Tissue Issues:
The Ethical Dilemmas of Collecting Human Tissues for Research

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Human tissues are becoming increasingly important for research, therapy, and training as well as nonmedical uses (such as forensic testing). In Washington, DC, a serial arsonist was recently identified from tissue samples left behind at various crime scenes. Several rapists have been definitively identified; others exonerated using cellular and tissue materials.

Our focus today, however, is specially on research use. I will take that to include both basic and clinical research. In at least some jurisdictions research uses of tissues are governed by the same laws and policies as other uses. In the U.S., for instance, tissues procured for research are subject to the same law that governs their procurement for transplant. This is true not withstanding the fact that transplanters may not conceptualize tissues exactly the same way a researcher would.

To examine the ethical dilemmas related to research use of human tissue, I need first to say a few words about the concept of "tissue." Then, in the second section of this paper, I will look at four ethical dilemmas related to tissues. Then, in a final section, I will say something about the regulatory issues. We will discover that there are many issues related to tissues.

The Concept of Tissues

The transplant community normally uses the term *tissue* to refer only to skin, bone, heart values, and corneas. Organ and tissue procurement organizations will have to specify explicitly in a consent form whenever other tissues are taken. These might include pancreatic tissue, joints, connective tissue, brain tissue, or even blood. All have significant research and training uses, but most lay people, when asked to donate "tissue," do not think of these body parts.

Since the procurement of cadaver tissue is governed by transplant law,

researchers seeking to obtain tissues need to be very specific not only in what they ask for, but also in what the person consenting to tissue procurement understands.

Researchers are potentially interested in both cadaveric and living tissue sources, and these may involve significantly different moral and legal norms for obtaining them for research use. In the U.S., for example, while cadaveric tissue is governed by transplant law, cadaveric tissue is generally not covered by laws providing subjects protection from research risks. On the other hand, much tissue from living sources may be obtained as waste products from surgical procedures such as amputation in which therapeutic consent might (or might not) include a provision about the disposal or biological wastes.

It is likely that medical lay people do not understand exactly what scientists mean when they speak of tissues. Whereas a scientist might carefully distinguish tissue from organs, cellular masses, or limbs, the lay person may not be cognizant of these technical distinctions. Most lay people, for example, do not think of blood as a tissue, but may well consider the heart or kidney as tissue. Thus consent for use must carefully specify what will be the focus of the research.

A real, but tragic case in the American state of Florida illustrates the problem. A low-income man with no fixed address died as a result of a myocardial infarction and was taken to the morgue. His family was found in a distant state and notified. They expressed financial difficulty in returning the body to their home for burial. A worker in the medical examiner's office who was affiliated with a tissue procurement firm offered to be responsible for the cremation of the body provided the family consented to the procurement of "tissues" for research. The family reluctantly consented.

Under the authorization of the consent for procuring "tissues" the firm actually procured actually procured the deceased man's arms, legs, head, spinal cord, and genitalia. The remainder of the body was taken to the crematorium for cremation and the ashes were returned to the family as promised.

Unfortunately, when the body parts were tested, there were positive serologies so they were not usable for the research and training purposes originally intended. They were left in the freezer in the medical examiner's office. When the procurement group attempted to dispose of the tainted body parts by transporting them to the crematorium, the manager refused to take them since they were only permitted to cremate one body per death certificate, and they had already created this body.

The group finally decided to dispose of the parts as "medical waste," so it was boxed and sent to the waste disposal station. Local practice, however, specifies that human tissues (such as amputated limbs be incinerated while bandages and other waste can be sent to a land fill. The cardboard boxes containing these body parts

were mistakenly sent to the wrong facility.

This was discovered late on a Friday afternoon. The boxes were left on the truck for re-delivery to the proper station on Monday. Unfortunately, this was in the sunshine state of Florida. By Monday morning the frozen body parts had warmed considerably. The packaging leaked so that when the worker picked up the box, the bottom fell out and a human head rolled out onto the ground.

The startled worker thought someone was trying to dispose of a murder victim and called the police. The police traced the family in the distant state to confirm the unlikely story told by the procurement group. The family, however, claimed that they had already received the cremated remains. They indicated that they had only agreed to the removal of tissues before the cremation and were shocked to discover that their loved one's head and other critical parts were in boxes at a land fill.

The procurement group insisted that they had a valid consent for procurement, claiming that, after all, the head, arms, legs, and other parts were made up of nothing more than "tissue," which the family clearly had consented to donation for research and training uses.

The distraught family sued the scientists for deception. They thought they had donated a heart when the head and limbs were actually procured. A good case can be made that each was using a possible meaning of the word "tissue," but that neither had the standard or proper understanding of the term.

Ethical Issues

This story is too bizarre to be fiction. It makes clear that serious legal and ethical problems can arise if the parties do not have a clear definition of tissue in mind. Even with a clear definition, however, ethical issues can arise. Five such issues should be noted:

(1) Problems of Ownership.

When researchers use human tissues, there is the possibility that something useful will result. If the product is nothing more than intellectual property, there is little doubt that the researchers (or perhaps their sponsors) are the owners of the product. Sometimes, however, the tissues themselves evolve into products with commercial value. Thymus tissue has important clinical uses. Blood can produce clotting factor or be sold for therapeutic purposes. Joints removed as tissues can generate replacement knees or hips.

Some tissues generate products that have valuable research uses. The most famous example in the U.S. is the cell line produced from hairy cell leukemia tissues of John Moore. The investigators were able to propagate a cell line that has considerable market value. The investigators sought to patent the cell line and eventually sold it to Sandoz Pharmaceuticals in exchange for a lucrative option to buy

Sandoz stock. The patient who provided the cells, John Moore, sued claiming he retained property rights to his tissues. He claimed he had not given adequately informed consent to the investigators for this use of the tissues. The American courts granted the investigators patent rights to unwitting patient's cell-line. Moore is quoted as saying, "How does it feel to be patented? To learn, all of a sudden, I was just a piece of material?... There was a sense of betrayal.... I mean they owned a part of me that I could never recover."[1]

Many in the U.S. and elsewhere have concluded this result is unreasonable. It permits investigators and a private corporation not only to profit from the individual's body parts, but literally to own a piece of another's body. Some would even go so far as to claim that biological materials, especially human biological materials, should not be subject to ownership.

Although John Moore finally lost his right to block the granting of the patent, he did win a judgment based on his claim that he had not given adequate consent to what the investigators did with his cells. In the future, researchers who procure body parts from human sources will have to get consent from those sources before valuable products are marketed.

(2) Consent for Use of Tissues

This suggests a second ethical issue in research use of tissues. Consent is, of course, required for research use of tissues just as it is for any other research involving human subjects. There are some special problems, however. While the John Moore case makes clear that consent is required for research use of tissues from living human subjects, the regulations pertaining to human subjects do not necessarily apply to tissues from the deceased. American federal human subjects research regulations define a human subject as a "living individual about whom an investigator...obtains data through intervention or interaction...or [obtains] identifiable private information."[2] This means that technically human tissues obtained from cadavers are not subject to these regulations. This is true even if the subject is explicitly named publically and the research subject is very controversial. Developing human cloning techniques on tissues obtained form a fresh cadaver would not be so regulated for example. This seems clearly wrong, indefensibly wrong. Moreover, research on tissues from a living person to develop human cloning would also not be regulated provided the source could not be identified. I could do research to develop new abortion procedures on the surgically removed uteri of living or deceased women without having to follow institutional review board review, for example. I find this an intolerable oversight in the American regulations.

Fortunately, at least in the case of cadaver tissues, although research is not necessarily governed by human subjects regulations, it is governed by organ and tissue

procurement laws. Any cadaveric tissues procured for research purposes must meet the same consent standards as do tissues procured for therapeutic purposes. Moreover, it is the general practice that most organ procurement organizations will not permit tissues to be diverted to research unless there is no need for them for therapy.

This practice leaves open the interesting question of whether investigators could ask donors of tissue to explicitly donate the tissues for research purposes even though a therapeutic need was present.

Aside from the question of whether consent requirements pertain to tissues procured for research, the most novel feature of research uses of tissues is that those who collect the samples may not be in a position at the time the tissues are collected to know what the eventual use would be. We are moving toward the development of "biobanks" that will store large collections of samples of human tissues anticipating that in the future important research ideas will need these samples.

This means that the one contributing the sample cannot give informed consent to those uses at the time the sample is provided. One of the key elements of an adequately informed consent is that the subject of the research be informed of the purpose of the study. Those who contribute samples to a tissue bank cannot be given that information. We can assume that most who contribute samples support the general idea of research on the samples so they could give an "uninformed consent," but they cannot consent to the specific purpose for which the sample will eventually be used. It is, in effect, a "blank check" consent.

The problem is that, even if the donor of the sample supports tissue research in general, there may be controversial project someone will think up years later. Researchers may want to investigate racial theories. They may want to use the sample to identify criminal tendencies. An adequately informed consent at the time of the donation of the sample should really include the statement, "I agree to all imaginable uses of my sample including those that I find morally outrageous." Reasonable people would probably not agree to such an arrangement once they realize that the blank check may be for something they would find unacceptable.

The only alternative is to include a commitment from the collector or the sample that an IRB will review all future purposes and determine that no reasonable donor would reject the purposes that some investigator might think up. To be effective, however, this could not simply involve agreement that most subjects would not object. The IRB would have to find that there is evidence at a very high level of confidence that no subjects would object. I have proposed that this would require an empirical basis that at least 95% of people similar to the subjects would agree to having their samples used without further permission.[3] That is a level of evidence

that is very hard, perhaps impossible, to achieve.

(3) The Commodification Problem

Even if these difficult problems of consent can be solved, there remain more fundamental issues to be addressed. One is sometimes called the problem of commodification (the treating the human body as property or a commodity).[4] Some challenge the conversion of human body parts including tissues into a commodity that can be owned, bought, or sold like merchandise.

Ethicists have begun exploring this commercialization of human tissues.[5] Some suggest that converting human tissue into a marketable product raises fundamental issues of justice, especially when it occurs in developing countries or among low-income people lacking other opportunities for generating income.[6] Others question even more fundamentally whether human body parts are not intrinsically different from commodities such that they must be excluded from market transactions.[7] They point out that sale whole human living bodies has been universally condemned as slavery. In many cultures free-market sale of human organs is similarly condemned. If human organs cannot ethically be bought and sold, it is hard to see why human tissues would be any different.

Not all tissue research raises commodification issues, but the banking of samples and cell lines for future research lends itself to charging of fees for the services rendered. In tissue banking in the United States, non-profit procurement agencies and profit-making middlemen are often hopelessly intertwined with tissues passing from non-profit procurement agency to profit-making processing and distribution agencies. The Washington Regional Transplant Consortium presently procures skin, bone, and heart valves and transmits them to a non-profit firm, but profit-making businesses play various roles in the process so that it becomes almost impossible to distinguish between the humanitarian non-profit motive and more traditional business transactions. That group is currently exploring the procurement of knee joints for transmission to an agency, which would process them and warehouse them for order by orthopedic surgeons and others needing them for therapy. There is no reason why such tissues could not be bought for research uses as well. Since the procuring agency quickly loses control of the tissues and has no direct role in deciding the final use, getting consent from donors of the tissue is becoming increasingly complicated.

(4) Confidentiality and Tracing of Sources

Assuming tissues can be procured and stored for future research, a fourth and final ethical dilemma emerges. Not only will tissue procurers be unable to inform donors of the eventual use of the tissue, they will also face new problems of confidentiality. If tissues are collected and banked for future use in research projects,

one must assume that eventually someone may learn something of clinical significance from that research. That raises the question of the duty of the researchers who eventually do the research to inform the subjects of their findings. Especially, if they should find something clinically useful, investigators now are generally assumed to be obliged to report any useful findings to the subjects of the research.

While more traditional medical researchers may find this obligation an inconvenience, it is a major dilemma for tissue researchers using stored tissue samples. Many researchers, particularly those oriented to commercial pharmaceutical research, appear to fall back on the position that, as scientists, they are committed to "absolute confidentiality." They think that solves the problem. Often the claim to fulfill that duty by not retaining identifiers of the tissue source.

It does not address the critical issue, however. If there is a possibility that the research may produce some clinically useful result, researchers have a duty to have a plan in place for how they will respond should information emerge that is potentially useful to the donor of the tissues. Donors of tissue would surely want to know if the scientist learns something that could be life-saving to the donor or the donor's off-spring. When we consider that the norm is that researchers will inform research subjects of such findings, it seems clear that avoiding collecting of identifiers is an inadequate policy. Collectors of tissue samples must have a plan in place to contact subjects (or at minimum inform the donors of the samples that they will not be reachable).The standard of respect for the subject probably rules out a policy of unilaterally refusing to notify donors of important findings.

On the other hand, if clinically significant information emerges, informing the donor may have serious harmful consequences. The information that the subject is at risk for a genetic disease or toxic response to an environmental stimulant could jeopardize the future employment. In other words researchers who is successful in a research project and learns something clinically meaningful is damned if they report findings to subjects and damned if they don't.

I have recently been involved in a lawsuit against a major American pharmaceutical manufacturer who discovered in post-marketing surveillance that its drug was causing serious liver toxicity to a small group of patients–probably those with a variant gene. The drug probably was responsible for as many as a hundred deaths. The legal issue in the court case was whether the consent and side-effect standards for Phase IV clinical research had to be met or merely the more lax standards for routine therapy.

The drug company's researchers collected blood and tissue samples planning to do pharmacogenic research on the patient/subjects. The collecting of those

samples was clearly not part of routine therapy and therefore the company had to acknowledge that it was engaged in research. That created a new problem for the company, however. Since research requires a plan to notify subjects of findings, the pharmacologists, many of whom were PhD bench scientists were asked what that plan was. They were reminded that failing to inform violated normal research ethics, but informing could cause serious social and economic risks for their subjects. When the researchers admitted they had no plan, they company was censured for failing to meet minimal standards for conducting their research.

In order to deal with this problem, an IRB on which I serve has developed a standard requirement for researchers collecting samples for future study. In cases in which any potential for clinically useful information could emerge and that information could also create employment and insurance problems for subjects, subjects must be asked at the time the sample whether they prefer that identifiers be retained or not. If they want to be contacted in the case of discovery of clinically meaningful information identifier must be kept. The subject bears the risk of gratuitously learning information that could cause social or economic harm. On the other hand, subjects can choose not to be contacted, sparing them the employment and insurance risks, but foreclosing the possibility of learning clinically important information. If the subject chooses this option, no identifiers are kept guaranteeing the subject will avoid learning harmful information. Giving the donor subject the choice of whether to have identifiers retained seems to be the only morally legitimate way of dealing with this dilemma.

Regulatory Issues

Having explored some ethical dilemmas involved in the use of tissues in research, I turn to the third portion of my remarks: consideration of the regulatory issues in tissue research. I have noted that cadaveric human tissue used in research is, in the United States, excluded from the federal regulations governing protection of human subjects. It is covered instead under the Uniform Anatomical Gift Act–the series of state laws governing the procurement of cadaveric organs for transplant. Those laws also apply to tissues and govern both organs and tissues used in research as well as transplant and other therapies. Meanwhile tissue samples from living humans may slip through the cracks and be governed by neither set of laws. This seems to be a serious error and gross oversight.

Many tissues are exempt from federal human subjects laws because those laws do no apply to cadaveric tissue and materials from living sources are exempt from regulation provided they were pathological or diagnostic specimens originally collected for clinical purposes. Moreover, even if tissues are collected specifically for research purposes, in some cases research may be approved by the much more lax

expedited review procedures that leave the judgment up to a single IRB member. These provisions include blood samples, samples collected by noninvasive procedures.

The moral logic behind the exclusion of cadaveric tissue and specimens collected for therapeutic purposes presumably is that these subjects are exposed to no research risks. (The dead cannot be hurt and waste tissue specimens collected for therapeutic purposes pose no medical risk for research purposes.) The problem, however, is that the regulation writers failed to grasp how many dangers can arise from such studies. The risks of procurement of the sample are clearly not the only moral concern. Studies of tissue samples pose serious risks to both the welfare and rights of subjects. That an adequately informed consent requires information about the purpose of the study makes clear that subjects have a real interest in being asked to consent or refuse consent even in cases in which they are at no risk from procuring tissues. Samples potentially can be used for controversial projects: testing racist hypotheses, promoting military causes, serving the interests of corporations some subjects may find morally offensive, and so forth. Further, the subjects are, as we have seen, at risk of having the results jeopardize employability or insurance. Confidentiality rights do not diminish with the absence of risk from collecting the sample. It makes no sense to exempt studies of tissue samples just because subjects were placed at no risk in the collection of the sample. Moreover, the right of the subject to consent to the research purpose makes clear that anonymizing data or refusing to collect identifiers doesn't solve the problem. Subjects might reasonably object to some studies even if they are placed at no risk and their identities are completely shielded from the investigator.

Expedited review is more justifiable provided the single person conducting the review is sensitive to all the moral problems that can arise in these cases in which collection of samples poses no risk and confidentiality will be adequately protected. The subject may want to approve of the purpose of the study, may want to refuse to cooperate with the sponsoring agency, or may want to insist on being informed of the results.

Clearly, these problems do not go away when the subject is deceased. Residual interests and rights survive the death of the sample donor just as they do when one has written an economic will. The right to have one's will honored does not cease with death. This means that cadaveric samples and tissues collected from people who have since died must still be governed by the regulations covering research with human subjects. The rules written for procuring organs and tissue for transplant help fill this gap somewhat, but cannot be a full basis for protecting the rights and welfare of the deceased. Tissue procurers from the transplant community

are not adequately attuned to the full range of risks to which research subjects can be exposed. These subjects are even more vulnerable than subjects who are still living. They deserve the full protection of the IRB process.

Conclusion

Tissues used in research are like a sleeping giant. At first glance it seems that no real risks are involved because the subject cannot be hurt in any physical sense by anything done with the stored samples. Once the samples are obtained, the donors are free from further physical risk. That does not mean, however, that they are not in serious jeopardy. Humans can be forced into cooperation in controversial projects without their consent if the full protection of the human subjects review process is not extended to tissue donors. These subjects can, in some cases, learn information from the studies that is literally life-saving–either for themselves or their children. They can also learn information that will cost them their jobs, their financial well-being, or their mental well-being. For all these reasons, we need to pay much more attention to research involving human tissues and make sure that it is reviewed by the rigorous standards that apply to all human subjects research.

ENDNOTES

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