Chapter 1
Overview and Introduction

Biomedical researchers have long studied human biological material—such as cells collected in research projects, biopsy specimens obtained for diagnostic purposes, and organs and tissues removed during surgery—to increase knowledge about human disease and to provide better means of prevention, diagnosis, and treatment. Today, new technologies and advances in biology provide even more effective tools for using such resources to improve medicine's diagnostic and therapeutic capacities. 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.

Yet the very power of these new technologies raise important and difficult ethical issues. Is it appropriate to use stored biological material in ways that were never originally contemplated either by the people from whom the material came or by those who collected the material? Does it matter whether the material is identified, or identifiable, as to its source, or is linked, or linkable, to other medical or personal data about the source? Based on the many successes of past research with human biological material, proponents argue that future studies will also benefit millions of people. How should this prospect be weighed against the risk that the studies could harm or wrong the individuals whose material is being studied, their families, or other groups of which they are members? Under what circumstances should researchers seek the informed consent from people whose biological samples (either existing or to be collected) they propose to study? How ought consent requirements be adjusted if the sources of the existing biological material would be difficult or impossible to locate or if they have died?

THE RESEARCH VALUE OF HUMAN BIOLOGICAL MATERIALS

The medical and scientific practice of storing human biological material is more than 100 years old. Human biological collections, which include DNA banks, tissue banks, and repositories, vary considerably, ranging from large collections formally designated as

repositories to the informal storage of blood or tissues specimens in a researcher's laboratory freezer. Large collections include archived pathology specimens and stored cards containing blood spots from newborn screening tests (Guthrie cards). Such tissue specimens 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.[1] Archives of human biological materials range in size from fewer than 200 specimens to more than 92 million. Conservatively estimated, at least 282 million specimens (from more than 176 million individual cases) are stored in the United States, and the collections are growing at a rate of over 20 million specimens per year (see chapter 2).

In this report, human biological material is defined to encompass the full range of specimens, from subcellular structures like DNA, to cells, tissues (e.g. blood, bone, muscle, connective tissue and skin), organs (e.g., liver, bladder, heart, kidney, placenta), gametes (e.g., sperm and ova), embryos, fetal tissues, and waste (e.g., hair, nail clippings, urine, feces, sweat, and shed skin cells).[2] The most common source of these materials is from diagnostic or therapeutic interventions in which tissue or other material is taken to determine the nature and extent of a disease or to remove diseased tissue. Even after the diagnosis or treatment is complete, it is routine to retain a portion of the specimen for future clinical, research, or legal purposes. Specimens are also taken during autopsies that are performed to establish the cause of death. In addition, volunteers donate organs, blood or other tissue for transplantation or research, and some donate their bodies after death for transplantation of organs 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 specimens for medical and research purposes.

[1] For the purposes of this report, the term "specimen" refers to the human biological material as it is stored in the repository. The term "sample" is used to refer to the material as it used in research. The Commission believes that this distinction becomes important when considering the applicability and adequacy of the existing federal protections for human subjects.

[2] Due to the fact that research using embryonic tissue is prohibited from federal funding, the current regulations do not apply to such research, and their use is not specifically discussed in this report. Should the moratorium be lifted, many of the issues addressed in this report would be relevant; additional ethical considerations might apply.

In addition to its future clinical use, a specimen of human biological material can be used to study basic biology or disease. It can be examined to determine its normal and abnormal attributes or it can be manipulated to develop a research tool or potentially marketable product (OTA, 1987). Just as a clinician will choose a biological material appropriate to the medical situation at hand, a researcher's choice of such materials depends on the goals of the research project. The selected tissue can be used just once, or alternatively used to generate a renewable source of material, such as by developing a cell line, a cloned gene, or a gene marker. In addition, proteins can be extracted, or DNA isolated, from particular specimens.

There is substantial research value both in unidentified material (*i.e.*, not linked to an individual or his or her on-going medical records) and in material linked to an identifiable person and his or her continuing medical records. In the former, the value to the researcher of the human biological material is in the tissue itself and often the attached clinical information about that individual, without need to know the identity of the person from whom it came. For example, investigators may be interested in identifying a biological marker in a specific type of tissue, such as cells from individuals with Alzheimer disease or specific tumors. In such cases, beyond knowing the diagnosis of the individual from whom the specimen was obtained, researchers may not need more detailed medical records, either past or on going.

Sometimes, however, it is necessary to identify the source of the research sample, because the value of the material for research depends on linking findings about the biology of the sample with updated information from medical or other records about its source. For example, in a longitudinal study to determine the validity of a genetic marker as a predictor of certain diseases, the researchers would need to be able to link each sample with the on-going medical records of its source in order to ascertain whether those diseases developed. A recent study of late-onset Alzheimer's disease linked the presence of the disease with the apolipoprotein-E allele by studying the stored tissues of 58 families with a history of Alzheimer's disease and then examining autopsy records for evidence of Alzheimer's disease in those individuals whose tissue revealed the presence of that allele (Payami, 1996). Already, findings from research on biological materials have produced tests to diagnose predisposition to

conditions such as cancer, heart disease, and a variety of familial diseases that affect millions of individuals. In some cases, prevention or treatment is available once a diagnosis is made; in those cases, knowing the identity of the specimen source would permit communication of medical information to the sources that may be of potential importance to their health. In other cases, when medical interventions are not available, having one's specimen linked with a disease predictor is likely to be of less value to the individual, at least at this time.

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

Through the power of new DNA technologies and other new molecular techniques scientists can potentially turn to millions of stored human biological materials as sources of valuable scientific, medical, anthropological, and sociological information. Indeed, these technologies are so powerful—even revolutionary—that they also hold the ability to uncover knowledge about individuals no longer alive and about those yet to be born. For example, in 1997 scientists at University of Oxford in England announced 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 currently residing in the village of Cheddar and established a genetic 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 to control infectious disease (Egyptian Mummy Tissue Bank, 1997). This ability means that human tissue and DNA specimens 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. Clearly the same is true for collections of such material that may be collected in the future. DNA, whether already stored or still to be collected, can be used to study genetic variation among people, to establish relationships between genes and characteristics, such as single gene disorders, or more generally, to conduct basic studies of the cause and progression of disease, all with the long-term goal of improving human health. Providing information towards this goal is the federally funded Human Genome Project, which expects to map and sequence the entire human genome by 2005 (Collins, 1993).

GENETIC INFORMATION

Genetic information is one form of biological or medical information. Like certain other types of medical information, genetic analyses can reveal sensitive information about an individual. Further, genetic information concerning an individual can sometimes reveal similar information about a person's relatives or entire groups of people (Knoppers, 1997).

In some instances, genetic and other biological information can indicate a risk for developing certain diseases (e.g., predisposition to cancer or likelihood of developing heart disease). This is also true, of course, for other types of medical information. At present, however, the detailed information contained in a person’s genes is largely unknown to that person. Moreover, because DNA is stable, stored samples can become the source of increasing amounts of information as new genes are mapped (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, pp. 129-130).

For these reasons, some observers have concluded that genetic information is a unique form of biological and medical information. They claim that the major distinguishing characteristics of genetic information are its predictiveness and its implications for individuals other than the person from which the information was derived (IOM, 1994). Gostin, for

example, has suggested that "genomic" data are qualitatively different from other health data because they are inherently linked to one person, that is, one's DNA is unique except in the case of identical twins (Gostin, 1995).

Others argue that genetic information is not inherently distinct from other types of medical information (Murray, 1997). First, other types of medical information may be strongly correlated with particular diseases. Moreover, infection with a virus has implications for people other than the person actually infected. Likewise, the health status of a person living in a toxic environment, such as near the Chernobyl nuclear accident site, has implications for others living in that same environment. Clearly, many of the concerns that pertain to the misuse of personal genetic information apply equally to certain other types of personal medical information.

Nevertheless, public discourse and concern about the potential availability of personal genetic information has been intense in recent years for a number of reasons, including: 1) people may fear the lack of any protection from the misuse of this information (e.g., employment discrimination) outside the research context; 2) its early beginnings in reproductive medicine and family planning; 3) a difficult history of and continuing concerns with relation to eugenics and genetic discrimination; 4) the unknown and somewhat mysterious power of these new technologies; 5) and of the rapid pace of the Human Genome Project and its associated spin-offs.

Recently scientific medical organizations have dedicated a great deal of attention to the appropriate protocols for gaining access to the use of genetic information that can be derived from collections of human biological materials. The growing number of position statements and recommendations issued by scientific and medical organizations regarding the use of human biological materials in research reflects this recent focus (see Chapter 4). Their efforts to work through complex ethical and policy issues have been valuable and have provided NBAC with an understanding of the range of positions existing among such organizations.

GROWING CONCERNS ABOUT THE RESEARCH USE OF HUMAN BIOLOGICAL MATERIAL

The increasing use of genetic information about individuals has fueled a recent debate about genetic privacy and discrimination. 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 an extraordinary amount of detailed information in a single cell raises the specter that information about individuals will be discovered and used without their consent and possibly to their detriment. The use of such information may result in potential loss of insurance, employment, or dramatically affect life choices (Powers, 1994). Although this type of information might also be obtained through a variety of other means, DNA analysis currently is the most powerful means and increasingly will be the method of choice.

The cases often at the center of the current debate usually involve single-gene, highly penetrant disorders of medically severe or socially stigmatizing natures, which are not symptomatically apparent at the time of the analysis. In the future, however, the majority of cases will deal with polygenic, multifactorial diseases whose genetic status will, at best, provide a probabilistic estimate of the likelihood of disease manifestation. In recent years these various concerns have caused consumer, scientific and professional groups to begin to address the issues surrounding the collection and use of human biological materials. (AAMC, 1997; ASHG, 1987; 1997; ACMG, 1995; HUGO, 1998; Pathologists, 1997).

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

- increasing public concern that personal genetic and other medical information could be used to discriminate against individuals in employment or access to benefits such as health or life insurance, or could be stigmatizing in some way;
- growing public concern about privacy of all medical records;
- increasing awareness in the medical and scientific communities regarding beliefs about the moral status of bodies and their parts;

- the emergence of new considerations regarding both the nature of consent to participate in research protocols and disclosure of results;
- disagreement among scientific and medical groups about conditions that need to be satisfied to ensure that appropriate ethical standards are incorporated into all research protocols using human biological materials, namely requirements for review and the nature of the required consent process.

Concerns about Discrimination and Stigmatization

There is growing recognition that human biological materials can be analyzed to ascertain significant amounts of genetic information about the person from whom the sample was obtained. In particular, there is increasing concern that genetic and other medical information could be used to discriminate against individuals in insurance and employment or could be stigmatizing for individuals and families (Cohen, 1995; Hudson, 1995; NIH-DOE Working Group, 1993). In March 1998, the White House released a report prepared by the U.S. Departments of Labor, Health and Human Services, and the Equal Employment Opportunity Commission, *Genetic Information and the Workplace*, which predicted that by the year 2000, 15 percent of employers plan to check the genetic status of prospective employees and cites a 1995 Harris poll, which revealed that more than 85 percent of Americans are concerned that insurers and employers may have access to their genetic information.

One particular area of concern centers on whether the information that can be obtained from the research use of human biological materials places those who are the sources of the samples at unacceptable 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 colon cancer or breast cancer). When there is an intervention that can be pursued to counteract the increased health risk, such as regular mammograms, dietary modification, or drug treatment, some might perceive the information worth receiving and worth the psychological and financial risks associated with the information. If, however, the analysis reveals information for which no intervention is currently available (e.g., susceptibility to Huntington's disease or

Alzheimer's disease), many individuals might perceive the risks of uncovering such information as outweighing the benefits. In any case, concern may arise when an individual did not consent, in advance, or show any interest in receiving such information. Many would agree that finding out about an adverse health status should be done knowingly and willingly since it can provoke anxiety and disrupt families, particularly if nothing can be done about it and the finding has potential implications for other family members (Wilcke, 1998).

Concern about insurers and employers having access to genetic information has a basis in fact. In the 1970s several insurance companies and employers discriminated against sickle cell carriers, even though their carrier status did not and would not affect their health (Holtzman, 1989). 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 may be used to deny individuals insurance or jobs (OTA, 1990; NCHGR, 1993). In addition to these possible financial harms, research findings about one's future medical status can, in some cases, inflict psychological or social harms (Davison, 1994).

Privacy of Medical Records

Health care systems increasingly rely on information technology, such as electronic records, to manage and facilitate the flow of sensitive and clinically relevant health information. This has had positive effects in clinical practice, but these trends also magnify concerns about privacy of certain genetic and other medical information. Recent debates about privacy of medical records and attempts to protect privacy through legislation are evidence of the growing public concern about these issues.

An ongoing concern in medical care and in the protection of research subjects is the potential invasion of privacy or compromise of confidentiality. Measures to provide appropriate protections to both individual privacy and for the confidentiality of clinical and research data are important if research using this information is to enjoy broad support. When research samples are identifiable, that is, linked to the person who provides them, special steps must be taken to ensure protections in the collection, storage, and use of the data. However, computerized

medical records and large informatics databases raise concerns about who has access to data (i.e., the security of these data bases) and whether or not these 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, 1997).

Many privacy issues can emanate from the research analysis of human biological materials since the information contained in these samples can affect individuals or groups of people (Foster, 1997). Moreover many of the privacy concerns arise within the context of "secondary use" of the samples collected. “Secondary use” 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 (Alpert, 1997). For instance, when materials are collected during surgical procedures and used solely for clinical purposes, the clinical use of these specimens raise very few privacy concerns (beyond concerns about 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, and because the custodian of that biological specimen does not allow others access to it. It is only when the use of such materials extends beyond the original clinical use that the majority of these privacy issues are raised. For example, if a sample is used as part of a research study into familial linkage of a specific disease, and the family pedigree is published as a result of the study, an individual might be easily identifiable even without any names attached to the pedigree (Botkin, 1998).

Moral Status of Bodies and Body Parts

There is increasing awareness in the medical and scientific communities regarding a spectrum of beliefs about the moral status of human bodies and their parts (Andrews, 1998). The use of human biological materials in research can raise ethical and religious issues about the relationships among body parts, bodies, and self-identity. However, many important ethical and

religious traditions do not provide clear guidance about the ways in which human tissues should be used or obtained. Although there are variations among them, selected Western religious traditions offer some insight about the significance of the human body and they generally favor the transfer of human biological materials as gifts (Campbell, 1997). As such, human tissues would warrant some measure of respect, which is the basis often expressed for restricting sales of human tissues and organs. But cultural differences can be significant because of the different symbolic nature or sacrality they attach to specific body parts or tissues (Campbell, 1997).

Nature of Consent to Research Participation

In most cases informed consent is a key foundation of the ethical use of persons as subjects in medical experiments. It is one of the basic mechanisms for protecting individuals from unanticipated medical and research harms. It is widely accepted and expressed in federal regulations that the informed consent of potential subjects must be obtained before enrolling them in particular research. For research involving archived human biological materials, the role of informed consent has been much less clear and new considerations have emerged regarding both the nature of the required consent in these cases and the guidelines that should apply regarding the disclosure of results. In particular the use of new genetic and other technologies to study human biological materials presents several problems for the consent process—particularly if the archived material is linked to a specific individual: 1) the full research uses of the material may have been unknown and unanticipated at the time of collection; 2) we now understand better that the analyses can provide information that may lead to stigmatization, discrimination, or psychosocial problems for an entire category of persons defined by shared characteristics (Foster, 1997); and 3) we are now more sensitive to the concern that the study may generate ambiguous results, tempting for clinical use but not really ready for reliable application (Reilly, 1980). In addition, physicians and hospitals have not customarily sought a patient's explicit, informed consent to permit the use of pathology specimens for specific research purposes; instead, permission to use stored material for other than clinical purposes has been general, that is, granted with the understanding that such use is merely a possibility. Once stored, the

materials have been available for research, usually without the knowledge or consent of the sources, particularly if unidentifiable.

According to the federal regulations governing research with human subjects (45 C.F.R. 46), research with stored DNA and tissue has been exempted from review by Institutional Review Boards (IRBs) and from requirements for informed consent when:

1) the samples are existing at the time the research is proposed; and
2) either the sources are publicly available or information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects

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.

Contention continues to surround a number of issues regarding the conditions for a waiver of informed consent and for IRB review. First there is the question of who defines and determines what constitutes "minimal risk." (Merz, 1996). Some analysts believe that certain genetic research (e.g., on a stigmatizing genetic predisposition to a disease, such as alcoholism or schizophrenia) surpasses minimal risk and should, therefore, not qualify for expedited, or be exempt from, IRB review. Second, there is some controversy regarding the meaning of such terms as "publicly available," "practicability," and "identified." Because of these ongoing concerns many observers, including some consumer and scientific groups, have called for increased attention to the consent process pertaining to the research use of archived and to-be – collected human DNA and tissues (Clayton, 1996).

How specific, for example, do the consent documents need to be with respect to materials collected in a clinical context? How detailed should disclosure be about the intended purposes of subsequent research studies with stored materials? How much information should be provided to patients in clinical settings about the possibility of post-diagnostic research on stored materials? These questions are likely to have different answers depending on whether the specimen has already been collected or if it will be collected in the future, and whether the material was initially taken as part of medical treatment or a research protocol. It stands to reason that a person's rights and interests are better protected if that person has some form of control over her/his removed biological materials, especially if it remains identifiable. That control may be best achieved by an improved consent process but can rarely be absolute.

Informed consent is a process, the effectiveness of which has been widely debated, and which many agree can be improved. Discussions about its relative value in clinical and research settings are by no means unique to genetics or the issue of human biological materials. What people are told, what they understand, and what they remember when consent is sought is likely to vary as much when providing DNA or tissue as when consenting to medical interventions. When human biological material is stored, people may not understand, for example, that it might be used for research unrelated to their own disease status. When told a specimen is being kept "for research," a patient may believe the material will be used only for research related to his or her own condition. Patients may not realize that federal and state regulations require that specimens be stored for a certain length of time. In most cases, the repositories where specimens are stored were designed for a particular purpose, and the protocols and procedures might not have addressed issues regarding access, destruction, or 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 since the sources of materials can be patients, volunteer research subjects, or cadavers. In addition, determining whether a person is a patient or research subject is relevant, for example, in determining the applicability of Federal regulations governing federally funded research using human biological materials (OTA, 1987).

Finally, information obtained through research may have implications for families, groups, and others. For example, because certain genetic research may reveal information about the family and community of the person whose materials are studied, informed consent becomes more complex and for some it takes on new and broader meaning. Recently, the concept of community consultation in research with human subjects has received increasing attention. NBAC heard testimony from the National Institute of Allergy and Infectious Diseases (NIAID) about the essential nature of community involvement in NIAID's AIDS clinical trials.[3] Representatives of the community of participants in those research studies participated in the entire research process, from the formulation of ideas through the design of the studies, recruitment at a community level, and the execution and analysis of the research itself. It was concluded that such participation provided invaluable benefits to the research.

The Centers for Disease Control and Prevention (CDC) has recognized the growing role of community involvement in public health initiatives, establishing a Committee for Community Engagement to consider a growing body of literature reflecting the experiences of those involved in engaging individuals and organizations in communities across the country. While community engagement increasingly has become a basic element of health promotion, health protection, and disease prevention, to date the only formalized procedures for seeking community involvement in research with human subjects exist in federal regulations governing informed consent procedures when research subjects are enrolled in studies under emergent circumstances. These regulations pertain to: (1) research subject to regulations codified by the Food and Drug Administration (FDA) and carried out under an FDA investigational new drug application (IND) or investigational device exemption (IDE), (see Title 21 C.F.R. Part 50); and (2) research for which the Secretary of Health and Human Services has waived the general requirements for informed consent (at 45 C.F.R. 46.116(a), (b), and 46.408). The regulations provide for consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research (or clinical investigation, in the case of the FDA regulations) will be conducted and from which the subjects will be drawn. Moreover,

[3] Presentation by John Y. Killen, M.D., Director of the NIAID Division of AIDS, to NBAC on December 9, 1997.

public disclosure of plans for the research and its risks and expected benefits is required of investigators prior to initiation of the research. Finally, public disclosure of the results of the study is required following its completion.

Conflicting Opinion Regarding the Ethical Research Use of Human Biological Materials

There is disagreement among scientific and medical groups about the conditions that need to be satisfied to ensure the ethical research use of human biological materials, particularly with respect to requirements for IRB review, and the nature of the required consent process.

Recent scientific developments have increased the scientific value and importance of human biological material. There can be expected to be, therefore, increased demand for the use of such material. This generates a greater level of responsibility for scientists and policy makers. From available public statements, however, it seems that the scientific community often disagrees about how to insure the appropriate respect for persons as well as their biological material and yet to facilitate important health and medical research. Within the past few years, many professional societies have issued policy statements regarding their views on these issues and on the appropriate use of these materials, particularly in the context of genetic research. The sheer variety of thoughtful approaches suggested is an indication that consensus on how to resolve the difficult challenges that the use of human biological materials raises has been difficult to achieve.

A stable consensus must strike the right balance between the desire to increase knowledge and the necessity of appropriately protecting individual interests. On the one hand there are those who think that emphasis should be placed on the distinctive importance of this type of personal and familial information, the right of personal choice about the continual use of one's body and, therefore, 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 emphasis on individual autonomy, renewed consideration must be given to the more extensive use of this invaluable and often irreplaceable research

resource, to the inestimable societal and individual benefits that have been gained and will continue to be 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, especially if risks are minimal, and the serious threat posed to the continuation of these critical research efforts by unnecessarily restrictive policies that might focus on various informed consent requirements or careful IRB review.

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 Genetics Subcommittee to address such issues. 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 relatively 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 and clearly defined conditions under which such materials can be used.
- Second, the rapidly advancing Human Genome Project and associated technologies, and the application of a molecular-based approach to understanding human disease have raised new issues of autonomy and medical privacy. These issues have relevancy to all areas of medical research, not solely genetic research, using human biological materials.
- Third, there is disagreement within the scientific community about the nature of risks to individuals 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.

Framework for Analysis

The Commission organized its assessment of the conditions under which research using human biological materials should be permitted around five considerations: 1) whether the samples were already collected and stored, or are to be collected in the future; 2) the conditions under which the materials were/are collected (e.g., clinical versus research setting); 3) whether the research sample used can be linked by anyone (or any combination of people) to the donor; 4) whether the risks posed by the research affect individuals, communities, or both; and 5) the types of protections that might be employed to protect against harms (specifically, coding schemes, individual informed consent, community consultation, and prior review and approval by Institutional Review Boards).

Organization of the Report

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 B). In addition, NBAC posted staff drafts of this report on its website (www.bioethics.gov) and solicited public comments.

To date, there has been a paucity of information concerning acquisition, use, and storage of human biological materials. There is, for example, no central database that captures information about stored materials. 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 storage and use of such materials, including where they are stored, the size of collections, and the sources and uses of the material. It also provides background on the various research uses of human biological materials and provides a schema for classifying the status of human biological materials according to their linkage to the source of these materials.

NBAC believes that any set of recommendations in this area must be informed by certain ethical considerations. Chapter 3 reviews several of these considerations necessary for deliberations about policy for the research use of biological materials. It aims to articulate in a systematic way the various kinds of moral considerations that ought to be taken into account when developing policies about the collection, storage, and use of human biological materials.

Chapter 4 describes the existing federal regulations governing use of human biological samples in research. When NBAC began its review of the use of human biological materials in research, it was aware that a number of scientific and medical organizations had done thoughtful work on the issue. A number of these organizations have developed position statements and recommendations that reflected their efforts to work through the many ethical and policy issues the topic raises. To gain an understanding of the range of positions that exist among organizations which have carefully considered this subject, NBAC conducted a comparative analysis of these statements as they applied to the issue of protections for the appropriate use of human biological materials in research. This analysis is also found in Chapter 4, as is a description of efforts in other countries to address these issues.

Chapter 5 synthesizes the various policy issues that emerge from the preceding chapters and offers recommendations for the future.

Finally, it is important to note that the Commission valued the input from members of the American public, those who are not clinicians, medical researchers, or ethical experts, regarding the used of human biological materials. In addition to hearing public testimony at each of its meetings on this topic, NBAC convened seven discussion forums held across the country to get a sense of what some Americans believe and feel about uses of such materials, about the ethical obligations of those who may learn significant health risk information from the research use of such samples, and about privacy protections. Input from all these sources assisted the Commission as it deliberated. Findings from the forums are summarized in Appendix A.

REFERENCES

1. Alpert, S., "Privacy and the Analysis of Stored Tissues," background paper prepared for the National Bioethics Advisory Commission, December 1997.

2. American Association of Medical Colleges Executive Council, *Medical Records and Genetic Privacy, Health Data Security, Patient Privacy, and the Use of Archival Patient Materials in Research*, 1997.

3. American Society of Human Genetics. Ad Hoc Committee on DNA Technology. "DNA Banking and DNA Analysis: Points to Consider." *American Journal of Human Genetics* 42 (No. 5, May 1988): 781-783. Adopted October 9, 1987.

4. American Society of Human Genetics, "Statement on Informed Consent for Genetic Research," *American Journal of Human Genetics* 59:471-474, 1996.

5. American College of Medical Genetics Storage of Genetics Materials Committee, "Statement on Storage and Use of Genetic Materials," 1995.

6. Andrews, L. and D. Nelkin, "Whose Body is it Anyway? Disputes over Body Tissue in a Biotechnology Age," *The Lancet* 351:53-57, January 3, 1998.

7. Annas, G.J., "Drafting the Genetic Privacy Act: Science, Policy, and Practical Considerations," *Journal of Law and Medical Ethics* 23:360-366, 1995.

8. Botkin, J.R., W.M. McMahon, K.R. Smith and J.E. Nash. "Privacy and Confidentiality in the Publication of Pedigrees: A Survey of Investigators and Biomedical Journals," *Journal of the American Medical Association* 279(22):1808-1812, June 10, 1998.

9. Campbell, C., "Research on Human Tissues: Religious Perspectives," background paper prepared for the National Bioethics Advisory Commission, October 1997.

10. Clayton, E.W., Steinberg, K.K., Khoury, M.J., Thomson, E., Andrews, L., Kahn, M.J.E., Kopelman, L.M., and J.O. Weiss, "Informed Consent for Genetic Research on Stored Tissue Samples," *Journal of the American Medical Association* 274:1786-1792, 1995.

11. Cohen, M.M., "Genetic Testing and Insurance," *American Journal of Human Genetics* 56:327-331, 1995.

12. Collins, F.S., and D. Galas, "A New Five-Year Plan for the U.S. Human Genome Program," *Science* 262:43-46, 1993.

13. Davison, C., Macintyre, Smith, G.D., "The Potential Social Impact of Predictive Genetic Testing for Susceptibility to Common Chronic Disease: A Review and Proposed Research Agenda," *Soc. Health Illness* 16:540-571, 1994.

14. Egyptian Mummy Tissue Bank, 1997, www.mcc.ac.uk/~mellorir/museum/general/mummy.

15. Foster, M.W., Eisenbraum, A.J., Carter, T.H., "Communal Discourse as a Supplement to Informed Consent for Genetic Research," *Nature Genetics* 17:277-279, 1997.1997.

16. Gostin, L.O., "Health Information Privacy," 80 *Cornell Law Review* 451, 1995.

17. Holtzman, N.A., *Proceed with Caution* (Baltimore, MD: Johns Hopkins University Press, 1989).

18. Hudson, K.L., Rothenberg, K.H., Andrews, L.B., et al., "Genetic Discrimination and Health Insurance: An Urgent Need for Reform," *Science* 270:391-393, 1995.

19. Human Genome Organisation Ethics Committee, "Statement on DNA Sampling: Control and Access," 1998.

20. Institute of Medicine, *Assessing Genetic Risks* (Washington, D.C.: National Academy Press, 1994).

21. Knoppers, B.M., Strom, C., Clayton, E.W., et al., "Professional Disclosure of Familial Genetic Information," *American Journal of Human Genetics* 62:474-483, 1998.

22. Merz, J.F., "Is Genetics Research "Minimal Risk?" *IRB: A Review of Human Subjects Research* 8(6):7-8, 1996.

23. Murray, T., "Genetic Exceptionalism and "Future Diaries." Is Genetic Information Different from Other Medical Information?" in M. Rothstein (ed.) *Genetic Secrets* (New Haven: Yale University Press, 1997).

24. NBAC transcript, October 4, 1996.

25. National Center for Human Genome Research, *Genetic Information and Health Insurance: Report of the Task Force on Genetic Information and Insurance*, NIH Publication No. 93-3686 (Bethesda, MD: National Center for Human Genome Research, 1993.)

26. Payami, H., Zareparsi, S., Montee, K.R., et al., "Gender Differences in Apoliprotein E-Associated Risk for Familial Alzheimer Disease: A Possible Clue to the Higher Incidence of Alzheimer Disease in Women," *American Journal of Human Genetics* 58(4):803-811, 1996.

27. Powers, M. 1994.

28. "Recommended Policies for Uses of Human Tissue in Research, Education, and Quality Control," Pathologists Consensus Statement, 1997.

29. Reilly, P. "When Should an Investigator Share Raw Data with the Subjects?" IRB 2 (No. 9, November 1980): 4-5, 12.

30. Reilly, P., Boshar, M., and Holtzman, S., "Ethical Issues in Genetic Research: Disclosure and Informed Consent," *Nature Genetics* 15:16-20, 1997.

31. Tri-Council Working Group, *Code of Conduct for Research Involving Humans*, 1997.

32. U.S Congress, Office of Technology Assessment, *New Developments in Biotechnology: Ownership of Human Tissues and Cells*, OTA-BA-337 (Washington, D.C.: U.S. Government Printing Office, 1987).

33. U.S Congress, Office of Technology Assessment, 1990.

34. Wilcke, J.T.R., "Late Onset Genetic Disease: Where Ignorance is Bliss, is it Folly to Inform Relatives? *British Medical Journal* 1998;317:744 (12 September).