Declining Availability of Human Eye Tissues for Research

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Research in modern investigative ophthalmology and vision science has two fundamental uses for human tissues: laboratory studies of anatomy, physiology, biochemistry, pathology, genomics, and proteomics, and ophthalmic device research and development. Because population aging focuses attention on chronic diseases such as age-related maculopathy (ARM), glaucoma, and diabetic retinopathy, it is instructive to note the experience of research in other age-related diseases. Thirty years after cholesterol-enriched lesions in coronary artery disease were characterized, 20 years after protein from Alzheimer brain was isolated, and even the current widespread availability of animal models and in vitro systems for both diseases, high-impact studies using human tissues still appear regularly in atherosclerosis and Alzheimer research. There will be a continuing need to examine well-characterized human tissues in light of new information from animal models resulting from gene-based investigations. For reference, the cardiovascular literature, with a century of animal models, periodically compares models to human disease. Because of the unique anatomy of the macula and the aqueous outflow tract in humans, human tissue will be a mainstay of ARM and glaucoma research for the foreseeable future. From this perspective, eye research using human tissues is an important component of the power grid that energizes clinical ophthalmology by providing relevance.

There are three basic strategies for finding eyes with chronic diseases, all of which rely on the harvesting of eyes from deceased donors by eye banks. These include a registry (obtaining donor pledges in advance of donor death), systematic harvesting (gleaning all available tissues from deceased donors at a single source to find tissues meeting specific criteria), and a clearinghouse (matching investigators in one city specific protocols with tissues meeting those criteria in another city). A well-known clearinghouse is National Disease Research Interchange (NDRI, Philadelphia, PA), with 125 active eye protocols, 115 sources (eye banks, tissue banks, organ procurement organizations, and hospitals), and 25 years of support from the National Eye Institute.

Figure 1 shows a trend that is slow, yet pervasive, and potentially of great significance for clinical ophthalmology: the number of research tissues from human donor eyes provided by U.S. eye banks declined 28% from 21,766 in 1997 to 15,780 in 2004. This trend shows no signs of reversal. What underlies this development? Should it concern us? What should ARVO members do in response? This article presents the results of a membership survey, the mechanics of how eye banks procure research tissues, eye banking developments that underlie this unpropitious trend, and short- and medium-term recommendations from the Research Tissue Acquisition Working Group (RTAWG) for ARVO members and eye banks in the United States.

A recent web-based survey of 240 U.S. ARVO members (6% of the U.S. membership) indicates continued demand for human tissues for research. The local eye bank ranked first among respondents as a tissue source, but in reality most investigators use multiple tissue sources, including remote eye banks. The major prohibitory factors in the use of human tissues are cost, nonavailability of tissue meeting stringent criteria, and lack of clinical documentation. Regarding costs, examining tissue from 10 ARM donors and 10 age-matched controls can cost $8000 to $10,000 and can take 1 year just to acquire the tissue. However, many investigators indicated they could bear higher costs if tissue were collected within a short death-to-preservation interval. Tissue quality is an increasingly compelling consideration due to the high sensitivity of current assays. The percentage of investigator requests to NDRI specifying death-to-delivery time of less than 24 hours was 26% in 1993 and 61% in 2003. However, due to the time spent complying with more regulations (see below), postmortem processing time has risen from 3.9 hours to 6.8 hours over the same interval. Although experiments involving histology, anterior chamber perfusions, proteomics, and cell isolations have different degrees of tolerance for postmortem delay, all uses benefit from tissues in which death-to-preservation time is minimized. The most stringent requirements apply to mRNA preservation for gene expression studies. Direct comparisons between donor eyes and simulated eye bank conditions indicate that a 5-hour postmortem upper limit for intact RPE mRNA can be extended to 24 hours by using specialized media (e.g., RNAlater; Ambion, Austin, TX). Regarding availability, much eye research requires tissues that do not meet transplant criteria (e.g., fetal tissue, older donors, i.e., >80 yr), thus requiring special effort from cooperating eye banks. Further, local eye bank practices affect research tissue availability. For example, in some states a medical examiner (ME) law does not permit whole eye enucleation in cases of violent or suspicious causes of death typically referred to the ME. Thus, tissues from younger individuals dying of these causes are off-limits, and accordingly, the average age of whole eye donors to NDRI has stabilized at 65 years. New rules requiring personal medical history interviews with someone acquainted with the deceased donors, will depress this already small source of young donors further. Other problems impacting tissue availability include lack of conformity with acceptance criteria, cornea-only donations, and family willingness to consent to eye donation for transplant but not for research. Regarding clinical history, 71% of respondents required clinical documentation for their work, and nearly as many (61%) indicated willingness to pay more for that service, which is noteworthy, because ophthalmic medical history for eye donors is not required of eye banks by regulatory agencies.

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To acquaint investigators with the mechanics of eye donation, we review the three R’s: referral, recovery, and regulation. Referral: Donor identification proceeds from patient death, which, if in a hospital, must be reported to an organ procurement organization (OPO), followed by OPO triage to eye bank. Eye banks and OPOs negotiate the extent of initial information sharing and responsibility. (Note that sources, such as hospice, law enforcement agencies, funeral directors, and non-Medicare/Medicaid participating hospitals do not need to comply with the OPO notice rule.) Criteria for eye donation, including those for research, must be constantly updated and communicated to eye bank, OPO, and hospital staffs. The eye bank, OPO, or both in concert may screen and obtain consent and detailed medical/social history. Research criteria pertaining to brain death, family history, or permission for later contact must be well known to staff to capture most viable research candidates at this stage. Donors potentially suitable for corneal transplants take precedence over research donors, based on revenue-generating potential and primary mission. Eye banks differ as to whether they rely on designated requesters among hospital staff (who must be regularly trained and motivated) or in-house staff to obtain consent. Recovery: large eye banks maintain technical staff around the clock for recovery operations and tissue delivery to a central location for evaluation, processing, and distribution. Recordkeeping at this phase includes review of consent form, review and possibly copying of donor’s medical chart, completion of a hemodilution algorithm to ensure blood sample suitability for serology testing, and microscopic review of corneal tissue for viability markers. Support services include human resources, accounting, information technology for donor database, supplies and equipment stocking and maintenance, administrative and non-technical support staff, physical plant costs, and insurance (liability, health). Regulation: Eye banks are accredited by the Eye Bank Association of America (EBAA) based on review of standard operating procedures compliant with EBAA Medical Standards developed by its Medical Advisory Board (successor to the Eye Bank Committee of the American Academy of Ophthalmology) and of procedures compliant with the EBAA Policy Statement on Research Tissue; U.S. Food and Drug Administration (FDA); state law; U.S. Department of Health and Human Services—Centers for Medicare and Medicaid; Offices of the U.S. Inspector General and Attorney General; and the Occupational Health and Safety Administration. Site inspections by EBAA include review of policy and procedures manuals, donor records, laboratory procedures and maintenance, technical staff, Quality Assurance, and the Medical and Executive Directors. Site inspections by the FDA include review of donor records, factors pertaining to transmissible disease, donor suitability, and Good Tissue Practices. Finally, it should be noted that although the cornea is nonvascular, many regulatory details more appropriate to the greater risk for disease transmission associated with vascularized tissues spill over to eye banks.

Numerous factors in the eye bank system during the past three decades converge toward the current climate of a smaller research tissue pool. Although in situ excision of the cornea was first reported in 1975, corneas were previously obtained largely from whole globes enucleated from deceased donors until hypothermic preservation media became available in the 1980s. In addition to the cornea, other eye parts had medical uses (e.g., sclera fashioned to cover drainage implant tubes in Molteno shunt procedures for glaucoma or to wrap hydroxyapatite prosthetic eyes). Regarding finances, all tissue was historically provided gratis to recipients due to the philanthropic support that funded all eye bank operations. A typical eye bank in 1975 may have received seed money from the estimable Lions Club, and generous Lions Club members donated time and effort. Funeral directors may have volunteered to perform enucleations across a state. Space may have been provided in a hospital (sometimes in return for abated tissue costs for surgeons), utilities donated, and supplies purchased through hospital stores. Processing fees for transplant corneal tissue did not become common until the late 1980s after the introduction of corneal storage media, EBAA Medical Standards, and serologic testing requirements. After 1990, pericardium, dura, and artificial biomaterials became feasible substitutes for sclera, thus drastically reducing demand for harvested sclera, and in turn, harvested whole globes. Concomitantly, in situ corneal excision, requiring more surgical skill, became the method of choice for obtaining transplantable corneas. This transition rendered impractical adequate training and quality assurance for occasional procurers such as funeral directors. On the logistic side, local Lions Clubs financial and programmatic support dwindled, requiring eye banks to self-support through processing fees. Hospitals can no longer afford to donate services and time. The Conditions of Participation (the required referral law promulgated by Centers for Medicare and Medicaid Services) requiring audits of all deaths imposed the need for a labor-intensive 24-7 call center. Heightened awareness of factors associated with transmissible disease, including the appearance of new diseases (SARS, West Nile virus) and continued concern about neurodegenerative diseases of uncertain etiology (Alzheimer’s) led to more extensive serology testing and increased scrutiny of all donors to avoid transmission of infectious agents. These shifts in toto demand more time and money for public education, human resource management, legislative issues, salaries, and less for investment and infrastructure upgrades. The net result is a contracted national eye bank apparatus (106 U.S. eye banks in 1997 vs. 88 in 2003), as smaller eye banks merge with others to survive or disappear outright.

It should now be clear that although freely given, donor eye tissues for research are not harvested, processed, and delivered for free. Yet until the mid-1990s, most eye banks received little ($25-$100) or no reimbursement for research tissue. A recent cost analysis for a typical eye bank identifies operational and nonoperational costs. Operational costs include direct contributions to tissue production (storage media) and indirect contributions (facilities, clerical support, and quality assurance). Nonoperational costs include hospital staff education, public education, and marketing. Further, harvesting a research donation requires two thirds to three fourths of the technician time required for a transplant donation (depending on circum-
stances of the individual eye bank) and benefits from all the equipment, supplies, public education, and marketing infrastructure established for transplant donations. These considerations have elicited more realistic cost estimates of $400 to $900 per single donor eye ($800–$1800 per donor) for research (once again, depending on circumstances of the individual eye bank).

It is indisputable that eye banks, due to a revised financial model, have evolved over the past decade into true nonprofit organizations that rely on processing fees to pay their operating costs. As a result, the cost of research tissue acquisition can no longer be absorbed by an eye bank and investigators must pay more. Fortunately, some eye banks established special programs/protocols to meet researchers’ needs, and as long as this situation persists, investigators willing to reimburse for procurement costs will continue to obtain the tissues they require. The RTAWG therefore offers the following short-term recommendations for U.S. ARVO members:

- With regard to costs, researchers should budget properly for tissue costs in grant applications. Providers will often assist with a letter to include with grant applications.
- With regard to availability, researchers should become acquainted with the limitations of a provider’s donor demographics.
- With regard to the death-to-preservation time, the researcher should be practical and flexible. A request for tissues at 1 hour postmortem on alternate Thursdays is not likely to be filled, and if fresh or rare tissues are required, be prepared for contact on weekends and at odd hours.
- The relationship between an investigator and an eye bank must be nurtured over time. The ability of a provider to meet specific needs is protocol-dependent and should be discussed in advance. Communicate regularly. Visit collaborating eye banks to determine whether they are equipped to meet particular needs. Be clear about experimental needs and expectations. Eye bank staff must be trained to adhere to any new protocols.
- Be aware that technical staff decides which tissues to harvest for research on a case-by-case basis and therefore should be trained and rewarded appropriately.

The RTAWG also offers the following medium-term considerations for U.S. ARVO members and eye banks:

- To generate sufficient volume and consistency from processing fees, a new approach could focus on developing large research-oriented eye banks, capable of on-site initial preservation of tissues. Currently, few eye banks are strongly committed to this model instead of the transplantable cornea model. Such tissue banks may need subsidy by a consortium of local and national research institutions, including pharmaceutical companies, who now compete with academic research centers for tissues.
- Developing donor programs for disease-specific tissues is a continuing challenge, but note that local eye banks can network with other eye banks to obtain such specimens.
- Collaborations between U.S. and international investigators, which exploit differences in national laws regulating organ donation, are likely to grow in the future.

From the RTAWG’s perspective, then, the decline in human research tissues may be reversed in small steps as individual investigators work with their providers to acquire valuable resources for continued progress in understanding chronic eye diseases.

For further information about human donor eyes for research contact, Eye Bank Association of America (http://www.restoreisight.org/), National Disease Resource Interchange (http://www.ndriresource.org/index.html), or VisionShare (http://www.visionshare.org/).

References


Appendix

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