disease: 1) When can such a treatment be justified on medical grounds?, 2) What are the criteria for defining fetal death? and 3) To what extent does the ethical status of abortion affect the use of research or therapy based on tissue derived from aborted fetuses?

Is Fetal Brain Tissue Transplantation Medically Justified?

The rationale for transplanting these neurons is that they will synthesize dopamine, thereby replacing the neurotransmitter that is lost in Parkinson's disease. Two features of the transplant paradigm that weaken the rationale are 1) the transplant is placed into a brain region where the tissue is not normally located

and 2) it is not possible to transplant only the cells of interest due to the inability to identify and isolate the dopamine-producing neurons in the midbrain at this age. As a result, interpreting the results obtained with such transplants is difficult since it is not clear what feature of the transplanted tissue might underlie the observed effects. In fact, the possibility has been raised that the effectiveness of the transplant may depend on the surgical procedure itself, not the tissue. Further support for this possibility is provided by the recent study from Yale in which the one patient who came to autopsy demonstrated no dopamine-B-hydroxylase activity in the transplant.³ Additional skepticism arises from the experience of using autologous grafts of adrenal medulla, which were initially reported to provide substantial benefit¹² but were later found not to be efficacious.^{13,14}

The lack of strong evidence for a specific mechanism by which fetal transplants might be expected to work, as well as the questionable efficacy of the procedure, raise the first of many ethical questions regarding this procedure. Specifically, should Parkinson's patients be submitted to a costly and invasive procedure for which there is no compelling rationale? Even if the procedure is ultimately shown to be effective, its relative effectiveness must be established. In other words, can one obtain comparable results with less costly or less invasive therapy? In addition, the human studies that have been carried out so far do not include any controls for the transplant procedure. Therefore, the possibility of a placebo effect needs to be kept in mind. This is especially true in studies where patients rate their own status.²

None of these questions relate to the issue of the source of the tissue (raised below) yet they require as much attention as the abortion-related questions do. One of the reasons that such issues get less attention is because the public is not in a position to assess the medical and scientific evidence. However, there is substantial disagreement within the medical and scientific community regarding the rationale and effectiveness of tissue transplants as a therapy for Parkinson's disease.¹⁵ Perhaps not surprisingly, the strongest proponents of the use of this procedure are those who are carrying out the work. This is all the more reason that dispassionate assessment is called for when evaluating the results of transplant studies.

Defining Fetal Death

It is important to recognize that the fetus, or the desired organ, must be living to serve as a useful tissue donor. However there is some disagreement about the term "living." The traditional biological definition includes the concepts of metabolism, growth, respiration, etc. Certainly, prior to the abortion, the fetus meets all these criteria. The suitability of fetal tissue for transplantation depends on the manner in which it is obtained. The ideal tissue is that obtained from an intact living fetus. However, with rare exceptions, current abortion procedures involve destruction of the fetus as an entity and corresponding destruction of the fetal body and its tissues. Due to extensive tissue fragmentation, it may take a long time to identify suitable viable tissue by quickly sifting through the remains resulting from suction abortion. This delay can compromise the usefulness of the

tissue. On the other hand, if the fetus is aborted relatively intact, it is much easier to obtain the desired tissue with minimal delay. Thus, it remains to be seen whether abortion procedures will be influenced by the demand for fresh intact fetal tissue as apparently was the case for initial studies in Sweden.¹⁶ Whenever researchers have a choice they prefer to use intact fetuses. One study assessed the viability of human brain tissue at various intervals after the abortion.¹⁷ All of the fetuses were obtained through prostaglandin-induced abortion. In other words, the fetuses were delivered intact and, quite possibly, alive, depending on what criteria of death are accepted as standard.

The most viable tissue for the purpose of transplantation is that obtained from fetuses between 8 and 12 weeks gestational age. This is a stage before the nerve cells in the midbrain have completed development and, therefore, retain their capacity to form connections with target tissue. This is also a period of development when the major brain and spinal cord architecture has been established and the fetus exhibits motor and sensory capabilities. Whether an 8-week old fetus perceives pain is still debated but fetal response to noxious stimuli and the presence of neural pathways that are known to subserve pain in maturity strongly suggest that the fetus perceives some pain at this stage. This issue has only been addressed tangentially in the political and scientific discussion of the ethics surrounding the use of fetal tissue. Mahowald, *et al*,¹⁸ suggested that if there was concern that the aborted fetus might perceive pain as a result of acquiring tissue this could be dealt with by using appropriate anesthetics. The irony of this suggestion is highlighted by the fact that abortion of a fetus at any stage of development rarely involves anesthesia of the fetus since most abortions are carried out under local anesthesia.¹⁹ The fetus is unanesthetized except in the relatively uncommon circumstance of general anesthesia provided to the mother.

Regardless of the precise age at which nociception is established, there is little question that the fetal brain is more resistant to anoxia and ischemia than the postnatal brain.⁹ This, along with the fact that many of the nerve cells have not yet established connections with their targets, makes fetal tissue more suitable for transplantation and tissue cultural studies than mature brain tissue. However, this greater viability of the fetal brain, as compared with the mature brain, raises the question of whether existing criteria for determining fetal death are sufficient to prevent vivisection when harvesting tissue from the aborted fetus. There is no question that most abortion procedures result in circulatory arrest. In fact, no one can argue with the simple statement that "abortion stops a beating heart" although the heart may continue to beat for some time after the abortion is complete. However, the criterion of cessation of fetal circulation appears insufficient in light of the continued survival of brain tissue both following transplantation and in tissue culture.¹⁷ Furthermore, the possibility of using brain death as the criterion for determining fetal death directly contradicts the goal of harvesting the fetal brain in order to obtain viable tissue. Until we know more about fetal perception it seems the most conservative course of action would be to provide anesthesia for the fetus prior to the abortion procedure in order to prevent the possibility of pain perception during the abortion or subsequent harvesting of tissue.

Moral Relationship Between Abortion and the Use of Tissue From Aborted Fetuses

Although it seems superfluous to review the semantics associated with using tissue from the intentionally-aborted human fetus, there remains a surprising level of ignorance on basic terms. The term human does not require further qualification because there is no scientific disagreement that from fertilization onward the organism is unquestionably human in the biological sense of the term (that is, of the human species). It is not bovine or feline or canine and, with increasingly sophisticated techniques, it can be demonstrated, from conception on, to constitute a unique human individual using genetic, biochemical or morphological criteria. Of course, the form each individual human organism assumes changes continuously throughout its life albeit at less dramatic rates than when first developing.

There is also no disagreement that the biological organism constituted by an individual zygote, embryo or fetus (each term representing different developmental stages) is unique in terms of its developmental potential. Such potential is contained within the genetic and cytoplasmic information of the organism that, if appropriately nourished, will develop into a more mature organism whose legal and moral status becomes universally accepted. Full protectable status is now granted at a relatively late stage, i.e., at birth. Although not the focus of this paper, it is of some interest that the latent legal doctrine on which the "right" to abortion depends is that the mother has absolute power over the fetus, that is, the fetus is completely dependent on the mother for survival (at least during the first 20 weeks of gestation).

It is important to recall that the term abortion (Stedman's: 1. Giving birth to an embryo or fetus prior to the stage of viability at about 20 weeks of gestation.) is not equivalent to feticide. In fact, with some abortion procedures the living fetus is expelled even though it has limited viability (able to survive independently). The AMA was well aware of this when passing resolutions condemning "the act of producing abortion at every period of gestation, except as necessary for preserving the life of either the mother or child." On the other hand it is possible, and usually the case, to insure fetal death by destroying the fetus prior to her removal. In fact, the gradual acceptance of vacuum aspiration as the method of choice for "terminating" early pregnancy is often defended on grounds that it is safer for the mother, but there is little question that another impetus for developing such methods was to hasten the death of the fetus.

Thus, from a scientific point of view, the fetal donor is a living (or dying) developing human being. The fact that the tissue is human, as opposed to deriving from other species, increases the chance of success when using the tissue for transplantation because of the reduced chance of immunological rejection. Non-human animal tissue is simply inferior in this regard. The fact that the fetus is in a stage of rapid development is also advantageous because the developing nervous system undergoes a period of tremendous plasticity that can theoretically be used to advantage when transplanted into a damaged adult brain or spinal cord. As mentioned above, fetal tissue is also more resistant to injury and lack

of oxygen, permitting it to survive the surgical procedures much better than mature tissue.

The fact that the tissue derived from the human fetus is genetically unique is only an advantage if attempts are made to match donor and recipient on immunological criteria. Such matching is commonplace for organ transplants between mature individuals in order to avoid rejection. The question of immunological rejection has not been answered regarding fetal tissue transplants. In one of the recent studies reported by Freed, *et al*,² immunosuppressive therapy did not seem to affect patient outcome. If immunological rejection did turn out to be significant, this would create a problem for those who argue that the best way to dissociate the transplant procedure from the abortion procedure is to insure that donors and hosts cannot be specified. In fact, in the many guidelines that have been suggested by various committees regarding transplantation of fetal tissue, strict precaution is usually taken to insure that relatives cannot be recipients of the human fetal tissue.^{11,20} This is precisely the opposite of the case when undertaking other types of transplantation where a related donor is much preferred over a non-related donor.

Of course the other feature of developing human fetal tissue that makes it especially desirable for research and transplantation is its widespread availability and abundance. This is a direct consequence of the legality and practice of induced abortion. As a result, it is clear that the ongoing research and transplantation attempts depend on the continued availability of living, developing human tissue and therefore, on the continued practice of induced abortion. In this sense there is a direct relationship between the two procedures. Whether this dependence provides additional incentive or conciliation for women seeking abortion is debatable. There is no direct evidence bearing on this question with the exception that in one survey some women stated they would be willing to conceive and abort for the purpose of donating fetal tissue.²¹ Although the potential incentive for abortion provided the basis for the Reagan administration's ban on federal funding of fetal tissue transplantation, recently overturned by President Clinton, there are several more compelling arguments for not only preventing the use of federal tax dollars to support such work but also to ban experimentation on the aborted fetus. Much of the discussion on this issue has failed to take note of the fact that federal funds can be, and have been, used to support widespread research with human fetal tissue that does not involve transplantation into human patients. Furthermore, even the administrative ban on federal funding did not prevent the use of private funds for this work. The only current restrictions that exist are individual state laws regulating experimentation on the human fetus.²²

Returning to the relationship of fetal tissue research to the abortion practice that makes the tissue available, several points should be noted. One is the amount of the tissue needed for individual experiments. This has ranged from one^{2,3} to several¹ fetal donors per patient. The availability of tissue from fetuses of the desired developmental stage relies on the timing of abortions and access to the aborted fetuses in a timely manner. These difficulties can be overcome by using frozen tissue so that a tissue bank can be established to provide tissue as needed.²³

In fact, this approach was taken by the group at Yale.³ Many of the proponents of fetal tissue use favor this approach because it permits greater spatial and temporal separation between the abortion and the use of the resulting tissue. Even so, someone has to take responsibility for dissecting the tissue as it becomes available to store for future use. The professional collaboration that must be established between the investigators who use the tissue and the individuals who acquire the tissue is evident from the fact that both types of individuals are listed as authors on publications describing the work.^{24,25} In one case, one investigator who collaborated on transplanting aborted fetal tissue also published his own technique of acquiring the fetal brain tissue prior to carrying out the abortion procedure.¹⁶

The problem of defining fetal death has already been addressed. A related issue is the question of consent in donating fetal tissue or organs. The precedent that has been established in other cases of tissue or organ donation is quite clear. Either the donor provides such consent on his or her own behalf or it is provided on behalf of the donor by someone who is considered qualified to represent and protect the donor's interest. In the case of infant organ donation, since the infant is never capable of providing such consent, the parents or guardians are usually the relevant proxies. The one clear exception to this is when the parent or guardian has directly or indirectly contributed to the demise of the donor. Thus, in the case of aborted fetuses it seems unlikely that the mother can be considered an appropriate proxy for the fetus that she has consented to abort.⁶ Nor can the abortionist be considered qualified to provide consent on behalf of the fetus he or she destroys. By the same token, the medical personnel who desire to use the tissue for research or transplantation should have no say in the decision for obvious reasons. In fact, it may be impossible to establish a consent procedure that is consistent with historical, ethically-sound practice.

Some Personal Observations

Every year I attend the annual meeting of the Society for Neuroscience, a gathering of scientists from around the country who study the brain. Every year, scattered among the posters and talks describing new techniques and insights gained from work on animals, are increasing numbers of studies using the human fetus. This partly reflects the development of new methods but also stems from the fact that there are many fetal human subjects available. Prior to 1973, scientists had to rely on spontaneous abortions to obtain "material" while today large numbers of healthy fetuses, aborted at various stages of development, provide much greater opportunities for research.

Wandering the rows of posters at the meeting, I am struck by the extent to which the human fetus has become just another experimental subject. In fact, there are fewer regulations guiding the experimental use of the human fetus than of most research animals. The philosophical and biological premise that humans are neither more nor less than other animals is common today. In fact, unborn humans aren't afforded the protection of "endangered" species or even of experimental animals. Those who object to experiments carried out on the

human fetus are usually less strident and violent in their opposition to human fetal experimentation than, for example, the Animal Liberation Front is in protesting the use of animals in research.

For scientists probing the mysteries of early human brain development, this is truly a windfall and almost irresistible. Not only does our society permit, and often encourage, women to "terminate their pregnancies," but victims of neurological, or other, disease can now be recruited as allies to seek society's approval for therapeutic use of the aborted. After all, the reasoning goes, if the tissue is going to be thrown away, why not let it be used to cure someone who has Parkinson's disease or Alzheimer's disease? Why let the tissue go to waste? Of course one obvious answer is that we should never permit such tissue to be generated in this way in the first place. Another less apparent answer is that we should treat fetal remains with the same respect we give to any other member of our society who has died by natural or unnatural cause. Rather than discard such remains in a trash bin, we should bury them with due respect.

Many physicians and scientists have historically used a common theme to justify their experiments on those considered expendable. Note the plight of a transplant team in Mexico, where abortion is still illegal. They say they were "limited to the use of fetuses only from spontaneous abortions" but "encourage those neural transplantation groups in countries where elective abortions are legal, to take advantage of their social circumstance."²⁶ In this country the social circumstances are more favorable and the new administration now sanctions all uses of the aborted fetus for medical research.

Surprisingly, proponents of abortion on demand and of the experimental use of the aborted fetus claim that we can, and should, separate the practice of abortion from the experimental use of the unborn.⁸ It is objectionable, they say, for a woman to abort for the purpose of donating tissue. It is deplorable, they maintain, to think that any woman would sell her offspring for medical experimentation. But advocates have difficulty defending their position. If a woman has a fundamental right to abortion, why shouldn't she be able to provide tissue for a relative or even sell to the highest bidder to generate income for her other dependents? The scientists who study the tissue, the physicians who transplant it and the patients who receive it, hope to benefit. Why not the mother?

Perhaps attempts to insulate the act of abortion from the use of the aborted reflect a tacit admission that we have slid about as far down the slippery slope as we can. It is said that the most telling attribute of a civilized society is the protection it affords its most vulnerable members. Issues of concern to women appeal to our legitimate desire to protect those women who have been exploited by the biological fact that they are the only ones who get pregnant. It is no surprise that many men support the "pro-choice" philosophy and the corresponding reduction in sexual accountability. That mothers accept the death of their offspring as a solution to their own vulnerability is harder to fathom unless they are desperate. But many are also unaware of the true nature of the life growing inside. Physicians and scientists could play a critical role in educating them about the lives involved. There is no question that we need to take a hard look at the issues surrounding "unwanted" pregnancies but still reject solutions

that cost lives.

What is it about the human fetus that attracts scientists to "utilize" her? No surprise. She is a living, developing, human being, as genetically and anatomically distinct from her mother as she is from her father. By studying her we study ourselves. If not "terminated", she will continue to develop, requiring nurture and protection for many years after the direct physical link with the mother is broken. But she is different from postnatal beings in a significant way. For the first nine months she is hidden from view. Displaying her secret life of kicking, sucking, jumping and responding to pain, requires modern technology. When confronted with the evidence many women change their mind. But for others the "solution" of abortion is too tempting to forego. Besides, educating the public on these issues would cut into the many "benefits" of abortion such as population control, income for abortionists and experimental subjects for scientists. Any discomfort that arises when confronting the aborted body parts is tempered by rationalizing that autonomous rights of women outweigh any conceivable rights of unborn "obligate parasites" or "non-viable" fetuses.

Ironically, the unborn are regaining status in our society. But only in the sense that they are more valuable dead than alive. So the lucrative clinics stay open and we solve our "problems" with technical skills refined for other purposes. And now, there is the promise that we can reap additional benefits from their demise. In the meantime, scientists gather together every year and compare notes, taking advantage of their social situation. In fact, prominent scientist leaders defend this practice. In a recent editorial in *Science* magazine,²⁷ Dr. Koshland called for "professionalism . . . without emotionalism" regarding the question of federal funding of fetal tissue transplantation research. He then provided arguments in support of such research while characterizing those who object to it as playing a "game of politics". He ignored scientific and ethical arguments raised against the use of aborted fetuses for medical experimentation. He did not refer to significant debate within the medical community, apart from the question of abortion, as to whether or not fetal tissue transplantation really "is of enormous value and can be used in actual therapy for certain illnesses like Parkinson's disease." Furthermore, he suggested that "fetal tissue should be placed in the same category as research on cadavers" without recognizing that there are valid medical questions regarding the definition of fetal death as I have alluded to earlier.

More troubling is Koshland's insistence that science has no role in the wider societal debate on abortion since "a death is preordained outside the research world." This view is highly reminiscent of the defense offered by Nazi scientists and physicians, such as Dr. Hallervorden, at the Nuremburg trials. If, as Dr. Koshland asserts, taking a stand against the use of tissue derived from elective abortion is "illogical" then the worldwide condemnation of many of the scientists and physicians in Nazi Germany, such as Dr. Hallervorden, is also illogical. The Nazi scientists argued, as does Dr. Koshland in support of fetal tissue, that they were "making the best of the consequences of a previous history". After all, "death was preordained outside the research world." They would also surely have agreed with Dr. Koshland that "the use of those materials should be termed as unrelated to the political issues."

Perhaps Dr. Koshland could defend his own position, while at the same time condemning Nazi scientists, by adopting the view that feticide is fundamentally different from the genocide practiced by the Nazis because the human fetus is not worth protecting. If so, one must wonder why he states in the same editorial that one of the goals of fetal tissue research is to treat "disease conditions in fetuses." How is it that a human fetus can be considered a patient in one context and just a source of tissue in another context? The answer is that in both cases the fetus is considered valuable, but in the latter situation he or she is perceived as a contributor to society, rather than a member, and more valuable dead than alive. It is precisely this view of the fetus as a commodity that drives much of the opposition to federal funding of research that depends on elective abortion.

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