ORGANIZATION AND ACTIVITIES OF HUMAN TISSUE BANKS IN THE U.S. WITH SPECIAL REFERENCE TO THE INTERNATIONAL INSTITUTE FOR THE ADVANCEMENT OF MEDICINE

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IIAM-Biotransformation

Abstract: The International Institute for the Advancement of Medicine (IIAM) was established in 1986 as a non-profit research tissue bank. IIAM is a division of the Pennsylvania Regional Tissue and Transplant Bank (PRTB), whose purpose as a not-for-profit organization is to obtain, process and distribute human tissues for transplantation, medical/scientific research, education and the advancement of medicine. As the research division of PRTB, IIAM facilitates the distribution of non-transplantable human organs and tissues for biomedical research, education and development.

I will describe the organization and operation of IIAM, including the requirements for tissue and the application process. Legal and ethical considerations, financial support, our resource network and our customer base will be covered. Potential commercial use of human tissue is an area of concern, legally and ethically, and will be discussed as well.

IIAM is a truly international organization, with a branch in Leicester, England that has been in operation for over two years. I will describe some of the obstacles that were encountered and lessons that were learned in setting up that research tissue bank for human tissue.

Future developments include the development of a cell biology laboratory within IIAM, in which primary human cells from various organs and tissues will be isolated, characterized and distributed for research.

Key words: human tissue, research, tissue bank

Organ Transplantation and Tissue Banking

As a research tissue bank, IIAM is absolutely dependent upon the generosity of families who have experienced the sudden, unexpected and tragic loss of a loved one. When it comes to organ or tissue donation, transplantation is always the first option due to its inherently life-saving nature. However, in many cases the gift of an organ or tissue, intended for transplantation, is not suitable for that purpose; possible reasons include lack of a matching recipient, age of the donor, anatomical abnormality, surgical damage, and cancer in the donor, among others. In such cases, with proper informed consent from the next-of-kin, organs or tissues may be referred to a research tissue bank such as IIAM. This provides an alternative option to the donor family, and some measure of comfort at a terrible time in their lives.

Either type of donation, i.e., for transplantation or research, is consistent with the mission of IIAM and PRTB: “We conceptually view this donation as a living memorial to the deceased. It is our charter to serve the public in a professional manner and to provide a continuum for the family and friends of the deceased by maintaining that person’s memory, while at the same time improving the quality of life for others.”

In 1986, when IIAM was established, public awareness of the option of donating organs and tissues for research was essentially zero, as illustrated in Table 1. Without awareness, there
can be no acceptance; thus, this was also non-existent. The awareness and acceptance of tissue and organ transplantation at the time were somewhat higher and have continued to grow. Today, there is widespread awareness of organ transplantation due to the commendable efforts of groups within the transplant community, focused towards advertising and public education. I believe that most people in America also understand the value of organ transplantation, thus accepting the concept. Awareness of tissue transplantation and the option of donation for research continue to lag behind, but have improved since 1986. In addition, there seems to be a fairly high level of acceptance of tissue transplantation and research donation among those who are aware of them.

This is a good place to explain the difference between “organs” and “tissues” in terms of transplantation. Solid “organs” must be transplanted fresh, at least with today’s technology; they cannot be cryopreserved and banked. In the United States, the following organs are transplanted: heart, lung, liver, kidney, pancreas and small intestine. “Tissues”, on the other hand, can be cryopreserved, stored (banked) and used when needed; they include cornea, skin, bone, heart valves, tendons and ligaments. Any of these, and more, are accepted by IAM for research distribution.

The magnitude and growth of the field of organ transplantation in the U.S. are demonstrated by the data in Table 2. In comparison, of course, considerably fewer organ transplants are performed in Japan. In spite of the large number of such operations, there continues to be a shortage of organs available for transplantation in the U.S. As shown in Table 3, over fifty thousand patients are currently waiting for an organ transplant (52,349 as of April 30, 1997). Nearly four thousand times last year, a suitable organ was not found in time to save the life of a patient on the organ transplant waiting list. The number of organ transplants is critical for the availability of human tissue for research because many of the most viable specimens for research come from this source, i.e., in those cases where an organ that is procured for transplantation cannot be used for

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<th>Table I. General Acceptance and Awareness of Organ and Tissue Donation for Transplantation and Research</th>
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<tr>
<td>Acceptance</td>
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<th>Table II. U.S. Organ Transplants: 1988–1996</th>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>Kidney 9041  8988  9879  10122  10230  11020  11392  11819  11949</td>
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<td>Liver   1713  2201  2690  2953  3064  3440  3652  3923  4058</td>
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<td>Pancreas 249  417  528  531  557  774  842  1027  1022</td>
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<td>Heart   1676  1705  2108  2125  2171  2297  2340  2360  2342</td>
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<td>Lung    33   93   203  405   535   666   723   871   805</td>
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<tr>
<td>Heart-Lung 74  67   52   51   48   60   71   69   39</td>
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<td>Intestine 5   12   22   24   23   45   45   45   45</td>
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<td>Total 12786  13471  15465  16199  16627  18291  19043  20114  20260</td>
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that purpose. Table 4 gives the percentages of several organs that are used for research vs. transplant; in the absence of the research option, many more would be discarded.

**Legal and Ethical Aspects of Research Tissue Banking**

Research tissue banks such as IIAM must, of course, comply with all federal, state and local laws and regulations that apply to human organs and tissues. Two points need to be made regarding such laws. The first is that most legislation specifically deals with *living* human subjects and/or organ/tissue *transplantation* rather than *deceased* donors of organs and tissues for *research*. There are no laws that strictly govern research on tissues obtained from donors who are no longer living. The second point is that laws such as the Uniform Anatomical Gift Act (UAGA), which requires that informed consent be obtained for organ or tissue donation, mandate nothing more specific than that. The specific content of the informed consent form is left up to the discretion of the individual or organization obtaining consent, subject to interpretation by the court system. In general, the laws establish a basic framework, which is refined over time by legal precedent.

IIAM abides by the National Organ Transplant Act, which prohibits buying and selling human organs and tissues. As a non-profit organization, it provides a buffer between donor families and transplant organizations, on the one hand, and researchers (some of whom work for for-profit companies) on the other. IIAM operates on a cost-recovery basis, assessing its customers a fee to cover the costs of procuring, processing, storing and delivering human biomaterials to the research community. In addition, limited grant support from various industrial sources helps to subsidize the development of new programs and services.

The U.S. Food and Drug Administration (FDA) does not yet regulate *research* tissue banks; in fact, it has only recently issued a set of regulations for *transplant* tissue banks. Eventually, research tissue banks will no doubt be regulated by the FDA. In the meantime, such organizations should adopt the model of industry self-regulation and standardization used successfully by the American Association of Tissue Banks (AATB), which has established, and monitors compliance with, standards of quality and safety among transplant tissue banks. IIAM is in the position of establishing standards of quality, service, safety and ethical behavior among research tissue banks.

Ethical considerations are paramount in dealing with donations of human tissue. Informed consent, donor confidentiality and compensation are, perhaps, the most basic issues; many other important and controversial topics can be traced back to one of these roots.
The consent that is given by the donor or the donor's next-of-kin must be specific (e.g., marking a specific checklist of organs and tissues is preferable to approving the blanket statement "any and all organs or tissues"), informed (the consentor should know what will happen to the cadaver and, in general, what the donated organs/tissues will be used for) and understood (the language must be understandable to the average lay person and not overly technical). An important issue that is currently under discussion is the development of commercial products from human tissues. Advances in biotechnology and tissue engineering have enabled the development of commercial products for diagnostic and therapeutic purposes. This leads to several issues regarding informed consent for tissue donations that may be used to produce such products. While there is no question that such products (e.g., diagnostic kits for earlier and more accurate diagnosis of diseases such as asthma, osteoporosis or cancer) hold enormous potential to save or improve the quality of lives, the donor or next-of-kin must be informed of the potential for commercial gain by the manufacturer. The challenge is to word the consent form in such a way that it is accurate yet understandable, is not burdensome for the person requesting consent, and avoids insensitivity to the donor family. One concern, which must be avoided, is that bringing up the question of commercial use of tissue could lead to a refusal to donate for any purpose (including research and/or transplantation). In our experience to date, implementation of a commercial consent has had no negative impact on the overall consent rate.

IIAM ensures and guarantees donor confidentiality, per Title 45, Part 46 of the U.S. Code of Federal Regulations (CFR). IIAM identifies each research donor by an internal identification number, which is used in all communications with researchers, thereby protecting the confidentiality of donors and end-users. The system ensures the trackability of tissue by IIAM for safety reasons, while at the same time preventing identification of donors by researchers. In addition, researchers cannot be identified by donor families.

There is no financial compensation for donors or their families, nor is there any cost to the donor family for organ or tissue donation for research. The controversial issue of monetary compensation for organs donated for transplant has been a subject of discussion for several years, as a possible means to alleviate the severe shortage of transplantable organs. The majority of experts in the field seem to be opposed to the idea, although the subject remains open.

IIAM-UK

Some of the lessons that IIAM has learned, in the process of establishing and operating a research tissue bank in the United Kingdom (U.K.) for the past two years, may be instructive to those individuals and organizations that are interested in doing the same thing in Japan. It was important to become knowledgeable about government regulations, especially with regard to non-profit or charitable organizations. There were cultural issues to deal with, including religion, superstition, public sensitivity and resistance to foreign (U.S.) involvement. The U.K. project could not have succeeded without the support of medical professionals (doctors, nurses, hospital administrators), the transplant community (transplant coordinators and administrators) and key government agencies (Department of Health, Medical Research Council, etc.). In addition, it was extremely helpful to have a local advisory board and a native coordinator/administrator. It was necessary to encourage the resolution of a number of key points, e.g., the issues of processing fees (assessed to customers by IIAM to cover costs) and acquisition fees (assessed to non-profit organizations such as IIAM by tissue-procurement or tissue-referral organizations to cover costs; exists in the U.S. but not in the U.K. at this time). An interesting distinction between U.S. and U.K. practice is the consent process, which requires a formal written document in the U.S. whereas verbal consent with a handwritten note is acceptable in the U.K. In addition, there is a distinction between the use of human organs and tissues for transplantation vs. commercial development vs. research purposes in the U.S., due to legal precedents such as the 1990 case of Moore vs. Regents of the University of California. In the U.K., there is no legal distinction between the different uses of human organs and tissues,
although the issue was considered by the Nuffield Council on Bioethics report titled “Human Tissue, Ethical and Legal Issues” (April 1995).

Operations

I would like to emphasize a number of points that are particularly important in the proper operation of a research tissue bank.

Application for tissue: IIAM requires that research customers complete a rather extensive application and agreement for human biological material for research use. The application specifies shipping and communication information (address, phone number, etc.), tissue and donor specifications (type and size of tissue sample, donor age, race, sex, etc.), specimen processing conditions (fresh, frozen, cryopreserved, fixed, etc.), information needed about the donor (medical conditions, medications, alcohol use, etc.), and a summary of the research project for which the tissue will be used. A letter of approval, expedited review or exemption from the applicant's Institutional Review Board (IRB) is also requested. Every application is scrutinized by the IIAM Application Review Panel for scientific merit and ethical concerns, then approved, rejected, or returned to the applicant with questions or for revision. In addition, the IIAM program is subject to general overview by agencies such as the National Health Service (in the U.K.). In some cases, input is actively solicited from other sources; e.g., the transplant community is being consulted regarding the issue of commercial consent.

Legal agreement: The Biological Materials Transfer Agreement is a legal document that specifies the responsibilities of IIAM and the applicant regarding the use of human tissue for research. The signature of an authorized representative of the applicant institution legally obligates that institution to abide by IIAM’s Tissue Use Policy, which requires that the applicant be the end-user of the material (unless otherwise permitted in writing by IIAM). The agreement constitutes a license to the applicant for use of the tissue; i.e., IIAM retains the right to recall the tissue if the conditions of the agreement are not adhered to. The conditions are obviously difficult to enforce, but are required for safety considerations (in case of a recall) and in order to ensure compliance with legal and ethical requirements. The degree of control embodied by the Biological Materials Transfer Agreement is an essential element of our program in the eyes of many members of the transplant community.

Informed consent: There are a number of required elements that should be included in the informed consent, although the exact wording, length and organization vary. (1) The donor and/or the next-of-kin (consentor) must be identified; the UAGA specifies the order of priority for determining the next-of-kin. (2) The organs and/or tissues to be donated must be specifically identified; blanket statements such as “any and all organs and tissues” should be avoided because the consentor may not have an accurate idea of what such a statement might entail. There should also be a place for the next-of-kin to decline donation. (3) The purpose(s) for which consent is given for the use of the donated organs/tissues must be specified, e.g., “transplantation, biomedical research and development, education, or development of a commercial product.” Non-specific statements such as “any purpose authorized by law” should be avoided because the average consentor is not likely to know which purposes are authorized by law. (4) There should be a statement explaining that the donation is offered without obligation on the part of the recipient organization and that there will be no reward or compensation to the donor family. (5) The consent must be signed and dated by the donor or next-of-kin and a witness. A recorded telephone consent is acceptable until a hard copy can be signed. Consent must be obtained prior to the procurement of the organs/tissues that are donated.

Safety: The primary safety concern is infectious disease transmission. To reduce that risk as much as possible, a serum sample from every IIAM research tissue donor is tested for the following infectious diseases by government-licensed clinical laboratories: HIV-1 and -2 antibodies, hepatitis B surface antigen, hepatitis C antibody, HTLV-1 antibody, syphilis, and hepatitis B core antibody (IgG plus IgM). In addition, one or more of the following tests are sometimes done: CMV antibody, hepatitis B surface antibody,
hepatitis B core IgM, and HIV p24 antigen. The tests are normally done prior to distribution of tissue, and any results that suggest that the donor is infectious preclude distribution. An exception would be researchers who have specifically requested infectious tissue, in which case written authorization is obtained in advance. When necessary, our medical director, an infectious diseases expert, is consulted to interpret serology test results. Serology testing is complicated somewhat by the issue of hemodilution (i.e., the dilution of the donor's blood due to transfusion of blood or other fluids), which could potentially invalidate serology test results. Hemodilution is taken into account when determining the suitability of tissues (skin, bone, eyes, cells, etc.) for transplantation, including tissues for clinical trials, but is not a consideration for organ transplantation. Transplanted hepatocytes will probably be regulated at least as stringently as tissues, in which case hemodilution will be a factor. At this time, hemodilution is not taken into account for research tissues/organs, but the issue is under discussion. Another step to reduce the risk of infectious disease transmission is the use of universal precautions (per the Bloodborne Pathogens Standard of the U.S. Occupational Safety and Health Administration: 29 CFR 1910.1030), as mandated by the IIAM Biological Materials Transfer Agreement.

Resource network and customer base: The IIAM tissue resource network is wide-ranging, literally encompassing the entire U.S., and varied, including sources as diverse as organ procurement organizations, tissue banks, university anatomical gift programs, hospitals, medical examiners and hospices. One of our departments is dedicated solely to developing new sources of tissue and maintaining good relationships with existing sources. The customer base is even more wide-ranging, covering the U.S. and many other countries, and includes researchers at academic institutions, pharmaceutical companies, government laboratories and clinical facilities.

Policy manual: IIAM maintains a current, detailed and complete policy manual, which guides every phase of our operation. Such a manual is good business practice as a decision-making guide, is useful in case of questions or inspections by governmental or other regulatory agencies, and is required for research tissue banking by the state of New York.

Donor information: The minimum information required about each donor includes age, race, sex, height, weight, cause of death, time of death, procurement time, consent for research, serology results, and medical/social history (including diseases, drug/alcohol use and medications). Other useful information includes fluid input/output data, which are needed in order to calculate the extent of hemodilution.

Hepatocyte Transplantation

As part of a clinical collaboration, IIAM provides non-transplantable livers to Dr. Bahri Bilir, a hepatologist at the University of Colorado, who is a leader in the field of hepatocyte transplantation. By isolating and cryopreserving cells from such livers, non-transplantable material (liver tissue) is converted into transplantable material (hepatocytes). Dr. Bilir and IIAM have established the first bank of transplantable cryopreserved human hepatocytes in the world. When needed, the frozen cells are thawed and, in a relatively minor surgical procedure, infused into the spleen of a patient with acute or chronic liver failure, where the cells take over some of the functions of the failing organ. The goal is to enable patients to survive until a suitable donor liver is located. Thus far, nine patients have been treated with this procedure by Dr. Bilir, with very encouraging results: the lives of patients with acute liver failure have been extended by periods ranging from several days to many months. When needed, the procedure can be repeated. This is a very exciting project, offering as it does a chance to save the lives of patients through a novel transplant option. The regulatory requirements are uncertain at this time; again, IIAM is trying to anticipate them and is helping to set the standards.

Conclusion

Without question, there exists a tremendous need for human organs and tissues for research and development. Beyond that, there remain significant questions that must be addressed regarding the acceptable uses of such materials.
We should bear in mind that the potential for life-saving and life-enhancing advances in medical diagnosis and treatment makes it worthwhile to pursue answers to these questions. In order to obtain a consensus as to the "right" (i.e., ethical correct and socially acceptable) answers, it will be necessary to have a dialogue including individuals with different viewpoints (e.g., researchers [academic, industrial and government], representatives of the organ-transplant and tissue-banking communities, bioethicists, attorneys and members of the lay public). I applaud and support the Ethical Subcommittee of the Japanese Tissue Culture Association (JTCA) for taking such an open and inclusive approach, as discussed elsewhere in this volume. The need is too great and the questions too important and sensitive to be left to the interpretation of any of the individuals involved. Some of the questions are:

1. What are the acceptable uses of human organs and tissues that are donated for research? as a tool for biomedical research? Or would this require consent for development of a commercial product?
2. Is it acceptable to process human organs/tissues that were donated with consent for research into a product that becomes commercially available
3. Does consent for "transplantation, therapy or research" allow the production of diagnostic kits from the donated organs or tissues?
4. Does consent for "transplantation, therapy or research" allow the use of donated organs or tissues to produce commercially available therapeutic products? What if the commercial product is used for transplantation?

Regardless of the ultimate resolution of these issues, it is important to pursue a consensus on socially acceptable answers. My message for the JTCA Ethical Subcommittee is a quote from Mohandas Gandhi: "Whatever you do ... it is most important that you do it."

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