

Human tissues have been stored for a long time. Some institutions in the United States have archived specimens of human tissues that are more than 100 years old. Historically, these stored tissue samples have been used by the biomedical community for educational and research purposes. More recently, stored tissues have played a major role in the understanding and treatment of such diseases as cancer, HIV/AIDS, and heart disease. However, the use and storage of human tissues raise several legal, ethical, and societal issues. Furthermore, as recent and rapid advances in biological and medical research made it possible to analyze DNA from almost any minuscule sample of human tissue, concerns about privacy and informed consent have been raised. Complicating these issues is the paucity of information addressing tissue acquisition, use, and storage.

Once removed, human tissue may serve many beneficial purposes. The most familiar and widespread use of human tissue is in the diagnosis and treatment of illness. Another common use of human tissue is for quality-control purposes in diagnostic and pathologic laboratories. Human tissue is also used for medical and biological research and for medical education and training. Other uses of human tissue include identification, such as in paternity testing, cases of abduction or soldiers missing in action, and forensic purposes in crime cases when biological evidence is available for comparison.

The most common source of tissue is from patients following diagnostic or therapeutic procedures. Tissue specimens may also be taken during autopsies performed to establish the cause of death. In addition, volunteers may donate blood or other tissue for transplantation or research, organs for transplantation, or their bodies for anatomical studies after death. Each specimen of human tissue can be stored in multiple forms, such as slides, paraffin blocks, formalin-fixed, frozen, tissue culture, or extracted DNA.

HISTORICAL PERSPECTIVE

The development of the use of human biological materials for research has been a slow process. Early Egyptians did not study the deceased human body for an explanation of disease and death, though some organs were removed for preservation. The Greeks and Indians cremated their dead without prior examination. The Romans, Chinese, and Muslims all held various taboos and beliefs against opening the body for examination, and thus, no study of human organs or tissues occurred in these societies. Human dissections were also not permitted in Europe during the Middle Ages.

The first real dissections for medical study of disease were carried out around 300 B.C. by Alexandrian physicians Herophilus and Erasistratus. In the late second century A.D., the Greek physician Galen was the first known person to correlate a patient's symptoms with what was found upon an internal examination of the "affected part of the deceased." Greek medicine was essentially the beginning of human medical study based on scientific investigations and observations. Medicine before the Greek advances was almost entirely confined to religious beliefs and rituals. Disease was considered a result of divine interference and human sin, and the maladies of those unlucky individuals were "treated" with spells and prayers.

During the Renaissance, the artists rather than the anatomists were intent on rendering an accurate picture of the human body. Leonardo da Vinci performed dissections and extensive analysis on the human body during the late 1400s and early 1500s. The study of human organs and tissues began to take hold in the nineteenth century. Early biologists viewed their work as a study of the organism. The German pathologist Rudolf Virchow introduced the cellular doctrine, which viewed changes in cells as the basis of the understanding of disease, through his work in pathology and autopsy. In 1838, Theodor Schwann and Matthias Schleiden announced their cell theory that postulated cells as the basic unit of all living tissues.

In 1912, scientists performed an experiment that demonstrated that cells could be kept alive indefinitely if proper conditions were maintained. The advent of transplantation surgery in the mid-twentieth century spurred organ donor programs and organ banks as the technology advanced for specific organs. It was found that without a blood supply, organs would deteriorate rapidly, although cooling could slow the deterioration process somewhat. Blood cells, spermatozoa, and certain other dissociated tissue cells were found to survive subzero freezing indefinitely. Special preserving fluids were shown to prevent cell destruction by ice crystals, but, unfortunately, these fluids have damaging effects if introduced into whole organs. Long-term storage and banking of organs seems unlikely in the near future, because preservation techniques for

heart, liver, and lung have not been extensively studied (the kidney can be preserved up to 72 hours).

Several historical examples have demonstrated the value of archived tissue samples. For example, research in tracking viruses and studies tracing the pathology of a particular disease have been extremely beneficial to medical research (NBAC, 1999). A recent case involved the rediscovery of slides stored by Alois Alzheimer and the confirmation of his original diagnosis by histological and genetic analysis (Graeber et al., 1997; 1998). Slides of the first brain known to have Alzheimer's disease were stored in 1906, and a paper was published in 1907 describing the disease. The search for the brain of patient Auguste D. began when her original hospital file was found in 1996 at an institute at the University of Frankfurt. In 1998, more than 250 slides of Auguste's brain were found in a basement at the University of Munich, where Alois Alzheimer worked at the time of her death. The reexamination of the slides clarified the definitive pathologic diagnosis of Alzheimer's disease.

TYPES OF TISSUE/ORGAN BANKS

Tissue collections vary considerably, ranging from formal repositories to the informal storage of blood or tissue specimens in a researcher's freezer. The form in which the tissue is stored can also vary widely, including solid organs, sections of organs, histology slides, cells, and DNA. Large collections include archived pathology samples, autopsy material, and tissue biopsies from diagnostic tests. These tissue samples are stored at military facilities, the National Institutes of Health and its sponsored facilities, other federal agencies, state collection agencies (e.g., state forensic DNA banks and newborn screening laboratories), diagnostic pathology and cytology laboratories, university- and hospital-based research laboratories, commercial enterprises, and nonprofit organizations.

USES OF TISSUE/ORGAN BANKS FOR BIOMEDICAL RESEARCH

A common use of stored tissues was to correlate changes in structure or appearance of a tissue with a diagnosis of a particular disease. Pathology exams were performed broadly with what could be seen by the naked eye and eventually with the light microscope. As the understanding of science advanced, tissue analysis was reduced to a smaller scale. Molecular biology and genetics research has minimized the need for viably stored tissue. Frozen tissue, paraffin blocks, or formalin-fixed tissue is sufficient for the study of protein and gene expression and genetic mutations. Research of tissue samples has evolved toward a much smaller scale, where once a large portion of an organ may have been required for study, a single slice or a million cells is now more than suffi-

cient to answer a researcher's question. Thus, a single freezer could store a lifetime of research samples on a particular tissue or disease.

Different areas of research that routinely use tissue samples include studies of gene or protein expression, initial analysis of tissues affected by a newly discovered viral or bacterial pathogen, studies of changes in genetic sequences over time or in different populations, genetic linkage studies in normal and affected populations to narrow the location of the mutant gene, and analysis of cell structure in affected and normal tissue. The older a tissue bank is, the more valuable it may be to ascertain changes over time as environmental or societal shifts occur. The need to achieve statistical significance requires large sample numbers, and thus researchers may need to use tissue samples from a number of different banks. The ongoing need for tissue samples in research calls for a handbook, such as this, to facilitate the process of finding particular tissues for research. Both public and private entities use tissue samples for both academic and commercial enterprises. The savings in time and money of avoiding collection of tissues for each new research study is invaluable to the researcher in an environment where both are scarce.

AN INVENTORY OF TISSUE SOURCES IN THE UNITED STATES

To date, no central database captures information about stored tissue samples. To obtain a better understanding of the magnitude of existing archives, the National Bioethics Advisory Commission (NBAC) initially requested information from RAND about stored tissue samples in the United States. The purpose of the report was to collect for the first time in a single document information about tissue storage in the United States. Although it was not meant to be a comprehensive inventory, the report identified the major sources of stored tissue. This handbook is an extension of the NBAC commissioned report and is meant to serve as an inventory resource of stored tissue samples in the United States. The abundance of such samples in the United States is essentially useless to scientific investigators unless they are aware of its existence and its availability. The report as well as this handbook attempts to provide information about several aspects of stored tissue samples by addressing the following questions:

1. Where are tissues stored? (e.g., repositories, pathology laboratories, blood banks)
2. How many tissue samples are stored at each institution?
3. Who are the sources of stored tissue samples? (e.g., patients, volunteers)
4. Why were the tissue samples originally collected? (e.g., diagnostic purposes, research)

5. For what purposes have the stored tissues been used? (e.g., cancer research, gene mapping)
6. Who has access to the samples? (e.g., researchers, insurers, employers)
7. How are the tissue samples stored (e.g., paraffin blocks, slides, frozen tissue) and for how long? (e.g., months, years, indefinitely)
8. What identifying information is kept with the tissues? (e.g., patient's name or medical record number).

We intend this handbook to serve the research community as a comprehensive reference source of tissue banks in the United States and to facilitate the distribution of tissues for individual research projects.