February 22, 1998: This is a draft paper developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced.

I. OVERVIEW

Molecular genetic and other new technologies have the potential to greatly expand our understanding of human disease and to provide better means of prevention, diagnosis and treatment. Indeed, these new tools have already benefited hundreds of thousands of individuals.

The technologies also hold the ability to uncover knowledge about the past and reveal the future, even for individuals no longer alive and for those yet to be born. For example, scientists at Oxford University in England announced in 1997 that they had compared DNA extracted from the molar cavity of a 9,000-year-old skeleton, known as Cheddar Man, to DNA collected from 20 individuals in the village of Cheddar and established a blood tie between the skeleton and a schoolteacher who lived just half a mile from the cave where the bones were found. Similarly, scientists have used enzyme-linked assays to analyze tissues more than 5,000 years old to track the historic spread of diseases such as malaria and schistosomiasis, obtaining knowledge that can enlighten current efforts infectious disease control (Egyptian Mummy Tissue Bank, 1997). The same technologies can be used in persons living today to diagnose predisposition to conditions such as cancers, heart diseases, and a variety of familial diseases, which affect millions of individuals. Human biological materials also constitute an invaluable source of information for public health planning and programming, through disease surveillance, and studies of disease incidence and prevalence.

The Research Value of Human Biological Materials

The medical and scientific practice of routinely storing human biological material is nearly 100 years old. Human biological collections, sometimes called DNA banks, tissue banks, or repositories, vary considerably, ranging from formal repositories to the informal storage of blood or tissues specimens in a researcher's laboratory freezer. Large collections include archived pathology samples, autopsy material and stored "Guthrie" cards from newborn screening tests. These tissue samples are stored at military facilities, forensic DNA banks, government laboratories, diagnostic pathology and cytology laboratories, university- and hospital-based research laboratories, commercial enterprises, and non-profit organizations. Archives of human

biological materials range in size from fewer than 200 specimens to more than 92 million. Conservatively, an estimated total of at least 283 million specimens (from more than 176 million cases) are stored in the United States, accumulating at a rate of over 20 million per year (see chapter 2).

In this report, human biological material encompasses a full range of specimens, from subcellular structures like DNA, to cells, tissues (blood, bone, muscle, connective tissue and skin), organs (e.g., liver, bladder, heart, kidney, placenta), gametes (sperm and ova), embryos, fetal tissues, and waste (urine, feces, sweat, hair and nail clippings, which often contain shed epithelial cells). The most common source of material is from diagnostic or therapeutic interventions in which biopsies are taken to determine the nature and extent of a disease or diseased tissue. The vast majority of currently stored samples were originally collected for such purposes. It is routine in these circumstances to retain a portion of the sample even after diagnosis for future medical, research, or legal purposes. Specimens may also be taken during autopsies that are performed to establish the cause of death. In addition, healthy volunteers may donate blood, tissue, or organs for transplantation, and organs or whole bodies may be donated after death for transplantation or anatomical studies. Each specimen may be stored in multiple forms, such as slides, paraffin blocks, formalin-fixed, tissue culture, or extracted DNA. Repositories provide commercial and noncommercial laboratories with access to samples for medical and research purposes.

Once removed, a specimen can be used to study basic human biology or disease. It can be examined to determine its own normal and abnormal attributes or it can be manipulated and developed to obtain a research tool or potentially marketable product (OTA, 1987). Just as a clinician will choose a biological sample appropriate to the medical situation at hand, a researcher's choice of tissue depends on the goals of the research project. The tissue selected can be used just once, or in long-term projects, such as in the development of a cell line, a cloned gene, or a gene probe. Proteins can be extracted or genes isolated from specimens.

There is research value in both unidentified material (i.e., not linked to an individual and his/her medical records), and in material linked to an identifiable person. In the former, the value to the researcher of certain types of human biological material results more from its availability

and accessibility than to its uniqueness or identifiability. Investigators are often interested in specific types of tissues, for example, cells from individuals with Alzheimer's disease or specific tumors. They may not need the detailed accompanying medical records of the individual from whom the specimen was obtained. Sometimes, however, the value of the material for research depends on linked medical information that would allow for identification of the person who is the source of the sample. For example, in some longitudinal studies, to determine the validity of a genetic marker as a predictor of disease, it might be scientifically crucial to be able to link a sample with the medical records of its source.

Human biological materials also may be used for quality control in health care delivery, particularly in diagnostic and pathologic laboratories. Other uses include identification, such as in paternity testing, cases of abduction or soldiers missing in action, and forensic purposes where biological evidence is available for comparison. The advent of technologies that can extract a wide array of information from these materials, however, has magnified the potential research and other uses of human biological samples that are unrelated to individual patient care.

Thus, the power of new DNA technologies and other new molecular technique means that scientists can potentially turn to millions of stored human biological samples as sources of valuable scientific, medical, anthropological, and sociological information. This ability means that human tissue and DNA samples that have been sitting in storage banks for years—even a century—could be plumbed for new information to reveal something not only about the individual from whom the tissue was obtained, but possibly about entire groups of people who share genes, environmental exposures, racial, ethnic, or even geographic characteristics. DNA samples can be used to study genetic variation among individuals in population studies, to establish relationships between genotypes and phenotypes, such as single gene disorders, or more generally, to conduct basic studies of the etiology and progression of disease at the molecular and cellular level, all with the long-term goal of improving human health. Major research efforts are underway to establish collections of human DNA for the purpose of research. The federally funded Human Genome Project, now in its 10th year, has entered a phase of large-scale DNA sequencing, in which DNA donors are contributing to a publicly accessible database.

Genetic Information

Genetic information is but one form of biological or medical information. In a sense, virtually all medical information derives directly or indirectly from genes and gene products. Like any other type of medical information, genetic information can reveal sensitive information about an individual. Genetic information concerning an individual can sometimes reveal similar information about a person's relatives or entire groups of people. For example, in families or groups disproportionately affected by certain inherited disorders, linkage studies using genetic markers have allowed scientists to map the genes responsible for susceptibility or predisposition to hundreds of human conditions.

In some instances, genetic information can provide a probabilistic prediction of the future health status of an individual (e.g., predisposition to cancer or heart disease). The information contained in a person's genetic code is largely unknown to that person. Because DNA is stable, once removed from a person's body and stored, it can become the source of increasing amounts of information as more is learned about how to interpret the genetic code (Annas, 1995). In the words of Francis Collins, Director of the National Human Genome Research Institute, "we are hurtling towards a time where individual susceptibilities will be determinable on the basis of technologies that allow your DNA sequence to be sampled and statistical predictions to be made about your future risk of illness" (NBAC transcript, October 4, 1996).

For these reasons, some observers have concluded that genetic information is a unique form of biological and medical information. They claim that its major distinguishing characteristics are its power, its predictiveness, and its implications for individuals other than the person from which the information was derived (ref.). Gostin has suggested that "genomic" data are qualitatively different from other health data because they are inherently linked to one person (Gostin, J. Law Med. Ethics, 1995).

Others argue that genetic information is really no different than any other type of medical information (Murray, 1997). Clearly, many of the concerns that pertain to the use of human biological materials to gather genetic information apply equally to the gathering of other types of

medical information.

Public discourse about genetic information has been intense in recent years, in part because of its early beginnings in reproductive medicine and family planning, in part because of a history of eugenics and genetic discrimination, and in part because of the rapid pace of the Human Genome Project and its associated spin-offs.

Growing Concerns About the Research Use of Human Biological Material

Whether or not one subscribes to the notion that genetic information should not be treated in an exceptional fashion compared to other types of medical information, it is the use of human biological samples to gather genetic information that has fueled the current debate. The cases most frequently cited at the center of the debate involve monogenic, highly penetrant disorders of medically severe, or socially stigmatizing natures, which are not symptomatically apparent at the time of the analysis. In recent years consumer, scientific and professional groups have begun to address the issues surrounding the collection and use of human biological materials. While medical research is generally considered a public good and is vigorously supported by the American public, the power of DNA-based technologies to find information in a single cell raises the specter that individuals will have something determined about them that they did not consent to and might subsequently wish had not been obtained, because of potential loss of insurance, employment, or life choices (Powers 1994: 80-81). Although this type of information can be obtained through a number of different scientific procedures currently it is most often DNA analysis that is used.

Media focus on highly contentious cases using biological samples, such as the use of stored neonatal blood spots for anonymous epidemiological studies of HIV prevalency, and efforts by the military to establish a DNA databank, have made the issue of research use of human biological materials a matter of public concern. In the course of its deliberations, NBAC identified several trends that are contributing to the need for a more comprehensive public policy concerning the use of these biological samples in research.

Certain genetic and other medical information can be used to discriminate against individuals in insurance and employment and can be stigmatizing for individuals and families.

Concern about insurers and employers having access to genetic information has historical bases. In the 1970s several insurance companies and employers discriminated against sickle cell carriers, even though their carrier status did not affect their health. In the absence of guaranteed access to health care or laws that prevent discrimination on the basis of health status there persists a real concern that medical information can be used to deny individuals insurance or jobs (OTA, 1990; NCHGR, 1993).[1] In a recent Harris poll, 86 percent of respondents said they were worried about health and life insurance companies or employers using genetic information to deny them coverage or jobs (ref.). In addition to these financial harms, research findings about one's medical status can in some cases inflict psychological or social harms.

There is growing recognition that human biological materials can be analyzed to ascertain significant amounts of genetic information about the person who is the source of the sample.

One area of concern centers on whether the information that can be obtained from human biological materials places those who donate samples at risk. Such data might reveal, for example, information about an individual's disease susceptibility (e.g., carrying a gene that is associated with an increased risk of breast cancer). When there is an intervention that can be pursued to counteract the increased health risk, such as regular mammograms or dietary modification, some might perceive the information worth receiving and worth the psychological and financial risks associated with the information. If, however, the information reveals information for which no intervention is currently available (e.g., Alzheimer's disease), many individuals might perceive the risks of uncovering such information as outweighing the benefits. In any case, concern arises when an individual did not consent, in advance, to receiving such

[1] NBAC will be addressing the issues of genetic privacy, stigmatization, and discrimination in a separate, upcoming report.

information. Finding out about adverse health status can provoke anxiety and disrupt families, particularly if nothing can be done about it and the finding has potential implications for family members (e.g., it is highly heritable or communicable) and therefore should be done knowingly and willingly.

Health care systems increasingly rely on information technology, such as electronic records, to manage and facilitate the flow of sensitive health information. These trends magnify concerns about privacy of genetic and other medical information.

A perennial concern in medical care and in the protection of research subjects is potential invasion of privacy or violation of confidentiality. Appropriate measures to protect privacy and provide safeguards for confidentiality of clinical and research data are paramount. When samples are identifiable, that is, linked to the person who donates them, steps must be taken to ensure protections in the collection, storage, and collating of data. However, computerized medical records and large informatics databases raise concerns about who has access to data and whether data are linked to individual patient records. Many people distrust computer technology and large, bureaucratic record keeping systems, and it is widely believed that current confidentiality practices are insufficient to safeguard medical information. In addition, different cultural and religious groups may have differing conceptions of what constitutes privacy or confidentiality (Tri-Council, 1996).

Many privacy issues can emanate from the genetic analysis of human biological materials. The information contained in these samples can affect individuals or groups of people. Thus, privacy and confidentiality issues sometimes encompass many individuals. Some of the privacy concerns arise within the context of "secondary use" of the samples collected. This means that the samples and the information derived from them are being used or analyzed for purposes that extend beyond the purpose for which the specimens were originally collected. For instance, when collected as a result of a surgical procedure and used solely for clinical purposes, the use of these specimens raises very few privacy concerns (beyond those of the confidentiality of the medical record itself, which are by no means trivial). This is because they are being examined for the primary purpose of determining appropriate medical care for an individual, because the analysis of

the sample will be limited and the amount of data produced will be small, and because the custodian of that biological sample does not allow others access to it. It is when the intended use of such specimens extends beyond this somewhat narrow use that the majority of privacy issues are raised.

Finally, genetic information may have implications for communities or "collectivities," although it is by no means unique in this sense. The Council for International Organizations of Medical Sciences describes collectivities as "population groups with social structures, common customs, and an acknowledged leadership." This can include nations, cultural groups, small indigenous communities, neighborhood groups, and families. Because genetic research can reveal information about the family and community of the person whose materials are studied, informed consent becomes more complex and takes on new meaning.

There is increasing awareness in the medical and scientific communities regarding beliefs about the moral status of bodies and their parts.

The use of human biological materials in research raises moral and religious issues about the relationships among body parts, bodies, and self-identity. Ethical and religious traditions do not necessarily provide clear guidance about the ways in which human tissues should be used or obtained. Selected Western religious traditions offer some insight about the significance of the human body. Although there are variations among them, they generally favor the transfer of human biological materials as gifts. As such, human tissues warrant some measure of respect, which is the basis for excluding human tissues and cells as possible objects of commerce. But cultural differences can be significant because of the symbolic nature or sacrality of specific body parts or tissues.

New considerations have emerged about the nature of consent to research and disclosure of results.

Informed consent is a basic means for protecting individuals from medical and research harms. It is widely accepted that informed consent must be obtained for research projects that

involve the direct involvement of research subjects. Researchers are required to disclose the purpose of a study, as well as potential benefits and risks, before enrolling subjects. The role of informed consent has been much less clear, however, for research that does not require such personal involvement but rather can be performed using tissue samples. The use of genetic and other newly developed and developing technologies to study human biological materials presents the following problems for the consent process: 1) the research uses of the material may be unknown and unanticipated at the time of collection; and 2) the analyses can provide information that may trigger stigmatization, discrimination, or psychosocial problems for an entire category of persons defined by shared characteristics (Foster, 1997). In addition, physicians have not customarily sought patient's explicit, informed consent to permit the retention of pathology samples; instead, permission to store material has been regarded as implied in obtaining it for clinical purposes. Once stored, the samples have been available for research, usually without the knowledge or consent of the sources (Merz, 1997).

Under 45 CFR 46, the federal regulations governing research with human subjects, research with stored DNA and tissue has been exempted from review by Institutional Review Boards (IRBs) and from requirements for prior informed consent when:

1) The samples already exist at the time the research is proposed; and
2) The identity of subjects cannot be readily ascertained directly or indirectly by anyone involved in the research.

Alternatively, research with stored, identifiable samples conducted in a manner such that the source of the specimen can be identified may be permitted by an IRB with a waiver or modification of informed consent if all of the following conditions are met:

1) The research presents only minimal risk to subjects;
2) The waiver of consent will not adversely affect the rights or welfare of subjects;
3) The research could not practicably be carried out without the waiver; and
4) That subjects will be provided with information about their participation afterwards, when appropriate.

As with so many debates about the language of 45 CFR 46, contention surrounds the question of who defines and determines what constitutes "minimal risk." Some analysts believe that certain genetic research (e.g., conducted in a manner such that sources can be identified) surpasses minimal risk and should, therefore, not qualify for expedited or waived IRB review. Because in such cases the perceived risks appear to outweigh the direct benefits to a given individual many observers, including consumer and scientific groups, have called for increased attention to the consent process pertaining to human DNA and tissues. How specific do the consent documents with respect to samples collected in a clinical context need to be about the intended purposes of a research study with stored tissues? How much information about the possibility of post-diagnostic research on stored tissue samples needs to be given to patients in clinical settings? These questions are likely to have different solutions depending on whether the sample has already been collected versus prospective collection and different depending on the context of the collection. In effect, a person's rights and interests are best protected if that person has some form of control over her/his removed tissue. That control may be best exercised by an improved consent process.

Informed consent is a process, the value of which has been widely debated and about which much research needs to be done. Debates about its relative value in clinical and research settings are by no means unique to genetics or the issue of stored tissues. What people are told, understand, and remember when consent is sought is likely to vary as much when donating DNA or tissue as when consenting to other medical interventions. When human biological material is stored, people may not understand, for example, that it might be used for genetic research unrelated to their own disease status. When told it is being kept "for research," they may believe the samples will be used only for research related to their own condition. They may not realize that in some states laws require that specimens be stored. In most cases, the repositories where samples are stored were designed for a particular purpose, and the protocols and procedures might not have addressed issues regarding access, destruction, or acceptable future uses of the materials, such as for research (Merz, 1997). Finally, the use of human biological materials raises subtle but significant distinctions in the applicability of federal regulations, the review of research protocols, and obtaining consent. Sources of materials can be patients, volunteer research subjects, or cadavers. Determining whether a person is a patient or research subject is relevant in

determining the applicability of Federal regulations governing federally funded research using human biological materials (OTA, Ownership, 1987).

There is disagreement among scientific and medical groups about the appropriate use of tissues, requirements for IRB review, and the nature of consent.

With the great promise that comes with these new scientific developments and the increased value and importance of human biological material, comes greater responsibilities for scientists and policy makers. Scientists and clinicians often disagree about the appropriate balance between public health and medical research on the one hand, and individual privacy and dignity on the other. Scientists such as pathologists, geneticists, and epidemiologists have an interest not only in the availability of DNA and tissue samples, but also in analyzing the samples in conjunction with information from the individuals' medical records. Those directly involved in medical care are often more concerned about issues of protecting the confidentiality of the information and patient privacy. Within the past few years, professional societies have issued no fewer than 12 policy statements on the appropriate use of these materials in the context of genetic research, while clinicians and bioethicists have written articles that propose very different methods of addressing these issues—a clear indication that these groups lack consensus on how to resolve the difficult challenges that genetic analysis raises.

In its simplest form, any consensus must strike a balance between the desire to increase knowledge and the necessity of protecting individual interests. Some see it as a dialectic between two positions. On the one hand there are those who think that emphasis should be placed on the distinctive importance of personal and familial information, the right of personal choice about the use of one's body and the information inherent in the materials taken from it, and the necessity of being able to exercise a measure of control over the research that can be done with one's DNA and tissues. On the other hand are those who think that in an era of increasing professional and legal regulations and emphases on individual autonomy, renewed consideration must be given to the invaluable and often irreplaceable research resource, the inestimable societal and individual benefits that have been gained by means of biomedical research done with these samples, the responsibility, explicit or implied, that an individual has to contribute to this common good, and

the serious threat posed to the continuation of these research efforts by unnecessarily restrictive policies.

About this Report

In response to its original charge to consider "issues in the management and use of genetic information, including but not limited to human gene patenting," NBAC formed a subcommittee to address issues in the management and use of genetic information. The subcommittee met for the first time in December 1996 to set priorities for the upcoming year and chose initially to pursue three topics: 1) the research use of human biological material; 2) genetic privacy and genetic discrimination; and 3) gene patenting. The research use of human biological material was chosen as the first topic because the issue is well-defined, clearly important, and the focus of a great deal of current interest.

There are three basic premises underlying the framework of analysis used by the Commission in the development of its recommendations:

- First, research use of human biological materials is essential to the advancement of science and human health. Therefore, it is crucial that there be permissible conditions under which such materials can be used.

- Second, the rapidly advancing Human Genome Project and the application of a molecular-based approach to understanding human disease have raised the issues of autonomy and medical privacy to a heightened level of public discourse. This discourse has relevancy to all areas of medical research using human biological materials, not just genetic research. An additional impetus is the interest by the public and private sector in the research use of human biological materials.

- Third, there is disagreement within the scientific community about the nature of risks and levels and types of protections needed to ensure that biological samples can be used in research with minimal harms for those whose materials are used.

To assist it in its deliberations NBAC reviewed relevant scientific, ethical, religious, legal, and policy literature, commissioned scholarly papers on several topics relevant to its tasks, and invited members of the public and representatives of professional and consumer organizations to provide written and verbal testimony (see Appendix x).

To date, there has been a paucity of information concerning acquisition, use, and storage of human biological materials; there is no central database that captures information about stored samples. To assist in its review, NBAC commissioned a study to assess the magnitude and characteristics of the existing archives of DNA and tissues. Chapter 2 describes what is known about these collections, for example, where they are stored, the size of collections, and the sources and uses of the material.

NBAC believed it critical to examine ethical and religious perspectives regarding the status of body parts and the body. Chapter 3 surveys current thinking in these areas *(more to be said after NBAC discusses Buchanan paper).*

Chapter 4 describes existing policies regarding the use of human biological materials, including comparisons of the positions of various scientific and medical organizations, and the extent to which existing laws and regulations address NBAC's concerns.

Chapter 5 describes the framework used by the Commission in its deliberations, as well as its recommendations. The chapter includes consideration of the distinctions between the collection of human biological samples in routine clinical care versus research, previously collected samples versus those to be collected in the future, research conducted in an anonymized manner versus research in which the individual source of the sample is identifiable to the researcher, the consent process, the role of Institutional Review Boards, the appropriateness of community consultation, and measures to ensure confidentiality and restricted access to samples.

It is important to note that the Commission saw the value in receiving input from members of the American public, those who are not clinicians, medical researchers, or ethical experts ,regarding the used of human biological materials. Public opinion provides a counterpoint to the

testimony that the Commission would otherwise hear. As part of its effort to explore public knowledge, beliefs, and feelings about the research use of human DNA and tissue, NBAC convened six discussion forums held across the country to get a sense of what some Americans believe and feel about uses of such samples, the ethical obligations of those who may learn significant health risk information from the samples, and privacy protections[2]. Findings from the forums informed NBAC in its deliberations and are summarized in Appendix X.

[2] Mini-hearings were convened in Honolulu, HI, Cleveland, OH, Boston, MA, Miami, FL, Richmond, VA, and San Francisco, CA.