RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE

VOLUME II
COMMISSIONED PAPERS

Rockville, Maryland
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a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

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   2) applications, including the clinical applications, of that research.

b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.

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Bartha Knoppers, CRDP (Public Law Research Centre), Faculty of Law, Université de Montréal, Québec, Canada, prepared a paper for NBAC on the topic of control of DNA samples and information. That paper was published in 1998 in the journal *Genomics*. The reader can find the article at the following citation:

Knoppers, B.M., M. Hirtle, S. Lormeau, C.M. Laberge, and M. Laflamme. 1998. "Control of DNA Samples and Information" *Genomics* 50(3):385–401.

PRIVACY AND THE ANALYSIS OF STORED TISSUES

Commissioned Paper

Sheri Alpert [1]

Preface

This paper resulted from a request by the National Bioethics Advisory Commission Genetics Subcommittee for an analysis of the privacy issues inherent in using tissue samples in genetic research. While this paper focuses mostly on genetic research, it does so with a broad view. The paper bases the definition of genetic research on the definition of genetic testing used by the National Institutes of Health/Department of Energy Task Force on Genetic Testing:

> Genetic research includes analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites, in order to detect heritable genotypes, mutations, phenotypes, or karyotypes. The purpose of this research includes assessing the prevalence, penetrance, and expressivity of these heritable traits within the overall population, a particular subpopulation, or an individual.

It must also be pointed out that most of the observations and much of the analysis presented in this paper may be equally applicable to other research using human tissue samples and/or medical records.

Introduction

One of the biggest challenges in addressing the issues surrounding the collection, use, and genetic analysis of tissue samples is making the issues accessible to the public—the same public which, as individual members, has been and will continue to be asked to surrender their tissues for medical care or for medical research. Why, after all, should the public care about issues that may seem so remote to their lives? The increasing use of genetic analysis on these tissues provides a large part of the answer.

It is important, therefore, to keep in mind the very fundamental kinds of questions that might be of most concern to most people outside the scientific, research, and medical establishments. Below are scenarios containing the types of questions and issues that may be most relevant to the public:

1. A consent form was among all the papers I received when I checked into the hospital. What does it mean when the form asks if I will let my tissues be used for research? What kind of research? Is it research that will help me with my medical condition? What happens to my tissues when they're done with the research? Will I find out what they learn from my tissues? Who else may find out what they learn from my tissues?

2. I recently had the occasion to look at my medical record from when I had surgery about eight years ago. I saw that the consent form I signed for the surgery had a clause in it that said that I authorized the hospital to "dispose" of my excess tissue. I thought that meant they'd throw it out after I was diagnosed. I have since found out that it may have meant they could do practically any kind of research on my tissues that they wanted. With all this news about genetics, I am uncomfortable with the thought that strangers know more about me than I know about myself. What can I do to make sure they don't do anything with my tissues that I don't want them to do? How can I find out what they've done with them so far? What else do they know about me? Who can answer these questions?

3. I am an Ashkenazi Jewish woman and have been asked to sign up for a research protocol looking for a genetic mutation for pancreatic cancer in Eastern European Jews. I am concerned because there has been some cancer in my family. I do not want to know how the research results turn out for myself, but I am afraid that just participating in the research will make me vulnerable when I apply for insurance. What do I need to know to decide what's best for me? I am also concerned, given all the other genetic mutations associated with my group, about contributing to research that will leave others thinking that Ashkenazi Jews are more "genetically damaged" than other people. Can the researchers assure me that this won't happen if they find the mutation?

These three scenarios are not intended to represent the universe of concerns surrounding the genetic analysis of stored tissues. They focus, however, on the personal kinds of issues that people may confront when they start to understand the implications of genetic analysis of their tissues. How the policymakers within the scientific, medical, and research communities address these concerns will play an important role in determining how much the public is willing to trust them with their most sensitive personal information.

Many of the most important advances made in medical science would have been more difficult were it not for the analysis of collected and stored human tissues. That fact is beyond dispute. However, the increasingly common practice of performing genetic analyses on these tissues is triggering a renewed interest in examining how these samples have been (and will be) collected, stored, used, and shared and how the results of the research performed will be disseminated.

Genetic information can, at least in principle, reveal sensitive information about a person; and, of course, genetic information about one person often embodies information about that person's relatives. According to one useful analysis (Powers 1994:80–81), there are several features that distinguish genetic information from other medical information. Genetic disorders generally affect people throughout their lives, and thus knowledge of genetic information may have a greater impact upon individuals than knowledge of other kinds of medical information; genetic information has potentially serious adverse financial, emotional, and social consequences; future analysis of genetic samples may reveal information not contemplated at the time of initial consent for testing or sample collection; genetic information has the potential to be misleading, incorrect, or inconclusive in particular cases; and genetic testing or research into familial patterns of genetic inheritance may reveal information about other family members as well as information about a single individual.

There are several fundamental policy issues raised by the genetic analysis of stored tissues—issues that have an impact on everyone. Moreover, these are often issues that are either unfamiliar to, or misunderstood by, many people. This is not surprising, considering that much of our detailed understanding of genetics has only been accumulated within the last 10 to 15 years.

Scientists and clinicians often disagree about the appropriate balance between public health and medical research, and individual privacy and dignity. Pathologists and epidemiologists have an interest in not only maintaining tissue samples, but also in analyzing the tissues in conjunction with information from the individuals' medical records, while those more directly involved in medical care are often more attentive to issues of protecting the confidentiality of the information and patient privacy, as their contact with patients is more direct. Within the past few years, professional societies have issued policy statements on the appropriate use of tissues and consent in the context of genetic research,[2] while clinicians, bioethicists, and others[3] have written articles proposing sometimes different approaches to the same topic. The net result of these statements and articles is a lack of clear consensus on how to resolve the difficult challenges that genetic analysis raises.

The following are several questions that can help frame the policy debate in determining how best to protect people as they interact with the medical community that may someday ask them to provide their tissues for genetic analysis.

1. What do people need to be told when their tissues are collected?
   - What do they need to be told about why their tissues are being collected?
   - What should they be told about who will have access to their tissues?
   - Should they be told that genetic analyses will or may be done with their tissues, and if so, should they be told what that may mean for them and their families?
   - Do they need to know whether there are any risks and/or benefits for them in either collecting the tissue or in the resulting analysis and what those risks and/or benefits are?
   - What guidance should people be provided to help them evaluate what is best for them?

2. Does it make a difference whether the tissues will be used for one's medical care or strictly for research?
   - Does it make a difference whether the tissues will be used for one research study versus several research studies?
   - Does it make a difference whether the tissues are used for both medical care and for research?
   - What do people need to be told in order to determine what is best for them, in light of their own circumstances?

3. What about already existing tissues?
   - How should they be used, especially if the person whose tissues they were didn't know the tissues might be used for other purposes?
   - How can their wishes be determined and/or honored (or should those wishes be determined and/or honored)?
   - What sort of oversight is appropriate for research using these already existing tissues?

4. Under what circumstances should tissues to be used for research purposes be stored with information that links them to the specific person from whom they were obtained?
   - Who should be able to have access to those linkages (e.g., researchers engaged in a specific protocol, pathologists conducting research on tissues, etc.)?
   - Under what sort of circumstances should tissues not be associated with any specific person?
   - How and by whom is it decided when the tissues can or should be associated with the specific person from whom the tissues were collected?

5. What should happen when information is obtained from a genetic analysis that could have a direct impact on the medical care of someone who provided a tissue sample, particularly when the only reason that person provided the sample was for research purposes?
   - Should there be a duty to recontact that person to provide medical care (assuming the tissues can be identified with that person)?
   - If so, should that duty supersede that person's wishes?

6. What obligations do researchers and medical care providers have to the individuals who provide tissues to protect their privacy and the confidentiality of their information?
   - How are these obligations different when the tissues are collected for direct medical care versus being collected solely for research?
   - What are the privacy and confidentiality obligations if research is conducted on tissues known to have been collected from a specific group, but not specific individuals?
   - What is the role of the institution in which the medical care or research is occurring to provide these protections?

7. Are there any special considerations that need to be taken into account when tissue samples can be identified with a specific group, but not with any particular individual?
   - How should researchers evaluate the possibility of harm from genetic research in relation to groups of people?
   - What, if any, responsibilities should researchers have to the members of groups who may be stigmatized as a result of the genetic research conducted on these tissues—and how should these potential responsibilities be carried out?
   - Do these considerations change when tissues that are associated with a specific group are used for additional research protocols that have different purposes?

8. When tissues are collected solely for research purposes, what should people be told about the control of their tissues and the resulting information?
   - Should people have any rights with respect to their tissues and the information gathered from the analysis of their tissues?
   - How can issues framed in terms of "ownership" and "property" interests in tissues and information best be addressed, given the fact that commercial products can result from research on stored tissues (and have traditionally flowed to those maintaining physical control over the tissue)?
   - Indeed, are the concepts of "property" and "ownership" appropriate constructs to accommodate all the parties that claim to have an interest in the tissues (i.e., the tissue source, the researchers and their institutions, commercial enterprises that develop products, etc.)?
   - Are there approaches that can be adopted by researchers that could benefit both the researchers and the individuals or groups who provide the tissues?

9. How can researchers help ensure that the results of genetic research are communicated to the public in a way that fosters better understanding of genetic traits and diseases and helps dispel common misconceptions?

This extensive list of questions is by no means exhaustive of the types of issues that can be raised when addressing the use of human tissues in medical care and research. Many of these questions extend beyond the scope of privacy interests, no matter how broadly privacy is defined. However, the analysis that follows attempts to address at least some of these questions.

This paper is divided into several major sections: The first major section provides an analysis of the myriad interests and values associated with privacy. In so doing, it identifies some of the key concepts used to describe privacy; examines the philosophical foundations of these concepts; explores "group privacy," an unusual conceptualization of privacy that is particularly relevant to the genetic analysis of tissues; and provides a corollary that helps in understanding why group privacy is of interest.

The second section discusses the privacy interests in the genetic analysis of stored tissues. The third section provides a contextual analysis. In today's society, we face a number of circumstances in which our personal information is collected, used, and disseminated. Many of these circumstances extend beyond our knowledge, let alone our consent. Highlighted in this section is the context of the medical record and its increasing computerization. The final section summarizes the implications of genetic analysis of stored tissue samples and makes policy recommendations to mitigate negative outcomes.

What Is Privacy?

The Concept of Privacy

One of the most influential articulations of what is meant by the "right to privacy" (as distinct from privacy as a value) appeared in a now-famous 1890 *Harvard Law Review* article by Samuel Warren and Louis Brandeis. The right to privacy, they said, is "the right to be let alone" (Warren and Brandeis 1890:193). It was from this simple articulation that common law began to recognize a right to privacy in certain circumstances. This recognition, however, has not made defining the concept of privacy any easier. Indeed, privacy is a "notoriously vague, ambiguous, and controversial term that embraces a confusing knot of problems, tensions, rights, and duties" (Bennett 1992:13).

Privacy is usually described as being related to notions of solitude, autonomy, anonymity, self-determination, and individuality: It is experienced on a personal level. Within socially and culturally defined limits, privacy allows us the freedom to be who and what we are as individuals. By embracing privacy, we exercise discretion

in deciding how much of our personhood and personality to share with others. Moreover, we generally feel less vulnerable when we can decide for ourselves how much of our personal sphere we will allow others to observe or scrutinize (Alpert 1995:102). Complicating the process of defining privacy is the fact that it often means something different to nearly everyone, and everyone's experience with and perception of what invades their own privacy will likely differ significantly from person to person.

Interests and Values Protected by Privacy

Much of the literature about the nature of privacy describes various values that are protected through its exercise. Furthermore, there are several different aspects of privacy that, taken together, encompass a broad array of interests. This subsection highlights some of the interests and values inherent in the notion of privacy and will provide the basis for analyzing the privacy issues inherent in the genetic analysis of stored tissues later in the paper. Please note that these privacy interests and values may well overlap with each other. The next subsection will provide an analysis of the philosophical foundations of these concepts in the realm of privacy.

Autonomy encompasses respecting the dignity of each individual to make decisions for themselves, free from coercive influences. Indeed, a National Research Council report stated that the protection of individual autonomy is a fundamental attribute of a democracy (Duncan et al. 1993:27). Autonomy is also addressed in other analyses as "decisional privacy" (Allen 1997:33).

Informational privacy is defined by how much personal information is available from sources other than the individual to whom it pertains. The less opportunity individuals have to limit access by others to their own personal information or to limit the amount of personal information they must give up to others (either voluntarily or by coercion), the less informational privacy they have. It also involves when such information should be communicated or obtained and what uses of it will be made by others. It encompasses the collection, storage, use, maintenance, dissemination/disclosure, and disposition of personal information.

Freedom from intrusion/surveillance encompasses, in part, an individual's desire to preserve his or her anonymity. This notion includes not only the individual's desire to limit access to information about him/herself, but also to be free from physical intrusion and observational surveillance by others. Surveillance can have a chilling effect on individuals, as noted by many sociologists and studies of electronic monitoring. Individuals often change their behavior to conform to what they believe those monitoring their movements/actions will find acceptable or normal.[4] Freedom from intrusion is addressed in other analyses as "physical privacy" (Allen 1997:33).

Freedom from encroachment on/violation of dignity encompasses the notions of group or collective privacy interests. These interests include those we have in being free from discrimination and stigmatization as a result of our associations with the groups of which we are a member. Moreover, the notion of "dignity" also accommodates that part of our own self-perception that is attributable to our membership in that group. (It is recognized that the concept of dignity is broader than group privacy interests; however, it is used here as a proxy for these interests in a group context.) Whether the interests relate to a cultural, racial, ethnic, or religious group, as long as people identify themselves fundamentally as members of a group, encroachment on that group can be viewed as a violation of the group's dignity, and by extension, the individual members' dignity as well.

Within the informational privacy context, the concept of privacy is often confused with or treated as synonymous with two other distinct concepts: confidentiality[5] and security. The following is a simple way to differentiate between these three concepts: *security* measures provide the technical (and sometimes physical) means to safeguard the *confidentiality* of personal information, which in turn protects the *privacy* of individuals. Within the doctor-patient relationship, confidentiality is used to describe the relationship of trust that must exist for appropriate clinical care to be rendered. In essence, confidentiality, even in this context, advances the protection of personal information that is exchanged or generated between doctor and patient (whether through verbal

exchanges of information or information generated through physical examinations). This is the most fundamental way in which the patient's privacy is preserved.

Moreover, addressing only confidentiality and security is insufficient to resolve concerns over informational privacy, because confidentiality and security measures ignore how the data are collected. Focusing on the overarching privacy interests will address questions of what information ought or ought *not* be collected. Asking what information ought *not* be collected is a question that is rarely asked.

Philosophical Foundations of Privacy

This subsection fleshes out the philosophical underpinnings of the four privacy interests described above. Understanding these underpinnings is important to acquiring a full appreciation of the values and interests that are at stake for individuals and groups of people when their privacy is at issue.

There have been many treatises on privacy that develop in more depth the ideas expressed above. Charles Fried focused on individual dignity in his writings about the nature and importance of privacy and described it as being crucial to fundamental relations of respect, love, friendship, and trust (relations with others that would be inconceivable without privacy) (1986:477). Indeed, privacy is what makes it possible for us to keep from some people aspects of ourselves we openly share with those with whom we have more intimate relationships. Legal philosopher Anita Allen writes that personal privacy "is a condition of inaccessibility of the person, his or her mental states, or information about the person to the senses and surveillance devices of others" (1988:15). Ruth Gavison, a legal scholar, speaks of privacy in terms of our limited accessibility to others, arguing that it is related to "the extent to which we are known to others [secrecy], the extent to which others have physical access to us [solitude], and the extent to which we are the subject of others' attention [anonymity]" (1984:379). We enjoy our privacy "because of our anonymity, because no one is interested in us. The moment someone becomes sufficiently interested, he may find it quite easy to take all that privacy away" (Ibid.).

Arnold Simmel likewise holds that privacy is related to, but not synonymous with, solitude, secrecy, and autonomy, but contends that it also "implies a normative element: the right to exclusive control of access to private realms" (1968:480). The difficulty with claiming a right of exclusive control, as Gavison sees it, is the way it suggests that the important aspect of privacy is "the ability to choose it and see that the choice is respected" (1984:349). To her, this implies that once people have voluntarily disclosed something to one party, they can maintain control over subsequent dissemination by others—and that is generally not the case. Gavison argues that the legal system should make a strong and explicit commitment to privacy as a value. Edward Bloustein has argued that we should regard privacy as a "dignitary tort" such that when it is violated, "the injury is to our individuality, to our dignity as individuals, and the legal remedy represents a social vindication of the human spirit thus threatened rather than a recompense for the loss suffered" (1984:187–188).

The informational aspects of privacy have also been emphasized by scholars. For instance, philosopher Jeffrey Reiman describes privacy as the condition in which other people are deprived of access to either some information about you or some experience of you. In his seminal work *Privacy and Freedom*, Alan Westin defined privacy as the "claim of individuals, groups, or institutions to determine for themselves when, how, and to what extent information about them is communicated to others" (1967:7). James Rachels sees privacy as being "based on the idea that there is a close connection between our ability to control who has access to us and to information about us, and our ability to create and maintain different sorts of social relationships with different people" (1975:292). From an informational perspective, Charles Fried defined privacy as the "control over knowledge about oneself" (1968:483). Not only does privacy have a quantitative aspect (how much information disclosure we can control) but "modulations in the quality of the knowledge as well. We may not mind that a person knows a general fact about us, and yet we feel our privacy invaded if he knows the details" (Ibid.).

Finally, James Rule, et al. distinguish between "aesthetic" and "strategic" privacy (1980:22). Aesthetic privacy means that personal information is restricted as an end in itself, that is, in instances where disclosure is inherently distressing or embarrassing. Strategic privacy is the restriction of personal information as a means to some other end. "The issue is not the *experience* of disclosing personal information, but the longer-term consequences of doing so" (Ibid.). Both aesthetic and strategic privacy interests are at risk in the context of genetic analysis of stored tissue samples.

When privacy is invaded, Gavison explains, we are hurt because we are exposed, which may cause us to lose our self-respect and thus our capacity to have meaningful relationships with others (1984:372). Gostin reminds us that if "sensitive information is linked to an individual it can cause him or her harm both of a tangible and intangible kind" (1991:196). Tangible harms include discrimination by employers, educators, landlords, or insurers, while intangible harms (or wrongs) result in a sense of personal violation, shame, or hurt (Ibid.). Journalist David Burnham sees the loss of privacy as a "key symptom of one of the fundamental social problems of our age: the growing power of large public and private institutions in relation to the individual citizen" (1983:9).

From the preceding discussion, the philosophical grounding for privacy provides support for the privacy interests and values laid out at the start of this section by explaining the rationale for the importance of each. Autonomy is supported by the elements of privacy that emphasize individual dignity, solitude, and intimacy. Informational privacy encompasses those privacy elements that emphasize the ability to limit access to one's personal information (which also supports the autonomy aspects of privacy) from both a quantitative and qualitative perspective—i.e., the amount and type of information being sought or limited. Freedom from intrusion is drawn from those aspects of privacy that support an individual's desire for anonymity and solitude (both in terms of physical and emotional solitude). These interests and values, plus the group issues discussed below, incorporate the majority of the interests that are associated with the philosophical foundations of privacy, and so are used for the analysis that follows in the next section of the paper.

The Concept of Group Privacy

Privacy has traditionally, and appropriately, been described in terms of an individual's interests. Very few scholars have concentrated on broader interests in privacy, such as the common interests that groups of related individuals have in maintaining the privacy of the group. Indeed, some privacy advocates reject the notion of group privacy, preferring instead to rely on legal protections afforded by the "Equal Protection" clause of the 14th Amendment to the U.S. Constitution. However, it has become necessary to address these group interests in broader terms because of what genetic analysis/research, even on an anonymous basis, may make possible.

Before discussing group privacy, however, it is crucial to appreciate how the concept of groups is used within this analysis. As used here, a group is a collective of individuals who are culturally or ethnically related, among whom shared genetic characteristics are either likely or possible (or perhaps simply inferred). Moreover, groups can usually be characterized by a demographic label; e.g., African-American, Pacific Islander, American Indian, Scandinavian American, Ashkenazi Jew. Note that this notion of group does not necessarily extend to nuclear families as the unit of analysis, although certainly nuclear families may be members of larger cultural/ethnic groups.[6] It is fully recognized that there are many other types of groups: e.g., extended families; groups defined solely by a particular disease known to have a probable genetic component (Alzheimer's disease or fragile X syndrome) or groups with other types of noncongenital diseases (adult-onset AIDS); and groups defined by geographic proximity (e.g., residents of a particular town). The discussion in the remainder of the paper focuses on culturally or ethnically related people because they are, for the *present time*, the most easily recognizable as members of particular groups, within social contexts, and therefore, are potentially the most

readily stigmatized (again, for the present time) for genetic characteristics predominantly associated with that group of which they are members. It is further recognized that the distinction amongst different types of groups may become less relevant in the future, as we accumulate more knowledge about the genetic makeup of the entire population and all its constituent groups.

In *Privacy and Freedom*, Alan Westin discussed some aspects of group privacy, but mostly in terms of "organizational" interests. Organizational privacy serves to facilitate groups' roles as "independent and responsible agents…assigned to them in democratic societies" (1967:42). He further defines organizations as including public and private bodies: law firms, fraternal groups, political parties, courts, juries, etc. For purposes of this analysis, however, this characterization of "organizational privacy" is neither wholly satisfying nor wholly relevant since organizations are not the focus of the current analysis.

Similarly, Edward Bloustein addresses group privacy from an "associational" perspective, defining it as "the right to huddle" (1978:123). "The interest protected by group privacy is the desire and need of people to come together, to exchange information, share feelings, and make plans and act in concert to attain their objectives….Thus, group privacy protects people's outer space rather than their inner space" (Ibid.:125).

Using communities as his unit of analysis, Richard Hixson states that community is "the place where the individual thrives, but the community must be so integrated so as to nurture the dignity and autonomy of its members" (1987:115). In a similar vein, Anita Allen observes that the "moral value of privacy is tied to the fact that opportunities for privacy make individuals more fit for social participation and contribution. Privacy restrains but also benefits group life" (1988:49).

Although his discussion occurs within the context of individual privacy, Charles Fried describes an aspect of privacy that is relevant to group values/interests. He states that if "we thought that our every word and deed were public, fear of disapproval or more tangible retaliation might keep us from doing or saying things which we would do or say if we could be sure of keeping them to ourselves or within a circle of those who we know approve or tolerate our tastes" (1968:483–484). In the context of group privacy, this might mean that those with whom we share similar characteristics, beliefs, and cultural and ethnic backgrounds (i.e., other members of our particular group) are those with whom we feel most comfortable sharing the information and experiences associated with that group.

Among the few other works that can be related broadly to group interests in privacy is the writing of Priscilla Regan. In her book, *Legislating Privacy*, Regan discusses the social importance of privacy. She argues that not only is the individual better off if privacy exists, but society, in general, is also better off, because privacy serves common, public, and collective purposes (1995:221). She posits that "privacy is becoming less an attribute of individuals and records and more an attribute of social relationships and information systems or communication systems" (Ibid.:230). While her arguments are not strictly related to group privacy per se, they have relevance to the fact that societal aims can be served by recognizing a social value of privacy both for individuals and for the society in which they live.

Even though little has been written explicitly about the interests related groups of individuals have in maintaining the privacy of the group, the rationale for such an interest is not too difficult to understand, particularly in an age where technological advances may well be making group identification easier to accomplish. Being afforded the opportunity to exercise autonomy and self-determination are important aspects of privacy which allow individuals to develop their own "sense of self." Likewise, however, many individuals find that their associations with groups make important contributions to their self-development, self-discovery, and even their self-image. The often mutually supportive nature of groups and collectivities plays a key role in making these contributions. This may be even more the case in groups in which the members have an ethnic, racial, or cultural commonality. In other words, group identification, particularly in these latter cases, can be as important to the development of an individual's self-definition and self-respect as it is to the group's self-definition and continuity. As noted in the above discussion of "violation of dignity," when an encroachment on an individual (as a

member of a group) or on the group itself occurs, the violation may be felt as being an affront to both the individual and the group. It is therefore important to factor in these privacy interests in the discussion of the analysis of tissue samples.

One other important, but perhaps obvious, point to make here is that when harm occurs in a group, that harm will likely be experienced by each affected individual member of that group, by virtue of being that group's member. In other words, if a group is stigmatized, so are its individual members. For instance, while many Japanese-Americans as a group were forced by the U.S. government into internment camps during World War II, the harm was personally experienced by each individual placed into the camps and only because they were identified as members of the targeted group.

A Corollary Relevant to Groups

In trying to present a clearer understanding of why privacy interests may pertain to groups in the genetic analysis of stored tissue samples, a corollary example may prove enlightening. One particular set of technology applications brings group privacy issues to the fore: Geographic Information Systems (GIS). GIS allow geographic areas to be mapped by various factors, including the demographic characteristics of the population. Although it is possible to identify individuals using GIS (depending on the specific application), generally the purpose of these systems is to identify population characteristics and trends on an aggregate level, i.e., groups are the most relevant unit of analysis. Indeed, the main value of this sort of analysis derives from the fact that "people with like interests tend to cluster" (Baier 1967:136). "In data profiling the aim is not to say what an individual or household is like. Rather it is to say what that individual or household is *probably* like" (emphasis in original) (Curry 1999: 11).

There are many sectors and organizations using GIS to do this kind of data analysis. For instance, retail businesses and the direct marketing industry make extensive use of these systems to analyze current and potential markets. When combined with information available from other sources, geodemographic[7] profiles can identify potential customers and allow for direct target marketing. GIS are also used to help companies determine what sorts of benefits and services to offer (or not to offer), and where to locate new or expanding businesses/franchises. A more subtle use of these systems may be to "redline" entire demographic groups, although few businesses would admit to doing so. (Redlining is the process of refusing home mortgages or insurance to areas or neighborhoods judged to be poor financial risks.)

The array of demographic characteristics that are analyzed and sold is astonishing.[8] There are currently some sophisticated uses being made of GIS. For instance, one system "maintains a database of financial information for over 100 million Americans on more than 340 characteristics, including age, marital status, move history, credit card activity, buying activity, credit relationships (by number and type), bankruptcies, and liens. This information is updated continuously at a rate of over 15 million changes per day" (Curry 1992: 264).

Another of these systems characterizes the different population groups with descriptors that can be somewhat pejorative: "Sharecroppers," "Hard Scrabble," "Shotguns and Pickups," "Furs and Station Wagons," "Bohemian Mix," "Back-Country Folks," "Public Assistance," and "Blue Blood Estates," to name a few (Ibid.). According to its Internet Web site, these descriptors are among the 62 market groups, or clusters, used in this system which cover every neighborhood in the United States.[9]

It is unlikely that most people in the United States know that their demographic groups and neighborhoods are being characterized and generalized by the private sector firms that devise these systems. It is also questionable whether most people would appreciate being characterized thus. In the case of this GIS application, these characterizations serve as inexact models of the population. People are being categorized on the basis of the observed behavior and characteristics (i.e., interactions with the marketplace), which may change over time. Moreover, the generalizations are based on the observable behavior of only small subsets of the entire population.

The possibility of genetic labels is within the grasp of the imagination, particularly when remembering that, to date, propensities for certain genetic diseases are often associated with a specific group (e.g., sickle cell anemia, Tay-Sachs, the BRCA1 and BRCA2 mutations for breast and ovarian cancers, the newly discovered mutation for colorectal cancer). Genetics can also be used to categorize groups of people, particularly where several characteristics (which may have negative connotations attached) are associated with a particular group. The major difference between categorizing people based on observed behavior (as in the GIS example above) and on genetics is that the genetic characteristics are often not observable or even known to people without a direct relationship with the individual (i.e., outside the individual's immediate family, health care providers, or for that matter, the individual him/herself). And certainly, a person's genetic characteristics are immutable when compared to the nature of their observed behavior. The more that genetic propensities and characteristics are associated with specific groups of people, the more likely it is for people without a direct relationship to a member of that group to *think* they know about the group's members—or to at least make similar sorts of generalizations about groups that direct marketers make using the systems described above. Generalizations in a genetic context can be far more dangerous and cause much more harm to groups (and their members) than generalizations made in the GIS context above, particularly because of the general naiveté about the meaning of "genetic predisposition" and its pervasiveness in any particular group or population. Moreover, group members themselves may feel violated at the thought that others (indeed, society at large) potentially know things about them that they do not know (or do not want to know) about themselves.

This corollary is not intended to suggest that the sorts of characterizations that have been commonplace within the marketing industry are likely to occur in a genetic context in the future, and particularly not using GIS.[10] This corollary is provided here to illustrate that, in a society as diverse as ours, categorization of people by various characteristics has become a convenient, albeit imprecise and often pejorative, method of describing and dealing with diversity in a variety of contexts. Indeed, Arthur Caplan, among others, warns that

> While it is possible that the genome project will reveal huge amounts of variation and difference among the genotypes of those persons who are currently lumped together as being in the same ethnic or racial group based upon their phenotypes, it is also likely that some genetic information will be found to be unique or prevalent among the members of certain groups. If this is so, then the temptation to cluster groups in the light of the information may well be unavoidable (1994:40–41).

Privacy and the Genetic Analysis of Stored Tissues

Many privacy issues emanate from the genetic analysis of stored tissue samples. Some of these issues affect individuals, and some affect groups (and by association, their members). Some of these issues arise from research uses of clinically obtained tissues, particularly when the tissues remain identifiable. Most of the other privacy issues that arise do so within the context of secondary use of the tissue samples collected. This means that the tissues and the information derived therefrom are being used or analyzed for purposes that extend beyond the purpose for which the tissues were originally collected. For example, at the time an individual has a surgical procedure to remove diseased tissue, some of that tissue may be diverted from diagnostic purposes for use by researchers for uses/analysis unrelated to clinical care.

Additionally, in this example, the removed diseased tissue itself is generally maintained by pathology laboratories for several years. (Indeed, some tissue archives retain samples that were collected over 100 years ago.) Many of the tissues that currently reside in laboratories and academic institutions were collected as a result of this sort of scenario and are used for follow-up clinical treatment, research, and education. The storage of many of these tissues (for varying lengths of time) is also legally required by many states.

There are several different ways in which privacy issues in the genetic analysis of stored tissues can be examined:

- prospective (analysis of tissues yet-to-be-collected) and retrospective (analysis of already collected/existing tissues);
- primary use (tissues are used directly and solely for the purpose for which they were originally collected) and secondary use (tissues are used for purposes that either extend beyond or are totally different from the primary purpose);
- clinical and research purposes (or both);[11] and
- whether privacy issues raised relate to individuals, to groups, or to both.

To facilitate the analysis of this web of interrelated issues, a chart is provided at the end of this section to illustrate representative examples of the types of uses relating to both the tissues and the information gleaned from the tissues.

The Use of Tissues in Genetic Research

How the tissues are used and the circumstances under which they are collected are at the foundation of the privacy issues that ultimately give rise to how the information gleaned from these tissues is used. For instance, when collected as a result of a surgical procedure and used solely for clinical purposes, the use of tissues raises very few privacy concerns. 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 tissue does not allow others access to it. Moreover, in this situation, it does not matter whether the tissues are being examined prospectively or retrospectively—privacy interests do not rise to the level of concern. It is when the intended use of tissues extends beyond this somewhat narrow use, which is often the case, that the majority of privacy issues are raised.

In research applications, for both primary and secondary uses, how tissues are collected and analyzed can raise concerns that affect both individuals and groups. Below is a summary of the relevant portions of the chart provided at the end of this section, to facilitate the analysis of the research uses of tissues. This and each subsequent portion of the chart will be analyzed using the relevant privacy interests set out earlier in the paper (autonomy, informational privacy, freedom from intrusion, and freedom from violation of dignity). In addressing the use of tissues for research, of the four privacy interests and values that will be used in this analysis, autonomy and freedom from encroachment on dignity are the most relevant privacy interests at stake, for reasons discussed below. (Informational privacy interests are more relevant to the discussion of the uses of information gleaned from the tissues. It is also assumed that the procedures used to obtain the tissue samples are no more intrusive than would be encountered within a clinical procedure already being undertaken, or within a research protocol, about which the subject has already been informed and consented to, so that issues related to freedom from intrusion are minimal.)

Uses of Tissues in Genetic Research

Retrospective Analysis	Prospective Analysis
Primary Use: reexamination of tissue specimen under the original research protocol, using new or improved techniques or technologies.	Primary Use: analysis of tissues to be collected for an existing, ongoing research protocol.
Secondary Use: examination of already existing tissues for purposes unrelated to the reason for which they were collected. If the tissues are not identifiable as to an individual tissue source, the research protocol can be exempted from Institutional Review Board (IRB) review and federal (but not necessarily state) informed consent requirements.	Secondary Use: specific protocol that uses tissues in a way that extends beyond the direct purpose for which the tissue source surrenders his or her tissues, e.g., using anonymous samples from random patients entering a hospital for surgery, in order to study phenomena unrelated to the clinical care of those persons.

Autonomy/Decisional Privacy

Most of the privacy issues in this area will arise from the nature of the informed consent the tissue source signed upon having his/her tissues removed. In the case of prospective analysis with an existing Institutional Review Board (IRB)-approved protocol, the more specific the information in the consent documents, as far as describing what will be done with the tissue, the more informed the consent will be. This information may include an explanation of:

- what tissue will be removed and how (blood draw, buccal swab, tissue scraping, etc.) and, most important, for what purpose;
- risks to the subject of participating in the research protocol;
- how the tissue will be stored and for how long and whether cell lines might be generated using the subject's tissue;
- who will be able to gain access to the tissues and for what additional purposes;[12]
- whether it will be retained with the ability to link it and resulting analyses to the research subject;
- what steps the researchers and the institution have taken to safeguard the confidentiality of any information linked to the subject;
- whether the subject will be able to find out their own results of any genetic analyses, including the risks and benefits to the subject of getting that information about themselves;
- whether/how the subject can withdraw from the protocol—and what happens to his/her tissue and information vis-à-vis the protocol; and
- whether the researchers have any financial stake in the conduct or outcome of the research, including the potential intent to patent any product based on the subject's tissues.

This, of course, presumes that consent is required to conduct the research. In many cases, particularly with retrospective analysis of already existing anonymous[13] tissues, consent can be waived (at least to be in compliance with federal regulations). The absence of consent in this case may have more of an implication for the privacy interests of groups and will be discussed below under dignity interests.

The consent process engenders trust between research subject and researcher. Apart from any legal requirements which underlie the consent process, fully informing potential research subjects about the research protocol (including the anticipated benefits of the research to society and the risks and benefits to the subject) is one of the best ways that researchers can demonstrate their respect for the subject—even if fully disclosing all this information costs the researcher some subjects. It is better for the integrity of the overall scientific research establishment to lose subjects by providing full information than it is to lose subjects because they lack trust in that research establishment.

Freedom from Encroachment on Dignity/Group Interests

Federal regulations (45 CFR § 46.101(b)(4)) specify that if research involves the study of existing pathological or diagnostic specimens using sources that are publicly available or recorded so as not to identify the individual subjects directly or through identifiers, then the research is exempt from IRB review. For analysis of already existing tissues (i.e., retrospective analyses for secondary purposes), from the standpoint of public policy, exemption from the regulations may need to be rethought, where the tissues are known to originate *within a particular group*. The current policies make the presumption that individual identity is the only form of identity that is relevant to the research being conducted—and to ensure the protection of human subjects. However, groups of genetically related individuals have an increasingly vested interest in much of the genetic analysis that is occurring using tissues, as more and more genetic traits and propensities for certain diseases are attributable to specific groups (e.g., Ashkenazi Jews). Given that reality, and the further possibilities for groups (and their members) to suffer tangible and intangible harms as a result, exempting from any regulatory oversight

research that will be conducted on tissues where the group identity is known may be increasingly ethically tenuous.

Similarly, another part of the federal regulations (45 CFR § 46.116(d)) allows for waiver/modification of informed consent when the IRB documents that:

1) the research involves no more than minimal risk to the subjects *(Note: this is also one of the two criteria to allow for expedited IRB review)*;

2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

3) the research could not practicably be carried out without the waiver or alteration; and

4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

For *prospective* genetic analyses (primary or secondary uses), where identifiers are connected with the tissues, the genetic analysis of tissues represents more than a minimal risk for individuals (Merz 1996:8) and should not be allowed to proceed under an expedited review or with a waived/modified informed consent. However, looking at the issues from a group privacy perspective suggests that where tissues are being collected within a particular group, even where the tissues contain no individual identifiers, if the research is attempting to associate specific genetic traits with these groups, full IRB review and informed consent requirements should be utilized prior to the protocol's commencement. Moreover, the informed consent in this case ought to include a statement about the potential for group harm (e.g., stigmatization, discrimination, etc.), and how research results are likely to be disseminated if a group-related genetic characteristic/mutation is discovered.

Where a group or identifiable community is the unit of analysis for the genetic research, the researcher should involve the community in the research process (from recruitment through to the publication of results). Much guidance has been written in this regard, particularly in the context of the Human Genome Diversity Project (HGDP). Henry Greely states that

> Research inevitably provides information about a group, as well as the individuals who constitute it. The group…is really the research subject. It is the group's collective autonomy that is challenged if researchers, with the informed consent of only a few individuals in the group, can probe for information about the whole group (1997:1412).

Indeed, it is partly for this reason that the model protocol for the HGDP requires that researchers obtain the informed consent of the population "through its culturally appropriate authorities where such authorities exist" (Northern American Regional Committee of the Human Genome Diversity Project 1997:1443) prior to sampling. Furthermore, if the population's authorities choose not to participate, the HGDP would not accept any samples from any member of that population. "We believe…that the population-based nature of this research requires population-based consent, and we will insist on it" (Ibid.:1444).

Within the United States, finding the "culturally appropriate authority" can be a difficult, if not impossible task for many groups. While it may be possible to find people who can facilitate discussions within the community (e.g., religious leaders), many groups are simply too populous and dispersed (e.g., Scandinavian-Americans or African-Americans) to have an authority with the power to make decisions for the entire group. In these cases, it is still important to hold frank discussions within the community to facilitate trust in the process.

Use of Information Gleaned from Tissues

To some extent, it may seem rather artificial to split the use of the tissues from the use of the information gleaned from those tissues. After all, it is largely the information that will be gleaned from the tissues that can have the greatest potential to harm or help individuals and groups. And the two sets of concerns certainly

overlap. However, different types of privacy concerns arise from each type of use. For instance, in the case of how tissues are used, the informed consent process generally sets out the parameters under which tissues are provided by the tissue source and used by at least the initial recipient. Once the tissue is obtained, confidentiality rules protecting informational privacy interests come into play to safeguard the information that results from the analysis of the tissues and ensure that the tissues are used in a manner consistent with that informed consent.

There are two aspects of the use of tissues that are important from a privacy perspective. First is that, as addressed above, the tissues themselves frequently are used in analyses and/or research that have a wide array of purposes beyond direct patient care. Using the parlance of modern information collection, storage, and retrieval techniques, tissue specimens are the ultimate data warehouse—potentially providing a wealth of information through genetic analysis about individuals and groups of related individuals for a virtually unlimited amount of time. As such, the individual or organization that has physical access to tissue samples may be quite relevant, as is the type of use to which those individuals/organizations put that tissue.[14] (For instance, some tissue sources might wish to object to specific, but initially unspecified, uses of their tissues.) This fact points to the second aspect: the use of information that is gleaned from these analyses, upon which the rest of this analysis will focus.

In the discussion of the *use of tissues, clinical-only uses*, whether prospective or retrospective, did not raise privacy concerns beyond those associated with the confidentiality of the patient's medical record, in which the clinical results are recorded. The same is generally true for the *clinical-only uses of information gleaned from the tissues*. When used solely for clinical benefit and to determine or alter a course of treatment, privacy issues are most acute with respect to the medical record in which the information is recorded. This certainly raises informational privacy issues, which will be discussed later in the paper.

As with the previous subsection, the remainder of this discussion will proceed by referring to the relevant portions of the full chart that appears at the end of the section and will analyze each portion according to the privacy interests implicated by each set of activities. This part of the analysis will start with the *primary uses for research purposes* of information gleaned from the tissues.

Primary Research Uses of Information Gleaned from Tissues

Retrospective Analysis	Prospective Analysis
Study of research techniques and technologies and/or improve the understanding of diseases/traits and their causes. Information might be entered in subjects' medical records, if research results are linked to specific patients. Could also include chart review research to follow up on clinical encounters and to determine whether patients contract genetic diseases for which they were tested within a clinical or research context.	Gain understanding of diseases/traits, and act as guide for additional research. If the research is conducted with patient links, information may be entered in subjects' medical records (e.g., if a subject elects to receive results of his or her genetic tests conducted in the course of a research protocol and preventive treatment is indicated. This presumes that receiving test results was an option provided to research subjects, which is often not the case).

Autonomy/Decisional Privacy

The main way in which autonomy issues will arise is in the context of how research subjects are able to exercise any control over what information may end up in their medical records from the research. For instance, for *prospective* research, in the informed consent documentation, if the subjects are asked whether they want to receive genetic test results, part of that choice might be whether they want the information entered into their medical record. Within the context of a specific protocol, there could conceivably be a gradation of choices provided to accommodate the different possible reported outcomes:

1. The tissues will be stripped of all personal identifiers, so no individual results will be available and cannot flow to the medical record;

If the tissues will be linked to the research subjects:

2. The subject can choose not to learn of the results and/or not to be recontacted under any circumstances;
3. The subject can choose to learn of the results, but prefers that the information not be reported to anyone else, nor recorded in his or her medical record (although this option runs the risk that information will inadvertently be reported to others); or
4. The subject can choose to learn of the results and wants that information to be passed along to his or her physician(s).

It is possible that providing this gradation of choices within an informed consent process will not be an option—it depends on the design of the research protocol, which may supersede all choices but one of the above. However, the possibility of providing these options, with explanations of the risks and benefits associated with each, is one that will allow research subjects to exercise their autonomy most robustly.

Informational Privacy and Freedom from Intrusion

As will be the case with most of the uses of information gleaned from tissues, informational privacy interests will be those interests most directly challenged by the activities occurring in retrospective analyses because the tissue source has less knowledge of how the information resulting from the analyses might be used or disclosed (based partly on the fact that they will have less a notion of what kind of research is being done on their tissues). (This will be particularly true when addressing secondary uses of information, below.) In the case of primary research uses of the information, informational privacy interests are closely tied to the anonymity aspects of freedom from intrusion. For retrospective research using methodologies such as chart reviews, patients' interests in preserving their anonymity may be quite important because medical records form the basis for analysis. It is one thing, from a privacy perspective, for researchers to have access to anonymous information from medical records. It may be quite another for researchers to have access to the complete record, with the identifiers attached. While the researchers may not "care" whose charts they are reviewing, the patients might. Reviewing anonymized charts will help mitigate the informational privacy aspects of this type of activity, and although as more discrete genetic information (e.g., genetic test results) is entered into the medical record, fewer promises of complete confidentiality may be possible. (Additional issues are discussed under the "secondary uses of research information" below.)

Freedom from Encroachment on Dignity/Group Interests

Where the primary use of tissues is for *prospective* genetic research, the information gleaned from the tissues may result in information (and provide the basis for additional prospective research) that group members may eventually consider to be detrimental to them. One need only look at the reaction to the several recent genetic studies of Eastern European (Ashkenazi) Jews that have shown that within the group there are several mutations that may predispose a small portion of that population to certain types of cancer and other diseases. Unfortunately, misunderstandings of what these study results mean abound—and fear of group stigmatization is but one consequence. The result is that suggestions are being made to abandon genetic research on Ashkenazi Jews altogether (Lehrmann 1997:322). Larry Gostin writes:

> Derogatory information associated with a group can result in real harms such as discrimination against members of the group in employment, housing, or insurance. Derogatory information can also cause intangible hurt to groups such as lowering their self-esteem or racial or cultural

> pride. Derogatory information about a sub-population can stigmatize and wound its people as much as breaches of confidentiality can affect an individual. The information collected from groups, just as information about individuals, need not be blatant or intentional to cause harm or hurt. Even the best intentioned and careful research can trigger concerns about privacy (1991:197).

As increasing numbers of genetic studies are done on distinguishable groups, researchers must become more cognizant of the potential for their research to cause tangible and intangible harms to groups, at the same time as it seeks to provide the foundation for medical treatments or preventive medical care. This may mean that the initial research plan incorporates careful consideration of how results of these studies should be reported. As stated earlier, it certainly means that members of the group to be the subject of the research should be involved in as many aspects of the study design as possible.

Secondary Clinical Uses of Information Gleaned from Tissues

Retrospective Analysis	Prospective Analysis
Look for new diseases associated with previously reported/ discovered diseases/traits (e.g., if clinical notes specify a particular mutation and other diseases are later discovered to be associated with the same mutation). Information may be entered into patients' medical records.	If secondary research elicits a clinically relevant result, additional treatment may be called for, presuming the tissue source can be identified. In the case of genetic research, this could include clinically relevant information for families.

Autonomy/Decisional Privacy

Evaluating the secondary clinical uses of information gleaned from tissues can get a bit tricky when secondary research elicits clinically relevant findings, as the line between uses for clinical and research purposes can get fuzzy. Indeed, that very fact makes some of the privacy issues more difficult to address. For instance, if *prospective* genetic research conducted on identifiable tissue elicits clinically relevant information[15] and the research subject wants to be recontacted with this information, it has implications not only for him or herself, but for his or her family, as well. To some extent, the implications for families may argue for designing genetic research protocols with no possibility of recontact or result reporting. This option, however, limits the autonomy of the research subject and provides researchers with the potential ethical quandary of not being able to inform subjects of preventive measures that can mitigate diseases for which they are discovered to have a predisposition.

Informational Privacy

Many of the informational privacy interests that flow from the secondary clinical uses of information gleaned from tissues relate to whether or how genetic information is shared not only with the patient, but with the patient's family, as well. In many cases, these privacy interests include the desire not to know certain information.

In the case of the patient, if additional diseases are found to be associated with a genetic mutation the patient is known to have (from having participated in a prior research protocol), the question becomes whether to inform the patient of that additional disease. Further, if the fact of the original mutation is recorded in the patient's medical record, regardless of whether that patient is told or not, anyone gaining access to her or his medical record will know. For instance, the results of ApoE testing may indicate not only a genetic basis for a cholesterol problem, but also for Alzheimer's disease. Anyone with sufficient training will be able to discern the two implications from the one result, even though the patient may be aware of only the mutation for cholesterol. The question is how (or indeed, whether) to present this information to the patient.

Secondary Research Uses of Information Gleaned from Tissues

Retrospective Analysis	Prospective Analysis
Apply information learned from retrospective analyses to other diseases being researched, and look for relationships that may prove fruitful for other research. Also could include follow-up research utilizing chart reviews on medical encounters where tissues were analyzed for specific diseases/traits or for outcomes research and epidemiological studies utilizing chart review methodology. In the near future, this could also include analyses of "raw" genetic data (i.e., a map of an individual's genome sequences) deciphered from tissues.	Alter a research protocol based on findings of prospectively collected tissues (e.g., if collection of anonymous tissues from randomly selected surgical patients does not elicit the intended or hoped-for results, a protocol could be altered—for example, changing the methodology for prospective collection of tissues—to elicit more relevant data. This could also include analysis of unanticipated information gleaned from prospective research, e.g., colorectal cancer mutation in Ashkenazi Jews was originally thought to be a normal variation in the gene).

Autonomy/Decisional Privacy

An important point to recognize in addressing the secondary use of already existing tissues (i.e., *retrospective* analysis) is that when most of these samples were collected, the techniques of genetic analysis were not sophisticated enough to allow for the gleaning of detailed genetic information (i.e., at the molecular level). Additional research on these archived tissues generally had been reserved for biochemical or histopathological analyses. Certainly this was the case up until the last decade or so. The significance of this fact is that at the time tissues were stored, even if the tissue sources knew that their tissues would be stored and used for other purposes, they probably would not have known or even contemplated the types of detailed genetic analyses that could be performed on those tissues in the future. Further, even if tissue sources did know their tissues would be used for research, most may have presumed that the research to be done would be directly related to the malady that brought them to seek treatment or testing. This may or may not actually be the case. As noted by Madison Powers:

> Moreover, as new genetic discoveries are made, available DNA samples can be reanalyzed to learn additional information about a person and existing data can be used for purposes substantially different from those for which consent was initially given. This potential of genetic testing to reveal new information not contemplated at the time of consent for testing ensures that one can never be certain of the final nature of, or potential uses for, information at the time of testing. More important, perhaps, is the fact that the individual has less ability to take additional steps to mitigate potential adverse consequences of disclosures if he or she has no basis for anticipating what genetic samples can reveal and no ability to exercise continuing control of the samples (1997:357).

Where genetic analyses are to be performed on identified, existing tissues, researchers should have the burden of proof before an IRB to justify the impossibility or impracticality of recontacting the tissue sources for consent for the additional research.[16] The level of proof that needs to be met should be rigorous. "Even if the results of the research will not be disclosed in an individually identifiable form, IRB procedures should be used to ensure that in any new research undertaken without obtaining additional consent the researchers have taken steps to eliminate or reduce the risks to subjects from group data" (Rothstein 1997:466).

Informational Privacy

The interests associated with informational privacy are among the most problematic when addressing the genetic analysis of stored tissues. The main reason that informational privacy concerns exist in the secondary use of information gleaned from tissues is the potential for misuse of the information. Granted, how others use

or misuse information gleaned from tissue analyses is not the responsibility of either the researchers or medical care providers. However, researchers and care providers must at least acknowledge that their work can result in unintended harms as well as benefits for individuals.

Where tissues maintain links to the tissue source, mechanisms to protect the individual tissue source may need to include an explicit commitment to not include these results in that person's medical or treatment record. As the techniques of genetic analysis becomes more sophisticated and larger portions of the genome can be mapped for individuals (still many years away), the temptation to include the "map" within the medical record will increase.

Further, it must be remembered that the medical record itself is becoming more highly computerized. Many organizations and associations have been working diligently for several years to make this a reality. One state already requires that information on every clinical encounter be entered into a statewide computer information system. In addition, the Health Insurance Portability and Accountability Act of 1996[17] (HIPAA) also bases many of its administrative simplification provisions on the fact of electronic records. In fact, Congress mandated that standards be in place to facilitate the flow of some of this electronic information potentially two years before standards or laws are in place to protect the confidentiality of that same information.

In the future then, where linked genetic research results on already collected tissues will exist, even greater care will need to be taken to ensure that no information is entered into an individual's medical record without their express written informed consent. Indeed, it is arguable whether it is ever appropriate to enter *research* results of genetic analyses of stored tissues into the research subject's medical record, even if the information is clinically relevant. (The appropriateness of entering *clinical* genetic test results in the medical record is a separate consideration and is beyond the scope of this analysis.)

Freedom from Encroachment on Dignity/Group Interests

The concerns raised under this privacy interest are nearly identical to those identified in the section describing prospective genetic research for primary purposes. In this case, however, instead of looking forward, researchers are "looking back," reanalyzing already existing tissues. Where groups have provided the basis for genetic screening, testing, or research, the tissues represent a "captive" gold mine of potential additional information. Before the advent of genetic analysis, as stated above, the privacy interests of groups in tissue research were acute.[18] Genetic analysis has made these interests even more acute today—a trend that will likely continue into the future.

When groups of related people provided their tissues for one research protocol (for a specific purpose), the consent they signed may have indicated that the tissues would be used for unspecified future (i.e., secondary) research. If that was the case, it was also likely that no limitations were placed on what that research might entail—largely because researchers themselves would find it impossible to make such a prediction. Because the regulations to protect human subjects address only the protection of *individuals*, and do not necessarily require these individuals to reconsent to other research uses of their tissues, individuals (as members of groups) have no recourse to prevent other uses of their tissues. The IRB provides the only mechanism to serve the interests of groups in these instances. As such, when researchers propose additional retrospective research on tissues belonging to identifiable groups of related individuals, they should be required to utilize the full IRB process (e.g., no expedited review) to justify that additional research. Again, part of the justification should be an indication of how the researcher can mitigate the harm that can be caused by the information obtained as a result of the research.

Uses of Tissues

Retrospective Analysis	Prospective Analysis
Primary Use: reexamination of tissue specimen for original purpose, using new or improved techniques or technologies. *(clinical and/or research purpose)*	Primary Use: analysis for diagnostic purposes or analysis for an existing research protocol. *(clinical and/or research purpose)*
Secondary Use: most of the analyses that occur with stored tissues involve the examination of already existing tissues for purposes unrelated to the reason for which they were collected. Includes analyses of tissues where the tissue source knew and consented to retention of and general research on his/her excess tissues; where the source knew and consented to specific research uses of his/her excess tissues; or where the tissue source did not explicitly consent to any further storage or use of his/her excess tissues. If the tissues are not identifiable as to an individual tissue source, the research protocol can be exempted from IRB review and federal (but not necessarily state) informed consent requirements. Most of the tissues used for secondary purposes were obtained when the tissue source sought clinical treatment at a medical facility. A smaller proportion of tissues were left from prior research protocols and may or may not include subject identifiers, depending on the research protocol. *(generally a research purpose)*	Secondary Use: an existing protocol may use tissues in a way that extends beyond the direct purpose for which the tissue sources surrender their tissues, e.g., using anonymous samples from random patients entering a hospital for surgery in order to study phenomena unrelated to their clinical care. *(research purpose)*

Uses of Information Gleaned from Tissues

Retrospective Analysis	Prospective Analysis
Primary Uses: *Clinical*: alter a course of treatment based on new, additional, or corrected information obtained through reexamination of tissue. Information about the new treatment might be entered in patients' medical records, as might information about the results of tissue reexamination. *Research*: study research techniques and technologies and/or improve the understanding of diseases/traits and their causes. Information might be entered in subjects' medical records, if research results are linked to specific patients. Could also include chart review research, to follow up on clinical encounters to determine whether patients contract genetic diseases for which they were tested within a clinical or research context. Information eventually could be included in medical records, if the information has direct implications for an individual's clinical care.	Primary Uses: *Clinical*: determine a course of treatment for patients. Information on treatment and test results would likely be entered in patients' medical records. *Research*: gain understanding of diseases/traits and act as guide for additional research. If the research is conducted with patient links, information may be entered in subjects' medical records (e.g., if a subject elects to receive results of his or her genetic tests conducted in the course of a research protocol and preventive treatment is indicated. This presumes that receiving test results was an option provided to research subjects, which is often not the case).

Uses of Information Gleaned from Tissues

Retrospective Analysis	Prospective Analysis
Secondary Use: *Clinical*: look for new diseases associated with previously reported/discovered diseases/traits (e.g., if clinical notes specify a particular allele mutation and other diseases are later discovered to be associated with the same mutation). Information may be entered into patients' medical records. *Research*: apply information learned from retrospective analyses to other diseases being researched, and look for relationships that may prove fruitful for other research. Also could include follow-up research utilizing chart reviews on medical encounters where tissues were analyzed for specific diseases/traits or for outcomes research and epidemiological studies utilizing chart review methodology. Depending on the protocol, where research results are unidentifiable for any research subject, information ought not be entered into his/her medical record. Where research results are identifiable to an individual subject, unless that person explicitly consents to it, no information ought to flow to his or her medical record. In the near future, this could also include analyses of "raw" genetic data (i.e., a map of an individual's genome sequences) deciphered from tissues using technologies such as "DNA chips." The sequence data can then be used for any number of secondary research analyses on genetic traits.	Secondary Use: *Clinical*: if secondary research elicits a clinically relevant result, additional treatment may be called for, presuming the tissue source can be identified. In the case of genetic research, this could include clinically relevant information for families. *Research*: alter a research protocol based on findings of prospectively collected tissues. (e.g., if collection of anonymous tissues from randomly selected surgical patients does not elicit the intended or hoped for results, a protocol could be altered—for example, changing the methodology for prospective collection of tissues—to elicit more relevant data. This could also include analysis of unanticipated information gleaned from prospective research, e.g., colorectal cancer mutation in Ashkenazi Jews was originally thought to be a normal variation in the gene).

Modern Threats to Medical Privacy

It is important to place within a broader context the activities described above, since they do not occur in isolation of other encounters and activities that may have an impact on privacy. Despite the fact that many people would like to claim a categorical right to privacy, in reality, such a categorical claim is not possible in today's world. Indeed, privacy is not an absolute value. In many circumstances, businesses and government agencies have a legitimate need to collect and use personal information. Certainly, the practice of medicine would come to a complete halt if personal information were not shared, at least between the patient and the caregiver. However, the increasingly frequent demands from various sources for more and more personal information will continue to place individuals' privacy at even greater risk in the future. Below are some of the ways in which privacy is being challenged within the context of medical care.

Issues in Medical Confidentiality[19]

Some argue that the assumption that medical information is confidential is no longer valid, in part because it can no longer be guaranteed (Siegler 1982) (if it truly could in the last few decades). For instance, some estimates hold that as many as 400 people may see all or part of a patient's medical record while he or she is hospitalized (Goldman and Mulligan 1996:5). While it is true that more and more parties claim legitimate need to have access to patient information, particularly in institutional settings, it is still crucial to the quality of care that patient information be protected. A major concern for patients is that revealing sensitive information will lead to adverse consequences. Vincent Brannigan and Bernd Beier contend "it is arguable that it is not the

number of persons given the information, but their relationship to the patient that determines the scope of concern; there may only be a small number of persons interested in the particular patient, but disclosure to any one of them could be devastating" (1991:70). They argue that the wide circle of persons many states consider to be "legitimately interested" in a person's health, including spouse or employer, can effectively destroy any rights of privacy and confidentiality.

Patients tend to expect that their communications with physicians, nurses, and other health care providers are and will remain confidential. Because patients may presume that such communications have strong legal protection,[20] they generally feel comfortable providing intimate details to advance their medical treatment: "Patients are not likely to disclose these details freely unless they are certain that no one else, not directly involved in their care, will learn of them" (Annas 1989:177).

Interestingly, the newly proposed revisions to the federal regulations protecting human subjects in research (45 CFR 46) would make eligible for expedited IRB review *prospectively collected* identifiable information and tissues gathered in clinical encounters.[21] This does not mean that the other provisions of the regulations do not apply (e.g., the need for informed consent). However, two points need to be made: 1) some patients already sign authorization forms for disclosure in clinical encounters (presumably to allow disclosures for third-party payors), and especially in a physician's office, that are often broad enough to include disclosures for research purposes, and 2) the IRB official who makes determinations for expedited review also has the authority to waive or modify the requirement for consent at the same time (assuming that the "minimal risk" criteria are met). In many ways, then, this proposed change to the regulations could make more routine the disclosure of clinical information and provision of tissues for nonclinically related research purposes, and potentially without informing patients.

Current state laws provide a veritable patchwork of protections for medical confidentiality. Only a handful of states have adopted meaningful laws to protect these records, and those vary in scope and applicability. "The degree to which current law requires confidentiality varies according to the type of information and who has control of it" (Donaldson, Lohr, and Bulger 1994:1392). For instance, most states recognize a provider-patient privilege. Some states also have specific laws to deal with highly sensitive medical information, such as mental health records and/or AIDS test results. A few states—for example, California, Washington, and Montana—have enacted laws defining access to health information generally, while others deal more with insurance transactions. In addition, different states may have laws governing patient medical records within their statutes dealing with licensing of medical providers and facilities, insurance transactions, or public health reporting. In several states, "the legal duties of physicians to safeguard patient confidences do not extend to other health care professionals, researchers, or health care institutions, even though the risk of harm from disclosure may be as great or greater" (Gostin et al. 1993:2489). Moreover, state laws often contain provisions more favorable to information exchange than to patient privacy. In only 28 states do patients have a legal right to gain access to their own medical records, although the extent of the access these laws grant are inconsistent across those 28 states. The fact that only 28 states allow patients some access to their records conceptually turns on the notion of informed consent on its head in the other 22 states. For instance, how can an individual make an informed decision to authorize disclosure of their medical records if they do not know what information about them is being disclosed? By definition, "blind" disclosures cannot be informed.

Current federal law has only protected patient information related to substance abuse and mental health when the facilities from which a patient seeks treatment receive federal funding. Additionally, medical information in the custody of the federal government is also protected by at least the Privacy Act of 1974 (5 USC 552(a)) (e.g., Medicare and Veterans Affairs records). The HIPAA provides a new set of federal mandates for managing health information, described below.

This discussion has so far dealt with medical information generally. Both state and federal legislatures have been very active, however, in proposing ways to address policy issues relating specifically to genetic information. At the federal level, these legislative proposals (none of which advanced in the legislative process during the first session of the 105th Congress) deal mostly with genetic discrimination: barring discrimination in health insurance based on "genetic information;" barring insurance companies from requiring genetic tests for underwriting or rate-setting purposes; and/or barring employment discrimination on the basis of genetic information. At the state level, in 1997, while genetic discrimination in various settings topped the list in the number of bills introduced (approximately 90 bills across all 50 states, with 9 enacted), bills relating to forensic analysis of DNA and/or DNA registries were the most enacted (14 bills enacted of 50 introduced). As of this writing, 48 states have DNA registries for at least some classes of convicted felons.

One of the more interesting pieces of legislation that was signed into law in 1997 came from Oregon. Oregon had been one of only a few states that provided that an individual had a "property right" in his/her own genetic information. At the explicit request of SmithKline Beecham, the Oregon legislature amended this provision to state that the individual has a property right to his/her genetic information and DNA sample *except* when the information or sample are used in anonymous research. The new law also states that an individual must authorize the retention of his/her DNA by another individual, *unless* the retention is for anonymous research. (Anonymous research is defined as research that does not allow the identification of an *individual*—it says nothing about group identity.) What makes this law interesting is that it highlights the whole concept of "ownership" of genetic material and the ways in which a measure originally intended to protect individuals' interests was seen as a threat to the research and commercial endeavors of the "medical-industrial complex" (Relman 1980).

Computers and Medical Privacy

In order to fully appreciate the new federal mandates for managing health information, a brief discussion of the trends in using computer technology in this domain will prove beneficial. Health care systems increasingly rely on information technology to manage and facilitate the flow of sensitive health information. This is the result, according to a key Institute of Medicine analysis, of several entities that want better health data to "assess the health of the public and patterns of illness and injury; identify unmet…health needs; document patterns of health care expenditures on inappropriate, wasteful, or potentially harmful services; identify cost-effective care providers; and provide information to improve the quality of care in hospitals, practitioners' offices, clinics, and other health care settings" (Donaldson and Lohr 1994:1). Indeed, the very fact that computers can make the collection, dissemination, and analysis of this data relatively easy and inexpensive is, in itself, often an incentive to collect more data.

Because of marked advances in computer and telecommunications technology, data do not even need to reside in the same database to be linked. The Office of Technology Assessment has noted that "patient information will no longer be maintained, accessed, or even necessarily originate with a single institution, but will instead travel among a myriad of facilities" (Office of Technology Assessment 1993:9).

Moreover, "Because of the efficiency of automated systems, violations of medical confidentiality may appear to be easier. Because of the amount of data which may be included in a comprehensive patient file, the damage to the patient whose confidentiality is violated may be proportionately greater" (Walters 1982:201–202). Without taking great care in the design and implementation of the systems developed to capture and transmit this data, significant concerns should and will be raised about individual privacy. A recent report of the National Research Council, documenting the increasing reliance of the health care industry on electronic medical records, warns of the vulnerabilities of many of the component systems to abuse. The report found that there are currently few incentives within the industry to provide comprehensive security measures to protect these records, but that the need to do so will increase as organizations increasingly rely on electronic media to manage them (National Research Council 1997).

Medical records contain information that has nonmedical uses, and access to that information is of interest to many parties. "Traditional medical records, moreover, are only a subset of automated records containing substantial health or personal information held by educators, employers, law enforcement agencies, credit and banking entities, and government agencies" (Gostin et al. 1993:2488). As the Workgroup for Electronic Data Interchange has noted, providers' obligation to maintain the confidentiality and integrity of information "does not change with the medium of health information transmission or storage. The provider's ability to meet an obligation to maintain confidentiality, however, can be greatly affected by use of the electronic medium to store and transmit health information" (Workgroup for Electronic Data Interchange 1992:3).

This obligation is further complicated by the fact that more and more individuals and entities are involved in health care delivery and financing, thereby increasing the number of people who have direct access to patient records. Additionally, "electronic storage and transmission of data enable interested parties to compile information on individuals from diverse sources, making computer based health data potentially valuable to a range of groups, including pharmaceutical companies and professional liability attorneys" (Donaldson, Lohr, and Bulger 1994:1392). For instance, since the early 1990s, four of the world's largest pharmaceutical companies have purchased either discount pharmacy chains or prescription benefits managers (firms that manage administrative aspects of prescription drug benefits for insurers). At least two of the four pharmaceutical concerns have made no secret of their use of prescription information (including patient and/or provider identifiers) to promote their pharmaceutical products (*Wall Street Journal* 1995) and/or study drug effectiveness (Kolata 1994).

Computers, particularly as used in clinical practice, currently store varying levels of detailed genetic information on individuals (e.g., information about known genetic disorders within a patient's family, such as Huntington's disease, breast cancer, or schizophrenia). In addition, the field of computational biology is progressing with remarkable speed in its ability to sequence genes, conduct linkage analyses, and construct reference maps. The convergence of these trends will lead, perhaps inevitably, to increasingly detailed genetic information about individuals (perhaps even to the sequence level) being available and processable by computers.

It is crucial to bear in mind that this is the context into which genetic information will be placed. Many people argue that genetic information should be treated as a part of the general medical record, and that the protections afforded the entire record should be as stringent as possible.[22] Considering the numbers of people and entities which gain access to these records, however, comprehensive schemes that could truly protect privacy will be difficult to achieve. (This is partly due to the fact that so many entities have received relatively free access to these records up until now, that reneging that access will raise a firestorm of protest from these entities that may make restrictions difficult to construct and implement.) As the results of genetic analysis become more sophisticated, this issue will be even more problematic if/when individuals discover the myriad places their medical information ends up.

To presume that privacy harms may accrue only to disenfranchised individuals is to deny the power of computer technologies within the medical context. Indeed, "[s]ome of the harms from the health data system are likely to be harms to classes of persons as a consequence of aggregating data without personal identifiers.… Losers will be identifiable as classes. They will be losers only by virtue of the fact that we now have aggregated information about the health status and health risks of classes of people, not because identifiable information about any particular person is improperly disbursed in the system. Hence, sticky issues of group privacy rights are likely to emerge in the not-so-distant future" (Powers 1993:82).

Administrative Simplification Provisions of the Health Insurance Portability and Accountability Act of 1996

HIPAA acknowledges the increasing computerization of medical information by codifying requirements for the electronic management of health information. Title II, Subtitle F of HIPAA is a section called "Administrative

Simplification" that in part calls on the Congress to pass legislation to protect the privacy of individually identifiable health information transmitted in connection with clinical encounters. The following are the major relevant provisions:

- Within 12 months of enactment (August 21, 1997), the Secretary of Health and Human Services must provide Congress with a set of detailed recommendations on standards to protect the privacy of individually identifiable health information. The recommendations must address rights individuals should have with respect to their data, procedures to exercise these rights, and authorized/required uses and disclosures of the information.
- If Congress has not acted on these recommendations within 36 months (August 21, 1999), the Secretary of Health and Human Services must promulgate regulations to put protections in place within 42 months of enactment of the legislation (February 21, 2000).
- States that already have stricter laws than what is called for in this bill (with respect to confidentiality protections) are not preempted. In other words, HIPAA sets a legislative floor.

That *could* mean that the default will have to accommodate these stricter laws. On the other hand, Congress may decide, in enacting subsequent legislation, that state preemption is preferable. In addition, no mention is made in HIPAA about the preemptive status of state common law. Many states have privacy protections in place for medical information that derives from common and not statutory law. Whether or not common law that provides more protection than federal law will be preempted is not clear.

- In devising the recommendations for Congress, the Secretary of Health and Human Services MUST consult with the National Committee on Vital and Health Statistics and the Attorney General. Those are the only two entities so named.
- Moreover, the Secretary of Health and Human Services must also put in place several health identifiers, including for patients, payors, and providers.

The bill does not specify the Social Security number (SSN) for the patient identifier; however, several entities are on the record as recommending the use of the SSN for this purpose, including several that are in the forefront of designing these electronic patient record systems.

- In addition, the bill establishes hefty penalties for unauthorized disclosure of personal health information, without establishing what rights individuals have to those records.

Without setting the parameters for fair use of records (apart from profiting from their sale), it is unclear how an unauthorized disclosure would be evaluated and punished, before the additional legislation/regulations are in place.

- Finally, the Secretary of Health and Human Services must adopt standards within 18 months (February 21, 1998) to facilitate the electronic flow of health care and encounter data, while privacy protections may not be in place for 42 months (February 21, 2000). The standards the Secretary must adopt (unless there are very compelling reasons not to) are any that have already been established by the private sector for the exchange of the records.

On September 11, 1997, the Secretary presented Congress with her recommendations to protect patient privacy. She listed five principles as being necessary for comprehensive confidentiality of medical information:

1. Boundaries: with very few exceptions, health care information should be disclosed for health purposes only;
2. Security: information should not be used or given out unless either the patient authorizes it or there is a clear legal basis for doing so;
3. Consumer control: citizens have the right to access their records, know who is looking at them, determine their accuracy, and change incorrect information;

4. Accountability: individuals and organizations would be accountable for violating health care privacy (with civil and criminal sanctions); and
5. Public responsibility: there must be a balance between protection of privacy (i.e., 1–4 above) and the need to support national health priorities, such as health research, fraud and abuse prevention, and law enforcement.

The Secretary's report to Congress suggests that a medical privacy statute protect individuals from inappropriate disclosures, but only in cases where these disclosures are in fact inappropriate. Moreover, the recommendations do not contemplate that any health information be treated differently due to its sensitivity (i.e., AIDS/HIV status, mental health information, genetic test results). The Secretary did recommend, however, that Congress enact genetic discrimination legislation to minimize harm from having this information in the medical record.

In the case of health research (under "public responsibility" above), the Secretary's recommendations are consistent with current regulations for the protection of human subjects—that an IRB determines that consent is unnecessary if there is minimal risk to individuals; that obtaining consent would make the research impracticable; and that subjects would not be adversely affected. In this case, the research could be exempt from further IRB review and oversight.

One of the most controversial aspects of the Secretary's recommendations was the codification of current practice of allowing the law enforcement and intelligence communities broad authority to access any medical record. While ostensibly this would be largely in the context of health care fraud investigations, their access would by no means be limited to these investigations only. As the report states, "in many instances, law enforcement authorities today can obtain, share, and use health information without patient consent and without legal process. We are not recommending changes to these practices" (Secretary of Health and Human Services 1997:11).

Emerging Technologies for Genetic Analysis

The use of computer technology in medical practice is not limited to the management of health information. Indeed, new tools and technologies are being developed to greatly enhance our ability to decipher genetic codes. One of the most promising technologies (and most advanced thus far) is modeled after computer chip technology and even uses a similar manufacturing process. Referred to as "DNA chips" or "gene chips," their manufacturer promises they will revolutionize the way medicine is practiced in the future. "They give medical researchers the ability to analyze thousands of genes at once—in effect, to speed-read the book of life....Researchers at the company [Affymetrix in Santa Clara, CA] are using gene chips in landmark studies on everything from the origins of cancer to gene mutations that make the AIDS virus resistant to drugs....The new biochips mark a turning point, though, because they promise to do for this second revolution [the genetics revolution] what silicon chips did for the first [the computer revolution]: make it personal" (Stipp 1997:2–3). Moreover, the gene chips are doubling in power every eighteen months (as are computer chips). In fact, gene chips can already decode genes 100 times faster than conventional technologies. The results of these analyses are computerized and "will contain either raw sequence, or the specific sequences of small portions of a large number of genes, in addition to the immediate interpretation of these sequences in terms of the presence or absence of specific known alleles of the specified genes" (Naser 1997:10).

> In one of the most profound studies, Affymetrix scientists have begun comparing genes of different people to identify the normal variants that make each of us unique. In a few years, researchers should be able to correlate patterns of these gene 'polymorphisms' with longevity, say, or a tendency toward shyness or a high IQ—and resolve burning questions about the degree to which heredity determines each. Says [Affymetrix President Stephen] Fodor, 'Ninety-nine percent of people don't have an inkling about how fast this revolution is coming' (Stipp 1997:7).

One of the main benefits promised by this technology is a new generation of gene-based drugs that can be tailored to particular patients, depending on their own genetic mutations, as well as the particular genetic mutations of the microbes, cancers, or other organisms that have invaded their bodies. The company currently has agreements with several pharmaceutical companies and at least one genetics-testing company to develop new drug therapies and genetic testing techniques. In addition, "Affymetrix and a consortium of other biotechnology companies and academic institutions is presently working under a $31 million grant with Stanford University from the U.S. Commerce Department to develop automated miniaturized genetics diagnostic systems for use in physicians' offices" (Naser 1997:4).

The technological advances promised by the gene chip and other similar technologies are profound, as are the implications for society. For instance, high-speed genetic analysis can lower costs of research, facilitate research on specific genetic mutations, and facilitate the discovery of genetic bases of infectious disease and toxicologies. As more purely genetic data are entered into medical records, retrospective epidemiological studies will elicit more detailed and powerful results. Prenatal and other genetic testing will also be easier and cheaper to administer.

The fact that these analyses can be done cheaply and easily in the future is also a source of concern. There are currently many contexts in which "genotyping" is not done because of how burdensome it is to do. With these barriers eliminated in the future, additional questions of discrimination in employability and insurability will arise.

Additionally, many questions will arise that will further complicate the difficult questions that currently need to be addressed in genetic research. For instance, will anonymity really be possible in the future, even on an individual basis? As genetic analysis and testing become more routine and are eventually introduced into clinical practice, what are the additional risks to patients as the information is entered into the computerized medical record? As the distinction between research and clinical encounters becomes fuzzier, what rules will apply to protect patients/subjects? Indeed, will it be possible that the need for large tissue repositories will diminish if genetic sequences can be computerized and studied instead of tissues? Could that also mean that more people will become subjects of genetic research without their explicit knowledge (e.g., under IRB exemption for research involving minimal risk on anonymous data/tissues/genetic sequence data)? These sorts of questions will raise difficult quandaries for research, clinical practice, and public policy.

Conclusions and Recommendations

The conclusions and recommendations are grouped into four main categories: groups, other genetic research, protecting anonymity, and harms both tangible and intangible.

Groups

The myriad issues and policy choices that arise when looking at privacy issues in the genetic analysis of stored tissues are complex and challenging. Among the most challenging set of issues that has yet to be addressed from a policy perspective pertain to the privacy interests of groups of related individuals. Federal regulations for the protection of human subjects currently do not accommodate risks for groups.

Another issue relating to groups is that of group consent/assent where research is done on prospectively collected tissues and only from members of a particular group. As discussed earlier, it is important to involve the communities in the research at the earliest possible opportunity. Researchers need to be sensitive to the fact that research on even a subset of that group can render information that may well be applicable to the entire group. Looking again at the Ashkenazi population within the United States, researchers have started to see a backlash from leaders within that community who are worried about how the research findings on a small group, but

extrapolated over the entire group population, may affect the dignity of all Ashkenazi Jews and may engender group stigma.[23] The guidance published in conjunction with the HGDP offers valuable insights into some of the issues associated with groups, much of which may be adapted to broader population contexts (North American Regional Committee of the Human Genome Diversity Project 1997).

Recommendation One:

The federal regulations for the protection of human subjects (45 CFR 46) should explicitly incorporate the notion of nonmedical group risks and harms from participating in genetic research. In incorporating this concept, the regulations should disallow the possibility of expedited review of research protocols where the research is being done on identifiable groups of genetically related people (i.e., people of the same ethnic, racial, or cultural group). Moreover, where protocols explicitly involve research on already existing tissues from identifiable groups of people, the regulations should *not* consider these tissues to be anonymous just because the individuals cannot be identified. The regulations should also specify that where group genetic research is proposed, researchers should seek leaders or other representatives from the relevant groups/communities (where possible) to obtain their groups' perspectives and involve them in the design of the research and potentially the communication of research results. Where this is not possible, researchers should seek other means to minimize the risk of the research to groups.

Until the regulations can be changed, a broad recommendation by the appropriate federal policymaking entity(ies) should be made to encourage IRBs to institute these sorts of procedures for genetic research on groups of people. In addition, when seeking consent for specific protocols from research subjects in *prospective* research, the consent documents should clearly state when harms relevant to groups may result and what those harms might be (e.g., stigmatization), even where individually anonymous tissues are being used. Similarly, benefits to the groups of such research should also be highlighted along with an explanation of the purpose of the research.

Other Genetic Research

IRBs are increasingly being asked to consider protocols that involve research on germline genetic composition. Current regulations allow these protocols to be exempt from IRB review, where anonymous (that is, anonymous for any *individual*) already existing samples are used. As more of this type of research is initiated, exemption from review may become more ethically questionable. Resolving the potential ethical dilemmas will depend on several things, including:

1. The consent form the patient originally signed (i.e., its specificity with respect to the use of excess tissues—for general research, for genetic research, for single or multiple research purposes, or for general disposition, and whether any medical record information would be associated with their tissue).
2. The level of identifiability or linkability of the tissues to individuals (i.e., whether *anyone* can link the tissues/data to the individual to whom they pertain or they are irrevocably anonymous).
3. The design of the research (i.e., is it sufficiently detailed to anticipate whether any harms may accrue to the research subjects, even when using anonymous tissues? Has the researcher contemplated how research results may be communicated to the public?).
4. The potential for clinical relevance of or incidental findings from the research. (Has the researcher addressed how he/she will handle clinically relevant or other incidental results on linkable tissues?)

Recommendation Two:

If the original consent is consistent with the purpose(s) for which the tissues will be used in the future (including genetic research); if it is explained whether the tissues would be used anonymously or with identifiers; and if it is stated that the tissues might be used for multiple protocols, then the researchers and the IRB can feel more assured that the research subject's wishes would be accommodated by using their tissues for additional retrospective research. If the original consent was not that specific, then the more identifiable the subject is in the context of the genetic research, the more important it is to obtain prior informed consent (Clayton et al. 1995, and Merz, Sankar, Taube, and Livolsi 1997:253), even if the research will use already existing tissues and data.

Moreover, to mitigate unintended harm to research subjects, where tissues are to remain identifiable and clinically relevant findings may result, researchers should either secure the informed consent of the research subjects to ensure they want to know these results or decide prior to the conduct of the research to sever the link between the identifiers and the tissues, so as to minimize the ethical and legal impetus for the researcher to become involved with the subject's clinical care (Merz, et al. 1997:254). This, of course, may be difficult in situations where the clinician is also the researcher.

In those clinical situations where patients are asked to provide consent for their tissues to be used in unspecified prospective research, offering these patients a range of choices will honor their dignity: for instance, that range could start from "no research on my tissues" at one extreme to "any kind of research on my tissues and medical information is acceptable as long as the tissues and information cannot be linked to me" at the other end of the spectrum. In between, two other choices might be, "research only on the disease for which I am seeking clinical treatment" and "research other than genetic research is acceptable." This range of choices assumes that the tissues and medical information are anonymous.[24] Another approach to this graduated consent could specify the level of identifiability of the tissues and associated data. In this case, the more that identifiable information is associated with the tissues, the higher the obligations are on the recipients/researchers to obtain subsequent consent for additional research (or additional information from the tissue source) and to ensure confidentiality of the information gleaned from the tissues. Within this scheme, "no research" and "anonymous only" research remain viable options. The main challenge with these sorts of graduated consents will be the ability to delineate the mechanics of *how* someone's choices can be honored in this regard, implement them, and ensure adequate safeguards are in place to prevent harm to the tissue sources.

Protecting Anonymity

Several commentators have suggested that the best way to protect individual privacy in the conduct of genetic research (and indeed, all medical research on tissues and data) is to construct a "firewall" between the researcher and the repository in which the tissues and medical data reside (see, for instance, Merz, et al. 1997 and Korn 1997), to ensure that data elicited from research are not allowed to commingle with the clinical records (Korn 1997), and to protect patient anonymity when consent for specific disclosures was not given by the patient (Merz, et al. 1997). The firewall would provide for a one-way flow of tissues and information about patients, but would be stripped of identifiers before reaching the actual researcher (although they would probably remain linkable so that additional clinical information could augment the research record in the future). Research results would not flow back from the researcher, so there would be no possibility of relinking the results to the patients. The firewall could take the form of an institutional entity, a "trusted third party" (i.e., an independent entity that could be trusted by all parties to the storage and transfer of tissues) or some other form of trustee. Whatever the arrangement, the function would be the same—to "de-identify" tissues and records for

the researchers (Merz, et al. 1997), presumably while retaining some linkability back to the patients. This arrangement, its proponents argue, is preferable to the onerous task of seeking re-consent from the tissue sources, while still protecting patient confidentiality. *It is important to note that the concept of a firewall to protect anonymity of research subjects applies only to research conducted on individuals—it will not provide anonymity for groups unless no group identifying information is provided with or can be inferred from the tissues. Where genetic characteristics known to be mostly associated with particular groups can be inferred from tissues, then anonymity is lost.*

Recommendation Three:

Mechanisms to provide for a firewall between researchers and repositories/tissue collections should be considered for analysis of already existing tissues (where the original consent was not specific as to the research uses of the tissues), as well as for prospective research protocols (even where consent can be—and should be—obtained). However, the existence of a firewall should not be presumed to replace other mechanisms to protect research subjects. The firewall should augment them.

Additionally, the parties on both sides of the firewall must be clearly defined. For instance, is the pathologist doing "genetic research" on his/her banked collections of tissues considered a "researcher outside of the firewall?" This will have obvious implications both for the institutional arrangements made to protect the specimens and on the type of research the pathologist is freely allowed to do. Will the firewall safeguard be applicable to all research or only to that research that is accompanied by a specific protocol? If only the latter, much of the medical research that is conducted will operate outside the very parameters the firewall seeks to enclose. If only the former, how would this work for researchers who currently receive fairly free access to tissue specimens? These are the sorts of questions that will have to be worked out if a firewall concept is to be successfully and meaningfully implemented.

Tangible and Intangible Harms

Much of the concern over the use of tissues for genetic research focuses on the possibility of discrimination in many contexts, with insurance and employment being the two contexts most frequently mentioned. Certainly, President Clinton, Congress, and many of the state legislatures are concerned that advances in genetic understanding might be used to discriminate against people with genetic predispositions to specific conditions and/or diseases. The paper briefly discussed earlier some of the legislative proposals that have been advanced and/or enacted to address genetic discrimination. However, it must be remembered that because of the potential for *intangible* harm (i.e., stigmatization, psychological harm, loss of self-respect, shame) to be experienced by individuals and groups from the discovery and use of genetic information, anti-discrimination legislation will not be adequate or sufficient to address these harms. That does not mean, however, that some form of anti-discrimination legislation should not be sought at the federal level. It serves a valuable social purpose.

Recommendation Four:

The research and policy communities should continue to be vigilant in trying to minimize the potential for harm (tangible and intangible) that genetic research can bring about. Part of this vigilance is the need for researchers to be especially aware of how research findings are communicated to the public. Sensitivity to the potential adverse reactions in the popular media will become increasingly important, particularly when a specific group of people forms the basis of the researched population. While the way in which the popular media reports scientific progress is beyond the control of the research community, researchers still need to remain aware that how they present findings to the media has much to do with how those findings are reported, and hence, perceived by the public. This sensitivity may go a long way in helping make people feel less intimidated by genetic research.

These recommendations address the research establishment as it currently functions, suggesting changes that will better protect the privacy values and interests described at the outset of this paper. As genetic analysis become more technologically sophisticated and more routine (both clinically and in the research contexts), the adequacy of policies intended to protect people in these contexts will need to be reexamined. Additionally, as legislative proposals addressing various issues related to medical and genetic research become law, particularly at the federal level, modifications to recommendations will also have to be examined.

The rapid advances in the techniques and technologies of genetic analysis and their application to research and clinical practice are forcing a reevaluation of the current rules under which they operate. This effort marks a further step in a progression that promises to continue well into the future.

Notes

1 I would especially like to thank Thomas Murray, Jon Merz, Curt Naser, and Elisa Eiseman for their heroic efforts in providing feedback for the final draft of this paper.

2 See, for instance, statements by the College of American Pathologists, the American College of Medical Genetics, the American Society of Human Genetics, and Stephenson.

3 See, for instance, articles by Clayton, et al.; Annas; Weir and Horton; and McEwen and Reilly, et al.

4 See, for instance, E. Goffman, *Behavior in Public Places*, 1963; A. Westin, *Privacy and Freedom*, 1967; V. Brannigan and B. Beier, "Informational Self-Determination: A Choice Based Analysis," *Datenschutz und Datensicherung*, April 1985.

5 Confidentiality "refers broadly to a quality or condition accorded to information as an obligation not to transmit that information to an unauthorized party.…Confidentiality has meaning only when the promises made to a data provider can be delivered, that is, the data gatherer must have the will, technical ability, and moral and legal authority to protect the data" (Duncan, Jabine, and de Wolf 1993:22–23).

6 In this respect, this notion of groups or collectivities departs from the definition used in the Canadian draft "Code of Conduct for Research Involving Humans" (which explicitly includes families in their definition), at least insofar as the present discussion is concerned.

7 Geodemographics are a combination of attributes that are used to describe demographic characteristics (e.g., race, income, purchasing preferences, home valuation, etc) of people living within a particular geographic area (e.g., ZIP code, Census tract, county).

8 Many of the inputs to these systems come from consumers interacting with the market in a variety of ways—subscribing to magazines, purchasing items through mail-order catalogs, filling out the lengthy questionnaires on product registration cards, etc. In addition, many local governments, strapped for money, are arraying their public records geographically and selling that data to marketers and others.

9 See www.claritas.com.

10 It should be noted, however, that the discipline of "medical geography" is growing because of the increasing sophistication of Geographic Information Systems (GIS). GIS are used in this context, among other things, to map epidemiological events and phenomena. Moreover, there is at least one major book, *The History and Geography of Human Genes*, which is described in the following way: "The authors reconstruct the history of our evolution by focusing on genetic divergence among human groups. Using genetic information accumulated over the last fifty years, they examined over 110 different inherited traits…in over eighteen hundred, primarily aboriginal, populations. By mapping the worldwide geographic distribution of the genes, the scientists are now able to chart migrations….This volume highlights the authors' contributions to genetic geography, particularly their technique for making geographic maps of gene frequencies and their synthetic method of detecting ancient migrations…." (description, as listed at www.amazon.com.) (L.L. Cavalli-Sforza, P. Menozzi, and A. Piazza. 1994. *The History and Geography of Human Genes*. Princeton: Princeton University Press).

11 Although only research and clinical uses are being highlighted here, it is acknowledged that there are other uses/applications for stored tissue samples, such as for educational purposes, quality control, to satisfy legal requirements, and for commercial purposes. These other applications extend beyond the main purpose of this report and hence are not dealt with an any detail in this analysis.

12 A survey of DNA banking and informed consent showed that about half of the informed consent documents analyzed contained no mention of the possibility of secondary use of stored tissue samples, and just over 10 percent mentioned third-party access (Weir and Horton 1995:6).

13 "Anonymous" as used here means that the links between the identity of the tissue source and the tissue sample have been permanently and irrevocably removed, so that identification of the *individual* from whom the tissue was obtained is not possible to ascertain, either directly or indirectly.

14 In the future, having physical access to the tissue samples may be of less importance, at least for some research applications, as the field of computational biology (and technologies such as "DNA chips") facilitates the deciphering of the genes contained within tissues. For research in which examining certain gene sequences is the focus, tissues may become superfluous—all one may need is a computer program that can accommodate the sequence information, and potentially perform "what if" analyses using various mutations. Although the ability to perform these analyses (and interpret their results) is probably still many years away, computational biology is quickly providing the foundation to make them possible.

15 One large medical institution has a special board that is convened when genetic research elicits clinically relevant findings. The purpose of the board is to determine whether or not the research subject should be told of the results. (The research subjects are informed of this possibility at the outset of their participation.) If the board determines that the subject should be told, that information will be entered into that person's medical record.

16 It is acknowledged that recontact raises difficult logistical and practical issues, such as who has access to the identities of the individuals, who should actually recontact them and how.

17 Health Insurance Portability and Accountability Act of 1996. Public Law 104-191, 110 Stat 1936.

18 For instance, much has been written about how, in the 1970s, the African-American community experienced the unintended effects of a well-intentioned set of policies aimed at helping carriers for or sufferers of sickle cell anemia.

19 Some of the material in this section is based on prior work of the author, printed as Alpert, S. (1998) "Health Care Information: Access, Confidentiality, and Good Practice." In *Ethics, Computing, and Medicine: Informatics and the Transformation of Health Care*, K.W. Goodman, ed., 75–101. (Cambridge and New York: Cambridge University Press).

20 Provider-patient privilege does not necessarily keep communications between doctors and patients confidential. In the United States, for instance, the privilege, legally recognized by some 40 states, is generally only applicable in a court of law. These laws do not apply to the many situations in which a doctor or nurse is allowed or compelled by law, regulation, or long-standing practice to reveal information about the patient to outside parties. Additionally, privilege statutes apply only in cases governed by state law. The Federal Rules of Evidence, which govern practice in federal courts, provide only a psychotherapist-patient privilege, not a general physician- or nurse-patient privilege. Therefore, the clinician-patient privilege is actually a narrowly drawn rule of evidence, not recognized as common law (as is, for example, the attorney-client privilege), and available only where it is specifically provided by statute (Hendricks, Hayden, and Novik 1990:155–156).

21 The proposal affects 45 CFR 46.110, and reads: "5. Research involving solely (a) prospectively collected identifiable residual or discarded specimens, or (b) prospectively collected identifiable data, documents, or records, where (a) or (b) has been generated for nonresearch purposes." This would be a new provision in the regulations.

22 For instance, in her report to Congress recommending privacy protections for medical information as required under the Health Insurance Portability and Accountability Act of 1996, Health and Human Services Secretary Donna Shalala made this argument.

23 From both scientific and social perspectives, it is dangerous to draw conclusions about a group and its genetic characteristics without comparing it with the population at large. It may well be that genetic mutations thought to be specific to certain groups are equally prevalent throughout the entire population. From a practical standpoint, however, research on germline genetic composition is more easily accomplished on discrete groups than on the population at large. That being the case, researchers need to be especially careful in how results are reported to the public.

24 Anonymous research is assumed here because for nonspecified research, people should not be asked to waive their right to informed consent to use of identifiable tissues/information, since the nature of any future research is unknown at the time of tissue collection, as are the risks that would be associated with that research.

References

Allen, A. (1988) *Uneasy Access: Privacy for Women in a Free Society*. Totowa, N.J.: Rowman and Littlefield.

Allen, A. (1997) "Genetic Privacy: Emerging Concepts and Values." In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*, M.A. Rothstein, ed., 31–59. New Haven: Yale University Press.

Alpert, S. (1995) "Privacy and Intelligent Highways: Finding the Right of Way." *Santa Clara Computer and High Technology Law Journal*, 11(1):97–118.

Alpert, S. (1997) "Health Care Information: Access, Confidentiality, and Good Practice." In *Ethics, Computing, and Medicine: Informatics and the Transformation of Health Care*, Goodman K.W., ed., 75–101. Cambridge and New York: Cambridge University Press.

American College of Medical Genetics Storage of Genetics Materials Committee. (1995) "Statement on Storage and Use of Genetic Materials." *American Journal of Human Genetics* 57:1499–1500.

American Society of Human Genetics. (1996) "Statement on Informed Consent for Genetic Research." *American Journal of Human Genetics* 59:471–474.

Annas, G. (1989) *The Rights of Patients: The Basic ACLU Guide to Patient Rights*. 2d ed. Carbondale: Southern Illinois University Press.

Annas G. (1993) "Privacy Rules for DNA Databanks: Protecting Coded 'Future Diaries.'" *JAMA*; 270:2346–2350.

Annas G., L.H. Glantz, and P.A. Roche. (1995) "The Genetic Privacy Act and Commentary." Boston: Boston University School of Public Health.

Baier, M. (1967) "Zip Code: New Tool for Marketers." *Harvard Business Review* 45:136–40.

Bennett, C.J. (1992) *Regulating Privacy: Data Protection and Public Policy in Europe and the United States*. Ithaca: Cornell University Press.

Bloustein, E. (1978) *Individual and Group Privacy*. New Brunswick: Transaction Books.

Bloustein, E. (1984) "Privacy as an Aspect of Human Dignity: An Answer to Dean Prosser." In *Philosophical Dimensions of Privacy: An Anthology*, F.D. Schoeman, ed., 156–202. Cambridge: Cambridge University Press.

Brannigan, V.M. and B. Beier. (1991) "Standards for Privacy in Medical Information Systems: A Technico-Legal Revolution." *Datenschutz und Datensicherung* 9:467–472.

Burnham, D. (1983) *The Rise of the Computer State*. New York: Random House.

Caplan, A. (1994) "Handle with Care: Race, Class, and Genetics." In *Justice and the Human Genome Project*, T.F. Murphy and M.A. Lappe, eds., 30–45. Berkeley: University of California Press.

Clayton, E.W., K.K. Steinberg, M.J. Khoury, et al. (1995) "Informed Consent for Genetic Research on Stored Tissue Samples." *JAMA*; 274:1786–1792.

College of American Pathologists. "Uses of Human Tissue." August 28, 1996.

Curry, D.J. (1992) *The New Marketing Research Systems: How to Use Strategic Database Information for Better Marketing Decisions*. New York: Wiley.

Curry, M. (1999) "Rethinking Privacy in a Geocoded World." In P. Longley, D.J. Maguire, M.F. Goodchild, and D.W. Rhind, eds., *Geographical Information Systems: Principles, Techniques, Applications, and Management*. 2d ed., 2 vols. New York: Wiley.

Donaldson, M.S. and K.N. Lohr, eds. (1994) *Health Data in the Information Age: Use, Disclosure, and Privacy*. Washington, D.C.: National Academy Press (Institute of Medicine).

Donaldson, M.S., K.N. Lohr, and R.J. Bulger. (1994) "From the Institute of Medicine: Health Data in the Information Age: Use, Disclosure, and Privacy: Part II." *JAMA* 271:1392.

Duncan, G., T. Jabine, and V. de Wolf, eds. (1993) *Private Lives and Public Policies: Confidentiality and Accessibility of Government Statistics*. Washington, D.C.: National Academy Press.

"Eli Lilly Plans to Use PCS Unit's Database to Boost Drug Sales." *Wall Street Journal*, May 11, 1995, West Coast Edition, B6.

Fried, C. (1968) "Privacy (A Moral Analysis)." *Yale Law Journal* 77: 475–93. Reprinted in *Philosophical Dimensions of Privacy: An Anthology*, F.D. Schoeman, ed. Cambridge: Cambridge University Press. 1984.

Gavison, R. (1984) "Privacy and the Limits of the Law" in *Philosophical Dimensions of Privacy: An Anthology*, F.D. Schoeman, ed. Cambridge: Cambridge University Press.

Goldman, J. and D. Mulligan. (1996) "Privacy and Health Information Systems: A Guide to Protecting Patient Confidentiality." Center for Democracy and Technology and the Foundation for Health Care Quality.

Gostin, L. (1991) "Ethical Principles for the Conduct of Human Subject Research: Population-Based Research and Ethics." *Law, Medicine and Health Care* 19:191–201.

Greely, H. (1997) "The Control of Genetic Research: Involving the 'Groups Between.'" *Houston Law Review* 33:1397–1430.

Hendricks, E., T. Hayden, and J.D. Novik. (1990) *Your Right to Privacy: A Basic Guide to Legal Rights in an Information Society*, 2d ed. Carbondale: Southern Illinois University Press (An American Civil Liberties Union Handbook).

Hixson, R. (1987) *Privacy in a Public Society: Human Rights in Conflict*. New York and Oxford: Oxford University Press.

Information and Privacy Commissioner. (1994) *Privacy Protection Makes Good Business Sense*. Ontario.

Kolata, G. (1994) "New Frontier in Research: Mining Patient Records." *New York Times*, August 9: A11, National Edition.

Korn, D. (1997) "Genetic Privacy and the Use of Human Tissues in Research." Paper delivered at the Uniform Services University of Health Sciences Interagency Human Subjects Conference, Bethesda, MD. June 26–27.

Laudon, K.C. (1986) *Dossier Society*. New York: Columbia University Press.

Lehrman, S. (1997) "Jewish Leaders Seek Genetic Guidelines…" *Nature* 389 (6649):322.

McEwen, J.E. and P.R. Reilly. (1994) "Stored Guthrie Cards as DNA 'Banks.'" *American Journal of Human Genetics* 55(1):196–200.

McEwen, J.E. and P.R. Reilly. (1995) "A Survey of DNA Diagnostic Laboratories Regarding DNA Banking." *American Journal of Human Genetics* 56(6):1477–1486.

McEwen, J.E. and P.R. Reilly. (1996) "Setting Standards for DNA Banks and DNA Databanks: Toward a Model Code of Conduct." *Microb Comp Genomics* 1(3):165–177.

Merz, J., P. Sankar, S. Taube, and V. Livolsi. (1997) "Use of Human Tissues in Research: Clarifying Clinician and Researcher Roles and Information Flows." *The Journal of Investigative Medicine* 45:252–257.

Merz, J. (1996) "Is Genetics Research 'Minimal Risk'?" *IRB: A Review of Human Subjects Research* 18(6):7–8.

Naser, C. (1997) "High Speed Genetic Testing Technology and the Computerization of the Medical Record." Presented at the Second Annual Ethics and Technology Conference; Loyola University; Chicago, IL. June 6–7, 1997.

National Research Council, Computer Science and Telecommunications Board. (1997) *For the Record: Protecting Electronic Health Information*. Washington, D.C.: National Academy Press.

North American Regional Committee of the Human Genome Diversity Project. (1997) "Model Protocol: Proposed Model Ethical Protocol for Collecting DNA Samples." *Houston Law Review* 33:1431–1473.

Office for Protection from Research Risks, National Institutes of Health, U.S. Department of Health and Human Services. (1997). *Notice; request for comments*. Washington, D.C.: Federal Register; November 10, 1997; 60607–60611.

Office of Technology Assessment. (1993) *Protecting Privacy in Computerized Medical Information*. Washington, D.C.: U.S. Government Printing Office (OTA-TCT-576).

Powers, M. (1993) "Consequences to the Individual: Data, Collection, Information Use, and Electronic Health Systems." Conference proceedings, "Health Records: Social Needs and Personal Privacy." February 11–12, 79–82.

Powers, M. (1994) "Privacy and the Control of Genetic Information." In *The Genetic Frontier: Ethics, Law, and Policy*, M.S. Frankel and A. Teich, eds., 77–100. Washington, D.C.: American Association for the Advancement of Science.

Powers, M. (1997) "Justice and Genetics: Privacy Protection and the Moral Basis of Public Policy." In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*, M. Rothstein, ed., 355–368. New Haven: Yale University Press.

Rachels, J. (1975) "Why Privacy is Important." *Philosophy and Public Affairs* 4(4) (Summer), Princeton University Press, Reprinted in *Philosophical Dimensions of Privacy: An Anthology*. F.D. Schoeman, ed. Cambridge University Press, 1984.

Regan, P.M. (1995) *Legislating Privacy: Technology, Social Values and Public Policy*. Chapel Hill: North Carolina University Press.

Reidenberg, J.R. (1989) "Privacy in the Information Economy: A Fortress or Frontier for Individual Rights?" *Federal Communications Law Journal* 44(2):195–243.

Reilly P., M.F. Boshar, and S.H. Holtzman. (1997) "Ethical Issues in Genetic Research: Disclosure and Informed Consent." *Nature Genet* 15:16–20.

Relman, A. (1980) "The New Medical-Industrial Complex." *New England Journal of Medicine* 303:963–970.

Rothstein, M. (1997) "Genetic Secrets: A Policy Framework." In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*, M. Rothstein, ed., 451–495. New Haven: Yale University Press.

Rule, J. (1997) "Our Data, Our Rights." *Washington Post*, October 7, A17.

Rule, J., D. McAdam, L. Stearns, and D. Uglow. (1980) *The Politics of Privacy*. New York: Elsevier North Holland, Inc.

Secretary of Health and Human Services. (1997) *Confidentiality of Individually-Identifiable Health Information: Recommendatons of the Secretary of Health and Human Services, pursuant to section 264 of the Health Insurance Portability and Accountability Act of 1996*. September 11, 1997.

Siegler, M. (1982) "Confidentiality in Medicine: A Decrepit Concept." *New England Journal of Medicine* 307:1518–21.

Simmel, A. (1968) *International Encyclopedia of the Social Sciences*, s.v. "privacy."

Stephenson J. (1996) "Pathologists Enter Debate on Consent for Genetic Research on Stored Tissue." *JAMA* 275:503–504.

Stipp, D. (1997) "Gene Chip Breakthrough." *Fortune*, March 31, 1997.

Walters, L. (1982) "Ethical Aspects of Medical Confidentiality." In *Contemporary Issues in Bioethics*, 2nd ed., T.L. Beauchamp and L. Walters, eds., 198–203. Belmont, Calif.: Wadsworth. First published in *Journal of Clinical Computing* (1974) 4(1):9–20.

Warren, S. and L. Brandeis. (1890) "The Right to Privacy." *Harvard Law Review* 4:193.

Weir, R. and J. Horton. (1995) "DNA Banking and Informed Consent: Part 2." *IRB: A Review of Human Subjects Research* 17(5,6):1–8.

Westin, A. (1967) *Privacy and Freedom*. New York: Atheneum.

Workgroup for Electronic Data Interchange. (1992) *Report to the Secretary of the U.S. Department of Health and Human Services*. Washington, D.C.: Workgroup for Electronic Data Interchange.

AN ETHICAL FRAMEWORK FOR BIOLOGICAL SAMPLES POLICY

Commissioned Paper

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I. Introduction

The scale of the practice. Upwards of 290 million human biological samples are currently stored in the United States, chiefly in pathology archives, blood banks, researchers' collections, and state public health department newborn screening facilities.[1] Some have been stored for decades, millions more will be gathered and stored in the next year, and tens of millions more in the next decade.[2] Samples include blood, bloodspots on laboratory paper, saliva, and tissue from virtually every part of the human body. The individuals who are the sources of the samples are identifiable in some cases, not in others. Some samples were gathered during procedures (such as surgery) in which some form of informed consent was attained, some were not. Even where there was informed consent for the procedure that produced the sample, often there was no informed consent to the storage of the sample, nor to some or any possible future uses of it after storage. In many, perhaps most cases, individuals had no idea that their sample was being stored, nor any inkling that it might be used for a variety of research purposes, by a variety of individuals.

For example, since 1970 blood has been taken from almost all persons born in hospitals in the United States to prepare bloodspots for purposes of screening for genetic disorders. In some states, public health departments keep these bloodspots indefinitely, in others they are discarded after five years. There is no uniform policy covering all states. Most individuals do not know that these samples were taken or that they are kept after screening is done or that they could be used for an indefinite number of purposes in the future, including a complete characterization of the individual's genome.

Special concerns about genetic analysis. Not just bloodspots, but any sample containing cells from any part of the body can be subjected to genetic analysis. This is because every nucleus of every cell of the body contains the complete genetic code of the person from whom the sample was taken. It is in part because of the seemingly limitless uses of genetic analysis—and the concerns that some possible uses evoke—that currently there is much interest in the ethical aspects of the practice of gathering and storing human biological samples that may be used for research.

The most obvious and tangible risk is that of insurance or employment discrimination on genetic grounds. There is also the risk of stigma or of adverse psychological reactions to information which the sample contains, given the special significance which genetic disorders has for some people. Nevertheless, as we shall see, the ethical issues raised by the practice of collecting biological samples do not depend, for the most part, on the possibility of genetic analysis, even if concern about "genetic privacy" may have fueled much of the current interest in the subject.

Framing the ethical issues. It is tempting to frame the complex set of issues involving biological samples as a simple conflict between the value of scientific research, on the one hand, and the rights to privacy and confidentiality, on the other. This way of formulating the issues is, however, quite unilluminating. The problem with this formulation is not simply that virtually all parties to the discussion acknowledge both the value of scientific research *and* the importance of privacy and confidentiality. More importantly, this simple formulation starts where ethical analysis should end, with the invocation of rights to privacy and confidentiality.

Formulating the issues *initially* in terms of rights is unfortunate in two respects. First, rights-language has a rather unyielding quality. There is a tendency to assume that if someone has a right to something, then that is the end of the matter. More specifically, there is a tendency to regard a clash between a mere value (such as scientific progress) and a right as an unequal one, whose resolution in favor of the right is clear and uncontroversial. Second, from the standpoint of ethical analysis, statements about what rights people have are better regarded as conclusions of complex strands of moral argument, rather than as starting points. It is necessary to dig beneath slogans about rights to privacy and confidentiality (or rights of individual autonomy) to unearth the *morally legitimate interests* that rights serve to protect.

Once a statement about what rights people have is properly supported by showing the importance of the interests the right protects, *then* that statement can be used to derive further moral conclusions. For example, if an individual has a right to confidentiality, then it follows that substantial protections ought to be provided to limit the access of other persons to information about that individual, and from this it follows in turn that the mere fact that allowing others access to that information would contribute to some social good does not itself establish that they should have access. Before these implications of the statement that the individual has a right to confidentiality can be drawn, however, it is necessary to establish that he has the right. In that sense, rights-statements are conclusory even though, once established, they can serve as premises from which further moral conclusions can be drawn.

Privacy and confidentiality are sometimes characterized as follows: privacy consists of appropriate limitations on access to the person as a physical being, especially to exposures of the body that are considered to be embarrassing or demeaning; confidentiality consists of appropriate limitations on access to information about a person. In order to ascertain what the *appropriate* limits are in both cases and hence what the contours of the rights to privacy and confidentiality are, it is necessary to articulate the various legitimate interests that are threatened by exposures of the body and by the dissemination of information about persons.

Rights as protectors of morally important interests. Even a sketch of a full-blown theory of moral rights is beyond the scope of the paper. Nevertheless, it is necessary to say something to elaborate the suggestion that we think of rights as protectors of morally legitimate interests. More specifically, rights-statements are assertions that certain interests are of such importance from a moral point of view that they deserve especially strong protections. The implication is that the interests in question are of such moral weight that they ought to be protected even if this means overriding what are otherwise typically taken to be powerful reasons for action.

Thus, even if the fact that doing something would maximize social utility is generally a very good reason for doing it, some interests are so important that they should be treated as being immune from calculations of utility. For example, when we say that there is a right to free speech, part of what we mean is that people should be allowed to express their views even if repressing them could be shown to produce more utility overall.

Notice that a rights-statement as it stands makes an assertion of what the moral priorities are but does not itself back up that assertion. Rights-statements by themselves, being conclusions of moral arguments rather than arguments, at best only indicate, in a rough way, what the interests are that deserve special protections. Thus, a statement that there is a right to free speech implies that by protecting speech certain morally important interests will be protected, but much more will need to be said both to make the import of the rights-statement clear (to show when speech should be protected and when it should not) and to give us some reason to accept the assertion it makes.

To clarify and justify a rights-statement, two things are needed: first, to identify the relevant interests, and second, to show why they are of such moral importance that they deserve the especially strong protections rights provide. In simplest terms, doing the latter means demonstrating that the interests in question play a significant role in determining whether individuals are able to flourish—to live the sort of lives that are appropriate for persons.

Once we dig beneath rights-talk to the morally important interests that rights protect, we are in a better position to appreciate that the ethical issues concerning biological samples are a matter of balancing interests. This crucial fact is obscured if we begin with talk about rights to privacy and confidentiality (or rights to freedom of scientific inquiry, for that matter), because assertions about rights presuppose that the proper balancing of interests has already been achieved.

Once it is understood that rights serve to protect interests, rights-talk becomes less mystifying. Rights no longer seem to be ghostly, abstract entities (things that go “ought” in the night). Instead, rights-talk is seen to be shorthand for assertions about what the moral priorities are, assertions grounded ultimately in the conditions of human flourishing.

This is not to say that there is no such thing as a right to privacy or to confidentiality. There are legal rights that go by these names. And we may even say that there are moral rights to privacy and confidentiality at the outset of the analysis, so long as we admit that this tells us very little, except that there is a presumption that certain interests ought to receive special protections through safeguarding privacy and confidentiality and that whatever the proper balance of conflicting interests turns out to be it must reflect this presumption. Invoking rights to privacy and confidentiality tells us nothing about the proper scope and limits of those protections, just as talk of a right to freedom of expression itself tells us nothing about the scope and limits of that right.

In order to determine the proper scope and limits of the right to freedom of expression, we must articulate and evaluate those interests that are at stake when expression is limited. These include, preeminently, the interest in being able to criticize government and thus hold it accountable, and the interest in moving closer to the truth through the free exchange of ideas. Similarly, we must determine what interests are served by the preservation of privacy and confidentiality.

For these reasons, the strategy of this paper will be to begin the analysis by cataloguing the members of two sets of interests that can come into conflict: those that weigh in favor of restricting access to biological samples (and hence to the information they contain) and in favor of giving the source of the sample more control over what is done with the sample, on the one hand, and those that weigh in favor of wider access to the sample, even though this means less control over its uses by the source. At the end of the analysis we may conclude that individuals from whom samples are taken have a *moral* right to privacy and confidentiality concerning those samples, but this will only be shorthand for a much more complicated ethical conclusion about how these two sets of interests ought to be balanced. If the analysis is successful, we will be in a better position, however, to engage in a reasoned debate to determine what the contours of the *legal* rights to confidentiality and privacy ought to be in this area.

After cataloguing the various interests on both sides of the ledger, we can then try to ascertain the adequacy of the requirement of *informed consent* as a means of achieving an appropriate balance of these interests. One conclusion that will emerge is that it is a profound mistake to proceed as if some version of an informed consent requirement by itself can provide protection for all the legitimate interests at stake in the practice of gathering and using biological samples. Instead, what is needed is an institutional division of labor in which informed consent plays an important but limited role. Furthermore, I will argue that attempting to safeguard against all *possible* harms to those who provide samples by an elaborate informed consent requirement is not only doomed to failure but would also be unconscionably costly and an excessive constraint on scientific research.

Interests, well-being, and harms. Before cataloguing the conflicting interests, we must be clear about what we mean by an interest. Put most simply, an interest is an ingredient in someone's well-being. If your interest is advanced, then, other things being equal, your are better off; if your interest suffers a setback, then, to that extent you are worse off.[3] Peoples' interests vary widely, but there are some interests that are basic to us all. The doctrine of human rights can best be understood as an attempt to identify these fundamental universal interests and to proclaim that they deserve the most stringent protections.

We can also distinguish between *welfare interests and ulterior interests*.[4] Welfare interests include access to food and shelter, as well as physical security, liberty of action, and access to information. Ulterior interests include the various ends that individuals give high priority to as they arrange their lives, choose an occupation, and plan for the future. Welfare interests are a very important ingredient in a person's flourishing, because if they are not secured she will not be able to pursue her ulterior ends. Nevertheless, once a person's welfare interests are secured, the pursuit of ulterior ends becomes not only possible, but extremely important to that person. Later we will see that the distinction between welfare interests and ulterior interests helps illuminate the full range of interests at stake in choosing a policy for regulating the gathering and uses of biological samples.

Given this understanding of what an interest is, a *harm* can be defined as a setback to an interest.[5] Typically, when rights-statements are made, what those who make them are most keenly conscious of is the potential for

harm if the right in question is not acknowledged and respected. Hence we will focus chiefly on the possible harms that persons can suffer if others gain information from their biological samples or use those samples in various ways. In doing so, we will bring to the fore the important moral concerns that lie behind the notions of privacy and confidentiality.

Biological sample information. Gathering information about an individual through the taking of a medical history or by interpreting the inscriptions on an electrocardiogram may have a different significance for the individual or others than biopsying a piece of tissue or drawing blood. But from the standpoint of many of the interests at stake in the way biological samples are used, what is most import is the information the sample can yield, not the physical embodiment of the information.

As technology advances, automated analysis of samples (for genetic and other information) may reduce significantly the need to store samples. Nevertheless, as we shall see, most of the ethical issues would remain, because they involve the uses of the information derived from the samples, not the sample itself. For this reason, I will use the term *biological sample information* to cover both the sample itself and the information that can be extracted from it, noting that once the sample has been taken, in most cases it is the information that matters.

II. Interests That Weigh in Favor of Restricted Access and Substantial Control by the Source of the Sample

Avoiding insurance and employment discrimination.[6] The potential harm of insurance and employment discrimination has already been mentioned above. It is worth noting that there is an unfortunate tendency in the media, and even sometimes in the bioethical literature, to suggest that it is only genetic information that carries the risk of discrimination. This is not the case. Persons known to have health problems are vulnerable to discrimination, regardless of whether they have genetic disorders or genetic susceptibilities to disease. Being listed in a tumor registry or replying truthfully to questions about one's family medical history may be just as risky as having a positive test for a genetic disorder in one's medical records.

The actual extent of insurance and employment discrimination on genetic grounds is a matter of speculation, because most of the evidence comes from surveys in which individuals say whether they believe they have suffered discrimination, with little or no independent check on the accuracy of their perceptions.[7] Moreover, the risk exists only for insurance policies whose issuance is conditional on medical underwriting, and most Americans who have private health insurance get it through large group policies in which there is no medical underwriting. Nevertheless, it is clear that insurance and employment discrimination do occur and that when they occur the results can be devastating for the individual.

It is also important to emphasize that the risk of discrimination is not an inevitable effect of the existence of information about illness or susceptibility. It is an artifact of a particular institution, namely, a private insurance market in which most medical insurance is employment-based and in which private insurers compete in part by attempting to avoid insuring costly (and therefore sick) individuals. If this institution were abolished or modified in certain ways so as to reduce the risk of discrimination, then to that extent the weight of the interest in avoiding discrimination would diminish and with it the case for restricting access to biological sample information in order to protect the interest in avoiding discrimination. (It is also important to emphasize, however, that discrimination in life insurance and disability insurance occurs in other countries that do not rely on private insurance for health care as heavily as the United States does.)

From this it follows that the specific contours of the rights to privacy and confidentiality or of other safeguards against insurance and employment discrimination cannot be ascertained once and for all, independently of institutional context. In a society like ours, in which there is a powerful institution that poses a significant threat of discrimination, greater restrictions on access to biological sample information will be needed, other

things being equal, than in a society in which different institutions for financing health care eliminate the possibility of discrimination. If federal and state laws prohibiting insurance and employment discrimination are passed and effectively implemented, the balance between interests that weigh in favor of more restricted access and greater source control and those that weigh in favor of freer access and more permissive uses of biological samples will shift accordingly.[8] Whatever policy is now developed must be subject to revision in the future.

Avoiding stigmatization. Even if an individual is not denied insurance or employment, he may suffer the harm of stigmatization. Although there is an unfortunate tendency to focus only on the stigmatization that results from being identified as having a genetic disorder, other types of illness can be equally or even more stigmatizing (e.g., sexually transmitted diseases, disfiguring diseases, and cancer, at least until very recently).

Stigmatization is closely related to discrimination; indeed it can be argued that it is a species of discrimination. Like stigmatization, it is a form of *exclusion* by labeling. In the case of stigmatization, however, there is usually at least an intimation of unwholesomeness, blame, or taint (as in the archetypal stigmatum, the Biblical "mark of Cain"). Some, but not all, forms of discrimination include this feature.

Perhaps the most familiar type of stigmatization is that which is imposed upon an individual from without, by the judgments and perceptions of other individuals. However, we may also speak of self-stigmatization. In part because individuals are so often deeply influenced by the attitudes of their fellows, they may internalize stigmatization.

We have already seen that the weight that should be accorded to the interest in avoiding insurance or employment discrimination varies with the magnitude of the risk and hence with the institutional arrangements that either magnify or diminish that risk. Similarly, the weight that should be accorded to the interest in avoiding stigmatization varies with cultural attitudes toward disease. For instance, to the extent that the public becomes better educated about the nature (and universal prevalence) of genetic susceptibility to disease, the risk of stigmatization on genetic grounds may diminish. And as with insurance and employment discrimination, the actual risk of stigmatization associated with various types of information contained in biological samples, as opposed to the mere possibility that stigmatization, is unknown.

Avoiding ascriptive (group identity-based) harms. Closely related to discrimination and stigmatization is another potential harm that individuals may suffer because of perceived links between medical information about them contained in a biological sample and what may be called their ascriptive (or group-based) identity. A concrete example will make this concept clearer.

African Americans typically suffer certain harms because they are identified as African Americans: others often perceive African American individuals through the distorted lens of negative racial stereotypes. The harm of negative racial stereotyping is a harm to individuals, but it befalls individuals because of their ascriptive group identity. The term *ascriptive* here indicates that the identity in question is assigned by others, independently of the choice of the individual thus identified.

Individuals who are vulnerable to ascriptive identity harms have a special interest in avoiding situations in which information obtainable from their biological samples may contribute to the reinforcement of harmful group stereotypes, not only because they themselves may be harmed but also because they may wish to avoid harm to other members of their ascriptive group. For instance, genetic information gleaned from biological samples might be used in research on the role of genotype in criminal behavior or in intelligence. In the past, such research has sometimes both embodied and been taken to validate negative racial stereotypes.

Avoiding familial conflict. In some instances, biological sample information, like other medical information, may be a source of intrafamilial conflict. For example, genetic analysis of a blood sample may reveal that the husband is not the father of a child. Or, in some cultures, if a family finds out that the prospective spouse

of one of their members has a genetic disorder, they may attempt to prevent the marriage from taking place. Regardless of whether the beliefs on which they are based are rooted in mistaken views about genetics or indefensible assumptions about responsibility for disease, the conflicts they can generate and the resulting harms are quite real.

Avoiding uses of biological samples that the source regards as impermissible per se. So far, we have concentrated on the harms that certain uses of the information that can be extracted from biological samples can produce or to which they can contribute. Individuals can also have an interest in the uses of the sample. For example, for religious or other reasons, some people may believe that DNA from samples should not be used for producing human beings by cloning because they believe that human cloning is wrong per se; or they may simply not want *their* DNA to be used for this purpose.

There are three factors that make it difficult to know how much weight this interest ought to be given in designing an ethically sound and feasible system for regulating practices concerning the uses of biological samples. First, at present no one knows the full range of possible uses for biological samples in the future; all we know is that molecular biology and genetic technology are evolving very rapidly and that there will be an expanding range of possibilities, including opportunities for manipulating genes. Consequently, we cannot now ascertain how likely it is that at some point in the future someone's biological sample might be used in ways that he would find inherently wrong. Moreover, our uncertainty here is not just a function of our ignorance of the technical possibilities; we also do not know how effectively or in what ways future cultural attitudes and regulations (e.g., concerning experiments on human subjects) will constrain possible uses of biological samples, independently of any control that might be exercised by the individual who is the source of the sample.

Second, in some cases, individuals' fears about how their tissue might be used in the future may be based on grossly mistaken assumptions. For example, at least part of the negative response to the possibilities of producing humans by cloning seems to be based on the fallacy of genetic reductionism (the false assumption that a genetic identity is personal identity). Of course, respect for autonomy may argue for giving some weight to an individual's preferences even when they are based on patently false beliefs, but nonetheless, the fact that a preference is based on patently false beliefs should surely reduce its moral weight, other things being equal. In other words, people can be mistaken about what is in their interest, and the strongest ground for devising constraints on the use of stored tissue is that this is needed to protect important interests, not to indulge individuals' clearly mistaken perceptions about their interests. In some cases, an individual's preference that his biological sample not be used for certain purposes may not be based on false factual assumptions and may reflect stable values and commitments. Here the individual does have an interest in avoiding such uses of his biological sample.

This brings us to the third obstacle to ascertaining the weight of the interest in avoiding certain uses of one's stored biological sample: the fact that many people are uncertain not only about what uses will become possible in the future, but also about what their own *evaluations* of those uses will be. These future evaluations cannot now be predicted with any reliability for two reasons. First, they will be "path-dependent"—shaped by our evolving reactions to a particular series of technological innovations developing over time—and we cannot predict the series of technological developments. Second, our evaluations of technological options in the future will depend in part upon the social context in which the technology would be deployed, but we cannot now know what that social context will be.

What does seem likely is that in some cases what we would now regard as wrong or at least problematic we may regard as acceptable in the future, when society has changed and we have changed with it. Thus, 20 years ago many people had negative or ambivalent attitudes toward the first "test-tube baby," but now *in vitro* fertilization and a number of other subsequent reproductive technologies are not regarded as ethically problematic by many people.

Concerns about profits, distributive justice, and "commercialization." We come now to a cluster of interests, some of which weigh in favor of restricting access to or uses of biological sample information, and others which concern the distribution of the financial gains that may be produced through the uses of samples.

Some individuals and groups have sought to share in the profits that are generated by patentable biologic inventions in whose development the use of their biological samples played a role. Perhaps the most famous case is that of John Moore, who claimed ownership of a cell line that was developed from tissue from his spleen.[9] The California Supreme Court rejected Moore's claim of ownership and hence any claim to a portion of the profits derived from uses of the cell line, but it did affirm that the physicians who used his spleen tissue to the develop the cell line had a duty to disclose this to him.

The two parts of the ruling mark an important distinction between two questions: The first is whether the individual is entitled to some or all of the profits gained from a product in whose development her biological sample played a role. The second is whether the individual is entitled to disclosure of the fact that her biological sample may be used to develop a profitable item and whether she is allowed to refuse to allow such uses. These questions implicate two distinct interests: the financial interest in profiting from the use of one's sample and the interest in determining whether one's tissue is used in a profit-generating endeavor. Though less tangible than the financial interest, the second interest may be extremely important for some individuals, for it may be rooted in their most fundamental values about distributive justice.

Strictly on economic grounds, there may be a case for not having a property rights system that gives individuals like Moore a legal right to a share of the profits of whatever products are developed from processes in which their samples played some role. For one thing, most of the products developed from biological samples are not uniquely dependent upon the particular sample from which they are developed. (What was needed were human spleen cells from a person with a certain type of cancer, not necessarily Moore's spleen cells.) And given the well-known relationship between supply and demand, this means that in most cases no particular individual's biological material will be valuable enough to generate a claim to a significant share of the profits and to justify the special property laws that would be needed to secure that claim.

However, there may be some cases where something profitable can be developed only through the use of a rather rare genetic mutation. (For example, it has been reported that there is a family in Northern Italy that has a mutation that protects against atherosclerosis, an "anti-cholesterol gene." Or, if it turns out that a small minority of the population has a natural immunity to HIV infection, this characteristic might be extremely valuable for the development of an HIV vaccine.) Whether or not it would be desirable to recognize a legal property right in such cases will depend upon the proper balancing of a complex array of factors and above all upon whether there is good reason to believe that individuals with extremely valuable genes will lack sufficient incentive to allow them to be used for producing significant benefits for large numbers of people without the sort of financial reward which such a property right would confer.

At this point it might be objected that it is misleading to talk only of the interest that individuals have in a share of the profits derived from uses of their biological samples and of whether this interest should be recognized by a legal property right. Individuals have not only an interest, but a property *right*, because their tissues, blood, and DNA are their property if anything is. And indeed, some moral philosophers have assumed or argued that a person's body is his property, in the sense of a moral property right.[10]

This objection is mistaken for reasons noted at the outset of this analysis: Statements about what moral rights people have, including moral property rights, must be understood as conclusory. Hence the statement that an individual has a moral property right to his biological material is to be understood as shorthand for the assertion that there are morally legitimate interests that require special protections and that these protections can best be achieved by allowing the individual control over the uses to which the sample is put. But, of course, there are many possible modes and degrees of control. Only by weighing the legitimate interests that

speak in favor of various forms of sample source control against the morally legitimate interests that speak in favor of allowing others freer access and a wider range of possible uses of the item in question, can we decide which bundle of forms of control among the indefinite range of possibilities is morally preferable. At this stage of the analysis, the most that can be said is that is that a person may have a legitimate property *interest* in the distributive effects of the uses of her biological sample. At present, not enough is known about the probable future value of particular configurations of genes to determine what sort of legal property rights in them would make moral and economic sense.

Avoiding dignatory harms. Each person has an interest in being treated as a person—as a moral agent with her own values, preferences, commitments, and conception of the good. In Kant's terminology, each of us has an interest in not being treated as mere means, or, more positively, in being treated with the dignity and respect befitting persons. Part of the moral justification for the requirement of informed consent is to ensure that patients and research subjects are treated respectfully as agents, not as passive objects to be used for the ends of others.

First and foremost, however, the requirement of informed consent protects individuals from nonconsensual invasions of their bodies. Because the right of informed consent, which includes the right to refuse treatment, allows the individual to decide whether the risk of these harms is worth taking, it can also protect individuals from other tangible harms that may result from the bodily invasion, if the individual refuses to give consent.

It is important to notice that these harms are not restricted to the potential but usually highly unlikely harms that might occur from techniques such as venipuncture or swabbing cells from the inside of the cheek. The point, rather, is that if one allows others access to one's body for these purposes, one is thereby in a position of vulnerability to other unwanted and more dangerous intrusions. For this reason, it is somewhat misleading to say that the only physical harm from which one is protected by informed consent for a simple procedure such as venipuncture is the extremely remote possibility of harm from the needle stick (beyond the unpleasant momentary sensation of the needle itself).

Even if informed consent was originally primarily a protection against physical harm, it has come to be used as protection against a broad range of nonphysical harms lumped under the heading "psychosocial." Thus, for example, Institutional Review Boards (IRBs) strive to ensure that informed consent procedures for psychological or other social science research protect individuals from being deceived and manipulated in ways that are demeaning or threatening to a person's sense of self-worth or that in some other way treat him or her as a mere means.

A strong case can be made that current practices concerning biological samples often fail to treat persons with due respect because they systematically mislead regarding why samples are being taken and their uses. It is true that the phlebotomist who draws the blood sample may not know that the sample will be stored indefinitely and may be used in any number of ways in the future and hence may have no intention to mislead the sample source. Nevertheless, the institutionalized practice of storing biological samples for future uses is one for which those who control the practice are responsible, and this practice, as we have seen, often keeps sample sources in the dark as to what may happen to the sample. Given the various interests already listed above, a practice that is misleading in this way fails to show proper respect to sample sources.

The most obvious way to correct this defect is to modify the practice by informing individuals that their biological samples will or may be used for a wide range of purposes where this is not already done. Whether or not in addition to such *disclosure*, specific or blanket *consent* is required in order to show proper respect for sample sources is a question taken up in section IV. The main point to be appreciated here, however, is that we should not simply assume that informed consent is the only means for protecting individuals against the dignatory harm of being deceived or misled. The alternative of disclosure ought to be seriously considered.

Avoiding invasions of privacy and confidentiality per se. Persons have an interest in not being subjected to unnecessary exposure of the body to the view of others and in not having embarrassing or intimate facts

about themselves disclosed, independently of whether such exposure or disclosure threatens *other* interests they may have or produces *other* harms. For example, one has an interest in others not knowing certain intimate information about one's reproductive history and in not having one's body unnecessarily exposed to view, even if these breaches of privacy and confidentiality cause no tangible harm, for example, by making one the subject of disparaging gossip.

This interest, which might be called the interest in privacy and confidentiality per se, is distinguishable from the various other interests catalogued above that serve to ground a right to privacy. It is closely related to the interest in avoiding dignatory harms, since in most if not all cultures, some modes of exposing the body, in some contexts, are thought to be undignified and demeaning, and some intimate information is thought to be embarrassing.

It is this interest in privacy and confidentiality per se that is invoked when a patient or subject complains that the setting in which she is examined or in which she answers questions about her personal medical history is "too public" or "lacks privacy." Unlike some of the interests already noted, the interest in privacy and confidentiality per se, is at stake as much in the process by which the sample is collected as in what happens to the sample after collection.

Confidentiality. For the most part, once the biological sample is removed from the body, it is the interest in confidentiality rather than the interest in privacy that is at issue. Etymologically the term *confidentiality* means *with trust*. Thus we speak of preserving the confidentiality of certain information, or of keeping confidences, of those we trust. With some risk of oversimplifying, confidentiality may be thought of as a kind of second best to privacy. In some contexts, medical and otherwise, persons must expose themselves to the gaze of others or divulge sensitive information to them in order to gain certain benefits, and the best they can hope for is that there will be no unnecessary or otherwise inappropriate viewing or disclosure to others and that those who gain this intimate knowledge will not use it detrimentally.

Sources of biological samples have an interest in confidentiality—in being able to trust that access to their samples and to the information they contain will be appropriately limited. But what counts as an appropriate limitation will depend upon a complex weighing of conflicting legitimate interests. Once again, we see that beginning with slogans about the right to confidentiality does not carry us far. To say that there is such a right is simply to assert that the interest in limiting intimate exposures is a high moral priority and as such warrants special protections; it does not tell us what the contours of the right are.

Surviving interests. Many existing biological samples were taken from individuals who are long dead, and if any sample is stored long enough it will outlast its source. It might be thought that once the source is dead, there are no interests to protect; but this is not so, for two reasons. First, the deceased source's family or other loved ones may have an interest in what is done with the sample, or members of the source's ascriptive group may have an interest in what happens to it (if, for example, research were done on the sample that contributed to racial stereotyping).

Second, persons can have interests that survive their own deaths. For example, persons ordinarily have an interest in what happens to their children and grandchildren after they themselves die and for this reason plan for the disposition of their estates. Similarly, one can have an interest in the uses to which one's biological sample are put, whether these uses occur before or after one's death. This is especially true if certain uses would be considered impermissible per se, from the perspective of one's deepest, life-long religious or ethical values. From this it follows that if a policy of unrestricted access to samples of deceased persons is to be justified, it cannot be justified on the grounds that no interests are at stake.

The "autonomy" interest in control per se. It might be argued that there is one remaining interest that weighs in favor of greater source control over access to biological samples that also matters and that is also served by informed consent requirements. This is simply the interest in being able to decide what happens to the sample, independent of any instrumental value that being able to decide might have for protecting one's

privacy or dignity, preventing discrimination, enabling one to determine who profits from the sample, etc. Thus it might be said that, independently of whatever functions requiring informed consent may have, a proper consideration of the individual's autonomy weighs in favor of allowing the source maximal control over his sample and that this in turn requires specific consent for particular uses of the sample.

However, it is a mistake to assume that whenever we increase a person's range of choices we thereby enhance her autonomy. In some cases, increasing the range of choices may actually diminish a person's ability to act autonomously, especially when the information needed for a responsible choice is not available.[11] Furthermore, it is also a mistake to assume that whenever we do not enable an individual to exercise choice over some matter we thereby infringe her *right* to autonomy or that we even slight a legitimate or important interest in autonomy. Not every possible choice counts so far as autonomy is concerned; in general, whether the ability to make a choice represents a legitimate autonomy interest (much less an interest that deserves the protection that rights accord) will depend upon how that choice is related to the individual's other interests, to her conception of herself and of what is important given her stable priorities in life. Consequently, what might be referred to guardedly as the "interest in autonomy per se" might more accurately be called the interest in *choice*, to signal that not all choices bear importantly on an individual's autonomy. And once it is understood that the mere ability to exercise choice over the disposition of one's biological sample is not to be confused with a legitimate interest in or a right to autonomy, it is not plausible to argue for a requirement of specific consent on the ground that it enhances individual autonomy, especially given the weight of the interests that weigh against the imposition of such an onerous and costly requirement.

III. Interests That Weigh in Favor of Fewer Restrictions on Access and Less Sample Source Control

The societal interest in the growth of scientific knowledge. Not everyone in our society values the growth of scientific knowledge, but most do, and more important, most if not all will benefit from it in some way or other. To that extent we can speak of a societal interest in the growth of scientific knowledge.

Whether or not the advance of scientific knowledge as such is valuable independent of the benefits that the application of this knowledge brings depends upon the resolution of deep and controversial issues in the theory of value that lie well beyond the scope of this paper. According to some views, the quest for knowledge is good in itself, and is an important ingredient in human good independent of its beneficial effects. According to other views, some individuals (especially scientists) may value scientific knowledge for its own sake, but there is no societal interest in scientific knowledge as such independent of the goods is application brings.

The instrumental benefits of the growth of scientific knowledge are obvious and manifold. Before proceeding to some concrete illustrations of benefits gained from the use of stored biological samples, it may prove useful to sketch a more general characterization of the value of progress in biomedicine. Scientific knowledge makes possible scientific health care, and scientific health care serves several basic human interests: the interest in avoiding pain and suffering, in restoring or preventing the loss of opportunities that depend upon normal functioning, in the avoidance of unwanted death, and in obtaining access to information about one's condition that can enable one to plan one's life more effectively or which may simply allay worries about one's condition.[12]

The weight that should be accorded to the societal interest in benefits of applied biomedical science will depend in part upon how widely these benefits are distributed. If there are gross inequalities in the distribution of benefits, it is misleading to speak of the common interest in medical progress. Consequently, the case for tolerating greater risks to the interests of sample sources for the sake of the societal interest in medical progress is weakened if some people, including some who provide samples, lack access to important health care benefits because they cannot afford them. Nevertheless, if the benefits of medical progress accrue to a large number of people, we may still speak of a societal interest even if not all benefit or not all benefit equally.

The range of medical benefits already obtained through the use of stored biological samples is extremely impressive. Here only a few instances will be mentioned to convey their importance and diversity.[13] 1) In the late 1960s, the study of samples of tissue from an unusual tumor of the vagina led to the discovery that a nonsteroidal estrogen hormone diethylstilbestrol (DES), then commonly given to women during pregnancy, is carcinogenic. 2) During the same decade a series of studies on tissue samples of precancerous lesions of the uterine cervix led to the routine use of the Pap smear, which has played an important role in the early diagnosis and more successful treatment of this type of cancer. 3) Analysis of tissue from autopsies of persons in certain occupations, such as chemical manufacturing and uranium mining, has established causal links between exposure to environmental substances and certain diseases, including a cancer of the liver known as hepatic angiosarcoma and cancer of the bronchial epithelium. 4) The analysis of autopsied lung tissue from smokers played a major role in establishing that smoking causes lung cancer, that the risk of cancer increases with the duration of exposure to the chemicals contained in cigarette smoke, and that precancerous changes in the bronchial epithelium can be reversed by cessation of smoking. 5) In 1953, autopsies of young American soldiers killed in the Korean conflict revealed that atherosclerosis begins at a much earlier age than was previously thought and that blockage of arteries can be far advanced in the absence of symptoms; this research contributed to findings concerning diet and exercise which have had a major public health impact in this country, evidenced by a significant reduction in coronary artery disease.

In many instances, access to stored biological samples collected over a long period has significant advantages over the exclusive use of new research protocols. Especially when the disease process under study takes place over years or even decades, studies that rely only on newly collected tissue may be very costly and produce results much less quickly than studies of stored samples.

The interest that some individuals have in contributing to scientific and medical progress. Some individuals have a preference, or in some cases a moral commitment, to helping to further scientific and medical advances. Frequently, the preference or conviction will be more specific—for example, to make some contribution toward developing a cure for a particular disease, perhaps one which has adversely affected oneself or members of one's family. Because of the important role which biological samples have played and can be expected to play in the future in scientific and medical progress, such interests generally weigh in favor of wider access to samples, other things being equal.

The interest in enhancement through biotechnology. Until recently, with a few exceptions such as cosmetic surgery, health care has been concerned primarily with preventing or ameliorating harms caused by disease and disability. In the future, however, genetic interventions as well as developments in psychopharmacology may make possible *enhancements* of normal human functioning. For example, it may eventually become possible to manipulate genetic material so as to raise the upper bound of some aspects of cognitive functioning, by enhancing memory or the speed with which information can be processed by the human brain; or augmentation of the normal human immune system may become possible.[14] Whether or to what extent we can speak of a substantial societal interest in enhancements made possible by the growth of scientific knowledge will depend not only upon whether these enhancements are really beneficial, all things considered, but also upon whether they will be widely available or available only to the rich.

Preventing disease and disability for identifiable individuals, present and future. In addition to contributing to the prevention of harms to large numbers of people through advances in the prevention and treatment of disease and disability, freer access to biological sample information can make it possible to intervene directly to prevent harm to identifiable individuals in some instances. For example, if the source of a sample can be identified, then he she can benefit from successful treatment breakthroughs. Or, if research shows that persons with a particular genotype have a high susceptibility to some serious disease, then it may be possible to intervene earlier with better results, if those individuals can be identified from stored samples. In some cases, the

individual who benefits may be the offspring of the sample source as, for example, when a genetic disorder that can be successfully treated can be predicted on the basis of information contained in the sample; in other cases it may be a sibling or other relative.

Interests in reproductive freedoms. Individuals have several important reproductive interests, including being able to have children if they wish and having control over when they have children and how many they have. They also have an interest in exercising some control over the characteristics of the child they have, for the sake of the child himself or herself, but also in part because these characteristics may affect their own well-being and that of their other children.

Few would question that prospective parents have a legitimate interest in whether the child they bring into being is spared avoidable diseases or disabilities. Whether, or to what extent they also have a legitimate interest in determining other characteristics, such as height, eye color, or cognitive abilities, is more controversial. But in general, the more their control over the characteristics of the child can be justified by appeal to the interests of the child herself, rather than simply to the interests or preferences of the parents, the stronger the case for protecting the parents' interest in exercising this control.[15]

In coming years, research on biological samples will most likely increase dramatically the range of reproductive alternatives available, furthering in significant ways interests in various reproductive freedoms. Not all of the interests served will be "medical" interests, in the sense of interests in the prevention or cure of diseases, but in many cases they will be important interests nonetheless. To invoke a distinction noted earlier: Research on biological samples not only serves peoples' welfare interests by preventing disease and disability, it may also serve their ulterior interests, so far as these include a conception of whether to have children, when to have them, how many to have, and even perhaps what sorts of characteristics they will have.

Interests of researchers and clinicians. For many researchers and clinicians, the ability to do their work effectively is of central importance to their well-being and their very identity. For such individuals, practicing the most scientifically informed medicine or engaging in cutting edge research is much more than a means of satisfying their welfare interests: It is an ulterior interest that plays a dominant role in how they live their lives. While these interests of researchers and clinicians in having access to biological samples may not be as morally weighty as the societal interests in medical progress, they are nonetheless significant. The pursuit of these interests is not only permissible (in the sense of not being wrong), but indeed laudable, especially when compared to some goals that our society allows individuals freely to pursue. Consequently, any policy regarding the uses of biological samples that impedes the pursuit of the interests of researchers and clinicians owes *them* a plausible explanation of why the restrictions it imposes are needed.

Commercial interests. It is common, and to some extent understandable, to divorce something so lofty as the interest in medical and scientific progress from economic interests, at least in political rhetoric concerning health policy. However, it is a fact, and an important fact about all societies in which biotechnology is flourishing, that economic incentives play a central role. Biotechnology not only produces great medical benefits for individuals and for society as a whole; it also creates wealth and provides productive careers for many people who are not clinicians or researchers. These include not only those involved in the manufacture and marketing of biotechnology, but also investors in biotechnology as well as all of us who benefit from the greater productivity of a healthier workforce. All of these economic interests also must be weighed in the balance, and for the most part they weigh in favor of less restrictive access to biological sample information.

The moral obligation to prevent harm. The analysis so far has focused on interests in an effort to determine which interests are relevant to the justification of moral claims concerning how practices regarding the collection, storage, and use of biological samples should be structured and regulated. The strategy has been to dig beneath familiar statements about rights and the obligations that are their correlatives to identify the important interests they serve to protect. However, it is important to note that there is not only a societal *interest* in

preventing harm to persons, but a *moral obligation* to prevent harm as well—and to determine the relevance of this moral obligation to the ethics of biological samples.

According to some ethical theories, the obligation to prevent harm is not as fundamental or as demanding as the obligation not to cause harm. Such theories maintain that one is not required to bear as high a cost to prevent a harm that one does not cause as to avoid causing a harm. (For example, one might be required to risk one's own life to rescue a stranger one has caused to be in peril, but not required to risk one's life to save a stranger whose imperilment one did not cause.) And there are a number of intuitively plausible reasons to distinguish in this way between the obligation to prevent harm and the obligation not to cause harm.[16] Nevertheless, it would be extremely difficult to defend an ethical view that recognized a fundamental obligation not to cause harm, but failed to acknowledge even a limited obligation to prevent harm.

Moreover, many of the reasons for holding that the obligation to prevent harm is weaker than the obligation not to cause harm disappear or at least become less weighty when we move from the case of the individual to that of society. Clearly an individual cannot be required to prevent all harms to anyone who may be harmed, if only because she lacks the resources to do so. When it comes to the design of institutional schemes, however, it is possible not only to marshal greater resources for preventing harm, but also to target which harms are most important to prevent, to provide more effective yet still affordable harm prevention through a coordinated division of labor, and to distribute fairly the costs of preventing harm. Given that this is so, whatever structures and regulations are developed for biological sample practices should take seriously the obligation to prevent harm, understood as a societal or collective obligation.[17]

Two obvious ways to honor the societal obligation to prevent harm have already been discussed: As a society we can attempt to develop protections for the various legitimate individual interests catalogued above, and we can facilitate the prevention of harm through the application of scientific knowledge in health care. The difficulty, of course, is that in some cases we can reduce the risk of harm to the individual who provides the sample only through safeguards that will impede scientific progress, and to that extent interfere with the use of scientific knowledge to prevent harms, especially those that result from disease.

However, as we have also seen, there is a third way in which how we structure and regulate biological sample practices will affect the prevention of harm: Restrictions on access to stored sample information may make it impossible to prevent harm to particular identifiable individuals, including the sample source. For example, suppose that in order to protect the sample source from possible insurance or employment discrimination we render the sample nonidentifiable. (By "nonidentifiable" here I mean not simply that the source's name is not attached to the sample, but that it is also not possible for anyone to identify the source as an individual by any combination of other characterizations of the sample or the medical record that is linked to the sample.[18]) Later it may turn out that the individual has a particular genetic mutation which makes him highly susceptible to a potentially lethal cancer, but one which can be successfully treated if detected early. If the sample source cannot be identified, then those who have access to the sample will know that there is someone whose life might be saved if he could be identified. An opportunity to prevent a very serious harm will have been lost, and perhaps lost in order to reduce what may be an already relatively low risk of insurance or employment discrimination. Furthermore, the opportunity to contact relatives of the sample source who are at risk for the same genetically based disease will also be lost.

IV. The Limitations of Informed Consent

A common assumption among many participants in the debate about biological samples is that some version of an informed consent requirement—perhaps a very detailed and complex one—is the appropriate instrument for protecting the various interests that could be adversely affected by the practice of collecting and storing biological samples, without excessively constraining scientific research or making it too costly to pursue.[19]

To evaluate this assumption we must clarify the resources and limitations of the idea of informed consent for balancing the conflicting interests involved. And to do this we must expand upon our earlier discussion of what informed consent is and what the main purposes of obtaining informed consent are.

Elements of informed consent. Informed consent is now generally recognized to be both a legal and moral requirement for medical interventions generally and for all experiments on human subjects that involve more than minimal risks. We saw earlier that "risks" here are taken to include not only potential physical harms from bodily invasions, but also "psycho-social harms," especially stigmatization, dignatory harms, and other assaults on the individual's sense of self-worth.

Five elements of informed consent can be distinguished: 1) disclosure (of relevant risks and benefits of the procedure); 2) competence (on the part of the patient or subject) to make a decision whether to accept the treatment or participate in the research; 3) comprehension (of the relevant risks and benefits); 4) choice (an expressed decision to accept the treatment or participate in the experimentation); and 5) voluntariness (of the choice to accept treatment or to participate in research).

Clearly, informed consent will play a role in any ethically sound system for collecting and using biological samples at least to this extent: The requirement of informed consent must be met for medical treatments generally and for research (involving more than minimal risk). The question is whether an ethically sound system for collecting, storing, and using biological samples will require additional or amplified applications of the requirement of informed consent in order to reduce the risks of the various harms catalogued above in section II. To answer this question, we must first clarify the rationale for the informed consent requirement in its paradigm applications.

As already noted, the requirement of informed consent developed as a safeguard against very tangible harms—the sorts of physical harms that the law generally regards as batteries.[20] In other words, informed consent first and foremost protects individuals from nonconsensual invasions of their bodies. Informed consent was not originally invoked as a general protection against all the various harms that can result, whether directly or indirectly, from medical interventions or from research. Even when understood as also providing protection against "psycho-social harms," informed consent cannot reasonably be viewed as protecting the whole range of heterogeneous interests that may be affected by the uses of biological samples.

Moreover, as we also saw above, even if informed consent can serve to protect the interest in avoiding the dignatory harms of deception and manipulation, that interest might be protected instead by disclosure of the fact that the sample will be stored and later may be used for a wide range of purposes, without requiring either blanket or specific informed consent. Hence it is one thing to agree that freedom from nonconsensual bodily invasions and from "psycho-social harms" is so important that informed consent is a necessary condition for the participation of human subjects in research, quite another to say that an adequate informed consent document for biological sample practices must ensure the sample source full control over every choice that may be made in the future concerning the uses of the sample. To emphasize a point made earlier, the mere interest in having more rather than fewer choices, as distinct from the interest in significant opportunities for genuinely autonomous choice, does little to support a requirement of informed consent so far as the uses of biological samples are concerned.

Two distinct but equally important points must be emphasized at this juncture. First, as just noted, the justification for informed consent focuses primarily on some, not on all possible harms, and not on the mistaken notion that informed consent enhances autonomy simply by virtue of multiplying choices. Informed consent is primarily a protect against nonconsensual bodily invasions and against dignatory harms that can generally be ranked under the category of treating persons disrespectfully, as if they were mere means for the pursuit of others' ends. It is not a device for maximizing an individual's range of choices; one would only view it in that way if one erroneously assumed that an individual's autonomy is violated whenever he is not given the widest range of choices possible.

Second, these two types of harms against which informed consent is designed to protect are certain to occur if informed consent is not secured, because nonconsensual bodily invasions and disrespectful treatment are themselves harms, quite apart from any further harms that may occur. Yet most of the harms catalogued above in section II are *not* certain to occur and in many cases are in fact extremely unlikely to occur. It is one thing to argue that the prevention of the certain and uncontroversially serious harms of nonconsensual bodily invasion and disrespectful treatment justifies a serious restriction on research, quite another to argue that the mere possibility of various harms, some of which are not so serious and which are very unlikely to occur, provides an equally compelling reason to restrict research.

Furthermore, it is important to stress that the primary harm against which the requirement of informed consent is supposed to protect is a serious one for this reason: If a person is not free from unwanted invasions of his body—if his body is treated as a mere object to be dealt with as others choose—neither his life nor his liberty are secure. As reasons for restrictions on scientific research, the need to prevent nonconsensual bodily invasions and the treatment of persons as mere means, on the one hand, and the "need" to protect against a range of possible but in some cases highly improbable harms of varying degrees of seriousness are not on a par. This is especially true if we are talking about possible harms that might occur *after* the sample has already been taken and hence after no risk of unwanted bodily invasion is at issue. Once this fundamental point is appreciated, it becomes clear that there is a large gap between identifying various potential harms that might result from a system in which sample sources lose control over what is done with their samples and making a plausible case for introducing an elaborate system designed to extend their control, whether through some system of specific consent requirements or in some other way.

Even if we restrict the role of proposed safeguards in protecting against harms (as opposed to maximizing choices), the mere *possibility* that a harm of significant magnitude might occur is not sufficient to warrant restricting potentially beneficial research. An appropriate *threshold of risk*, a level of probability of harm high enough to warrant protective measures, must be identified and defended, and the question of whether we are likely to be able to determine reliably when that threshold has been met must be addressed. Yet without exception, current proposals for specific consent requirements for various uses of stored samples proceed as we know what that threshold is and that it would be exceeded without the protective measures they advocate. Or, even worse, they simply assume, quite erroneously, that the goal is to eliminate risk entirely. Such approaches simply fail to address the problem of bridging the gap between the identification of potential harms and the conclusion that special arrangements are needed to safeguard against those harms.

Reduction of risks, not elimination of risks. It is worth dwelling for a moment on why any approach to structuring and regulating biological sample practices that assumes that the various risks identified above are to be reduced to zero is radically misguided. This assumption would only make sense if risk-reduction measures were costless. But of course they are not; efforts to reduce risk are costly not only in terms of the resources needed to devise them and to apply them and monitor their application, they also are detrimental to the various interests that are furthered by freer access to samples (listed in section III above).

Blanket consent. One measure that has been proposed to protect against the various risks that can arise from the uses of stored tissue information is blanket or open-ended consent, either alone or with a requirement of specific consent for some particular uses of the sample or for those types of research that might be regarded as especially problematic. Thus, for example, it has been suggested that at the time a biological sample is to be taken the potential source must be told that at that time she may consent to or object to any future research uses that may be made of the sample, so long as the sample is rendered nonidentifiable with the source, with the additional requirement that specific permission is to be obtained from the source for any use of the sample in which the source's identity could be ascertained. The chief attraction of the blanket consent component of such an arrangement is that it requires lower administrative costs than specific consent for each future use, since one informed consent process authorizes an indefinite number of future uses.

However, the difference between blanket consent and what is ordinarily understood by informed consent is so great that it is problematic even to use the same term, "consent," to refer to both. As noted earlier, a key element of informed consent is disclosure of the relevant risks and benefits of the procedure that is to be accepted or refused. "Relevant risks" here does not mean all possible risks. In general, what counts as a relevant risk is the risk that a reasonable person would want to be apprised of, though for some types of decisions a case can be made for a more "subjective" standard, a requirement that the individual must be informed of those risks that he would need to know to make a reasonable decision, given his particular values. But regardless of whether an "objective" or a "subjective" standard of relevance is employed, the rationale for informed consent presupposes the ability to identify a much more determinate and limited set of relevant risks than is generally available in the stored biological sample setting, if we include all of the various possible and often highly improbable risks listed in section II as reasons for restrictions on uses of stored samples.

Just as significant, the less determinate the set of potential harms and the more uncertain it is that they will occur, the less likely it is that a second essential element of informed consent will be present, namely, comprehension. Moreover, as we also saw earlier, once the sample has already been taken, the primary harm against which informed consent provides protection, namely, nonconsensual bodily invasion, is no longer at issue.

For these reasons, it must be acknowledged that blanket consent requirements are only distantly related to informed consent and do not perform the functions of informed consent. The question, then, is whether, despite this difference, blanket consent requirements serve any useful purpose effectively enough to warrant changing current practices to incorporate them.

It seems clear that blanket consent requirements will not provide protection against most of the more tangible and serious harms that might occur from the uses of stored biological samples—unless it should turn out that most potential sources refuse to give blanket consent. In that case, the blanket consent requirement would serve a protective function, but only at the cost of thwarting the various important interests that are served by scientific research which we listed in Section III.

Recall that when a person gives ordinary informed consent, she thereby avoids a definite harm—the harm of nonconsensual bodily invasion—and in addition, because the relevant risks and benefits of treatment or participation have been disclosed for her consideration, she is in a better position to avoid a choice that is likely to produce other harms to her on balance. But when an individual gives a blanket consent to future uses of her tissue, she does not thereby avoid a harm, and her choice is not likely to reflect a reasonable estimate of what is good for her on balance, simply because the information she has about possible future risks is too indeterminate. Furthermore, as we saw in Section II, there is another source of indeterminacy that can undermine the requirement of comprehension: The individual may be uncertain about her own evaluation of the events that might occur in the future.

At this point, a proponent of blanket consent might object that protection from harms, whether physical or dignatory, is not the only point of the requirement: It also shows respect for the individual's autonomy by giving him or her control over what happens to the sample in the sense that he may refuse to allow any future uses. Now, it may be true that a system that includes a requirement of blanket consent for future uses of nonidentifiable biological samples in some sense shows more respect for individuals than one that merely requires disclosure of the fact that the sample may be used for various purposes in the future. But it would be hyperbole to say that a system that does not include the requirement of blanket consent violates anyone's "right to autonomy." For one thing, as I have already noted, not all choices warrant the stringent protections that talk about a right to autonomy implies; some choices are relatively insignificant because they are largely irrelevant to a person's well-being and values. And, as we have already seen, blanket consent may not be the *only* way to protect the interest in not being treated disrespectfully: Simply disclosing that the sample will be stored and

may be used for an indefinite number of uses in the future would go a great distance toward protecting this interest.

Finally, given the fact that blanket consent is only a pale shadow of informed consent and given that it does not provide significant protections from the various harms it is supposed to avert, it is far from clear that the deference to individual choice it expresses is worth the costs. Among those costs is the risk that the genuine informed consent will be devalued through confusing it with blanket consent.

None of this is to say that it would be impermissible to institute a requirement of blanket consent for future uses of samples. Rather, the point is that if such a requirement is instituted we should recognize it for what it is: a largely symbolic expression of respect for individual choice and one way, though not the only way, of avoiding the disrespect that would be shown by a practice that keeps sources in the dark, not a case of genuine informed consent, not a vindication of the right to individual autonomy, and almost certainly not an effective protection against the various other possible harms that might result from uses of biological samples.

V. Policy Implications

Future samples. Most current proposals for biological sample policy draw a distinction between what should be done regarding informed consent and other protections *from now on*, that is, with future cases of the collection, storage, and uses of biological samples, and what should be done regarding existing stored samples. Current opinion is divided concerning safeguards and restrictions that ought to be instituted concerning biological samples gathered in the future. Our analysis has already cast some doubt on the efficacy of the proposal for blanket consent for future uses. For as we saw, blanket consent, like disclosure, may protect against the dignatory harm of being treated in a deceptive manner or otherwise treated disrespectfully, but it is not clear that it provides significant protection against many of the various other harms that might result from future uses nor that it provides a meaningful exercise of autonomy, much less that it is required if violations of autonomy are to be avoided. Moreover, blanket consent is only distantly related to genuine informed consent. Given the radical uncertainty concerning both the nature of particular future uses and our evaluative responses to them, adequate disclosure and comprehension of risks are not obtainable. The question remains, however, as to whether, instead of blanket consent, specific consent for each use or type of use of the sample should be required, at least for samples that are linkable to the individual source.

I have already argued that it is simplistic and misleading to assume that the justification for informed consent for the procedures by which samples are taken from persons' bodies applies with anything like equal force to a requirement of informed consent for the various uses to which samples can be put. The requirement of informed consent for medical treatment or research protects a person against two types of certain and significant harms, the harm of bodily invasion and the dignatory harm of being treated as a mere means. It also serves individuals' interest in autonomy to the extent that the choice whether to receive a treatment or to participate in research bears on an individual's stable values and conception of the good. The interest in autonomy, the need to avoid these harms and the certainty that they can be prevented if the informed consent requirement is met justify the quite considerable constraint on treatment and research which the informed consent requirement poses. But it does not follow that informed consent is needed for every use of a person's stored biological sample in the future. Future uses will not involve a risk of bodily harm to the individual and if some indication of the range of possible uses is disclosed in advance, dignatory harms can be avoided. In general whatever autonomy interest (if any) an individual has in whether or not his sample is used for specific purposes in the future will tend not to be as significant as his autonomy interest in being able to accept or refuse medical treatment or to participate or not participate in an experimental protocol. Consequently, an informed consent requirement for each future use of the sample is much more problematic than the requirement of informed

consent for medical treatment and participation in experimentation, given the costs that implementing it would inflict on the pursuit of scientific progress and other legitimate interests.

There is a policy alternative that steers a middle course between requiring consent for each research use of stored sample indefinitely into the future, on the one hand, and a system which gives the source no control whatsoever over future uses of her sample, on the other, once she gives blanket consent. IRBs could be required by new federal regulations to develop screening criteria, based on a consideration of the taxonomy of interests developed above, to identify research protocols that bear significantly on important interests that sources may have beyond the interests in avoiding nonconsensual bodily invasions and in not being treated as a means that the informed consent requirement is primarily designed to protect. This approach would allow for *selective consenting* by sources, assuming that it could be combined with a secure system which allowed for authorized, confidential de-coding of encryptions designed to remove individual identity.

To use an example already alluded to above, given the history of racism in this country and the special vulnerability of African Americans as revealed by the Tuskegee Syphilis Experiment and other instances of unethical behavior by researchers and doctors toward this group, there is a special concern about group-based harms. Consequently, the selective reconsenting guidelines for IRBs might well require special arrangements for research protocols that raise questions about negative stereotyping, such as studies that test hypotheses about links between genotype and intelligence or genotype and criminal behavior. The attraction of the selective consent approach for "special scrutiny" protocols is not simply that it is less costly and cumbersome, and thereby better serves the interest in scientific progress, but also that it does so in a principled way, by rejecting the assumption that every interest that might be adversely affected by a particular use of the sample is as weighty as the interest in preventing nonconsensual bodily invasion and in not being treated as a mere means that the requirement of informed consent is primarily designed to protect.

Such a selective consent requirement might be combined with a blanket consent requirement. A person would first be offered the option of consenting to all future possible uses of the sample (compatible with human subjects regulations and other relevant law), but then the IRB would examine each future use to see whether it fell into the "special scrutiny" category. If a proposed use fell into this category, then specific consent would be required at that point.

Given the remote resemblance that blanket consent bears to informed consent and given that disclosure that the sample may be used for a variety of purposes in the future provides protection against the dignatory harms of deception and manipulation, it is not obvious that the selective consent approach would need to be supplemented with a blanket consent requirement; it appears that adding a disclosure requirement instead would suffice.

The selective consent approach for samples to be collected in the future just outlined does not envision sources as generally having the option of choosing to have their samples rendered nonidentifiable. Nor does it empower researchers to decide to render samples permanently nonidentifiable (though of course it allows the possibility of double blind experiments in which the identity of the sample source is shielded from the researcher). There are two reasons for the presumption that in general samples collected in the future should not be rendered nonidentifiable. First, doing so makes it impossible for sources to be contacted in the future if discoveries are made from which they might benefit. For example, future research may develop treatments for diseases that are now untreatable, and if samples are rendered nonidentifiable their sources will not be able to benefit from these advances. Second, if samples are not identifiable, it will not be possible to provide benefits to relatives of the sources. For example, research may yield successful treatments or preventive strategies for genetically based disorders that are currently untreatable, such as Alzheimer's dementia, or others that are not treatable with only limited success, such as breast cancer. In such cases, it will be crucial to give relatives who may be at risk for the disease the opportunity to be tested to see if they have the genotype in question and hence whether they are candidates for treatment or prevention.

At present, the ability to diagnose genetic conditions generally far exceeds the ability to treat or prevent. Thus in many cases the only way to prevent the phenotypic expression of genetic disorders is to prevent the existence of an individual who would have the genotype in question. However, in coming decades, there will almost certainly be many cases in which genetic testing will reveal potentially serious, but treatable or preventable conditions. The ability to identify stored biological samples—all of which will include information about genotype—may become a keystone in the application of genetic science to the improvement of human health. Consequently, an ethically sound policy for stored tissue to be collected in the future ought to operate on the presumption that in general identifiability of sources is to be the norm.

One of the most difficult ethical issues to be faced as more genetic tests become available and the gap between diagnosis and treatment or prevention narrows is whether or how public policy should encourage or require individuals who test positive for genetic conditions to inform relatives that they are at risk. The United States, like most developed countries, has public health laws that represent an attempt to balance respect for individual privacy with the need to prevent harm to individuals by the transmission of disease from one person to another. The clearest examples are laws requiring individuals with sexually transmitted diseases to cooperate with health care workers in notifying sexual partners that they are at risk. Assuming that these laws are appropriate, there is no obvious reason why it would not also be proper to use the power of the law to enforce a "duty to warn" relatives who are at genetic risk, in those cases in which 1) the genetic condition is a grave threat to health or life; 2) the condition is effectively treatable or preventable if detected early enough; 3) the treatment is safe and without serious side-effects; 4) the probability is low that relatives at risk will be diagnosed as having the condition unless they are informed that a relative has been diagnosed; and 5) the costs to the index case of informing relatives that they are at risk are not excessive.[21] Whether or not there are now genetic conditions that meet these criteria, it is very likely that there will be in the future.

This brief discussion is not intended to advocate a legally enforceable "duty to warn relatives at genetic risk." Such a proposal would only be plausible, if at all, if the proposed legal duty were carefully limited and qualified, and this is not the proper place to explore such limits and qualifications. My point, rather, is that it would be a mistake to rule out serious efforts to encourage the prevention of genetically based harms, whether through the force of law or by relying on the individual's sense of moral responsibility, by making samples nonidentifiable.

To say that there should be a general presumption in favor of identifiability is not to say there should be an absolute requirement of identifiability in all cases. There may be some special cases in which the risk of harm from breaches of confidentiality are so great that they outweigh the interests in preventing medical harms to the source or his relatives that might be averted if the sample were identifiable. For example, in some "special scrutiny" cases where history suggests a significant possibility of special vulnerability for members of an ethnic or racial minority, it might be appropriate to offer potential sources not only the usual option of not participating at all, but also the option of participating under conditions of nonidentifiability. Whether any particular research protocol is a valid exception to the norm of identifiability should not be left to the determination of the researcher; it should be determined, within the framework of appropriate guidelines, by the IRB.

Assuming that the general norm is to be identifiability for samples collected in the future, the great challenge will be to capture the benefits of prevention and treatment that depend upon identifiability while at the same time providing adequate safeguards for confidentiality. It is beyond the scope of this discussion to pursue the technical details. However, it is worth emphasizing that once again the goal is not to provide encryption systems and other safeguards that reduce the possibility of inappropriate access to source identity to zero, but to strike a balance between maximal accessibility to identities for the sake of prevention and treatment, on the one hand, and maximal protection of confidentiality, on the other.

The use of existing, nonidentifiable samples. Some have proposed that for existing samples for which no identification of the source is possible, no special conditions or restrictions should apply beyond those already involved in requirements for review of research involving human subjects. The intuitive idea is that since it is not possible to contact the sources to ask their permission for any specific uses or to gain blanket consent, no special restrictions should apply.

Though it seems quite reasonable at first blush, this proposal is not as uncontroversial as it first appears. It will not do to say that no special restrictions are required simply because "ought" implies "can"—that is, to cite the fact that it is impossible to contact the sources to ask permission for various uses because they cannot be identified. For there are, after all, two feasible alternatives: proceed with whatever uses of the samples are otherwise allowed under existing regulations for the protection of human subjects, *or do not use these samples at all.* What is needed is a reason for choosing the former alternative.

Nor is it correct to assume that because the sources cannot be identified they cannot be harmed. For as we shall see shortly, there are some interests of the sample sources that may be harmed even if the sources are not identifiable, and there may be some interests of others at risk as well.

The best case that can be made for allowing use of existing, nonidentifiable samples is that the balance of interests weighs in favor of this policy. We have already seen what these conflicting interests are, but it will be useful to emphasize those that are especially significant in this context.

Because we are assuming that the samples are not linkable by anyone to individuals, some of the most important interests that speak in favor of restricted access do not apply: If the individual cannot be identified, then there is no risk of insurance or employment discrimination, nor of stigma, nor of adverse psychological reactions or familial conflict. So to that extent, the case for not allowing use of nonidentifiable stored samples is significantly weakened.

There are at least three interests, however, that are relevant, and each adds some weight to opting for the alternative of not allowing use of nonidentifiable samples. The first is the interest that some individuals may have in avoiding uses of their tissue that they regard as impermissible per se (recall the example cited earlier: the use of cells for producing a human being through cloning). Simply not allowing any uses for existing nonidentifiable tissue would protect this interest. However, given the factors cited earlier (in Section II) that reduce the weight of this interest, and given the importance of the conflicting interest in medical progress and other legitimate interests, it is doubtful that anything so drastic as a prohibition on all uses of nonidentifiable existing samples is required. This conclusion will be strengthened in proportion to how well existing regulations for the protection of human research subjects, combined with the force of public opinion and scientific professional ethics, rule out at least some of the uses which individuals might find most objectionable per se.

Here we come to a clear illustration of a point made at the outset of this inquiry: It is a mistake to assume that protection for the sample source's interests must be achieved exclusively through protections tied specifically to the practice of collecting samples, as if there were no other factors that serve to protect these interests (such as regulations for the protection of human subjects, the force of public opinion, and the constraints of professional ethics). Approaches to policy that envision elaborate and costly consent requirements at the point of sample collection look much less plausible once this point is appreciated.

The second interest whose weight is not diminished by the fact that the samples are not identifiable is the interest in either benefiting from the profits generated from the sample or in expressing a preference about who if anyone ought to profit—what was referred to above as the interest in distributive justice and in commercialization issues. There are two reasons for concluding that this interest does not weigh significantly in favor of prohibiting the use of existing nonidentifiable stored samples. First, it is far from clear how many people actually have a preference, much less a strong preference, about the distribution of profits from products involving the use of biological samples; and given that the samples are not identifiable we cannot ask the sample sources

what their preferences are. But second, and more important, if all that exists in this regard is a preference and not a property right or legitimate expectation that the source will share in the profits, then the interest in determining how profits are distributed should be given very little weight.

An analogous case will make this point clearer. I may prefer that the next winner of the New York State lottery divide the money equally with me, and I may be said to have an interest in her doing so to the extent that her doing so will enhance my well-being. But unless I have a property right in a share (as I might if we had split the cost of the ticket) or have on some other grounds a legitimate expectation that she will share it (for example, if she promised to do so), my interest does not count for much in the moral scheme of things.

Similarly, it would not be plausible to maintain that individuals presently have a *legal* property right in their stored biological samples and to argue from this right to the conclusion that they have a right to profits generated by the use of their samples. Nor is it plausible to say that they have a *moral* property right that *ought* to be recognized by the law. It is true that individuals have a moral right to control over their bodies (whether it is misleading to call this a property right or not is a matter of dispute). However, in the present context the proper acknowledgement of that moral right was either adequately acknowledged or not, depending upon whether the ordinary requirement of informed consent was observed for whatever procedure was used to collect the tissue in the first place. Even if the requirement of informed consent was not met for some existing samples, it is not plausible to argue that sample sources have a moral property right in their stored tissue on the basis of their expectations of control over their stored samples, simply because nothing in the practices concerning sample collection and storage has encouraged such expectations. (Below I consider two quite different types of circumstances in which there was a failure of informed consent, and distinguish their moral implications.)

There is a third interest that is *not* rendered irrelevant by nonidentifiability and which raises a troubling question about what should be done with existing nonidentifiable samples, however. This is the interest in avoiding group-based or ascriptive identity-based harms. The problem arises because the ascriptive identity of a sample may be ascertainable even if the identify of the individual is not.

For example, biopsied tissue might be identified as having come from a member of the Ashkenazi Jewish group or from a person of African descent. Some existing members of the group may be concerned that certain uses of such tissue may contribute, if only indirectly, to the reinforcement of negative stereotypes concerning their group. (To reiterate one of the examples used earlier, some African Americans are understandably concerned about the misuses of data concerning members of their group by racist researchers or the misinterpretation of scientific studies based on such data to bolster racist views.)

Although such concerns are legitimate, it is important to remember that there are other ways of addressing them than by prohibiting the use of existing samples that can be identified according to ascriptive groups (or ascriptive groups that historically have been special targets of discrimination and negative perceptions). Informed public opinion, the professional ethics of researchers, and criteria for sound scientific research applied by IRBs, can all play a significant role in reducing the risk that uses of biological samples will contribute to racist or ethnic stereotypes. (For example, IRBs might be required to place in a "special scrutiny category" those research uses that may present a risk of racial or ethnic stereo-typing.) The stronger these other safeguards are in a particular society, the less compelling is the case for avoiding the risk of group-based harms by the drastic step of prohibiting research on existing samples that can be identified by ascriptive group.

Rendering existing identifiable samples nonidentifiable. Some participants in the debate over stored biological samples have recommended that for any existing identifiable sample, unless the sample is rendered nonidentifiable for a particular use, specific consent for that use must be obtained. The rationale for this highly restrictive proposal is that in many cases existing samples were collected without anything resembling adequate disclosure that they would be used for a range of purposes unrelated to the context in which they were collected.

Given the cost of a policy of requiring specific consent for all future uses (rather than just for those falling under a "special scrutiny category"), this proposal should be examined very carefully.

There are two significant drawbacks to rendering existing samples nonidentifiable for every use that is not specifically consented to by the source. First, there is the administrative cost of rendering such samples truly nonidentifiable by anyone. Second, and more important, if a sample is not identifiable opportunities may be lost to protect the well-being of the source or her relatives (in the case of genetic conditions), when later research discovers therapeutically significant links between various diseases or between diseases and genotypes.

There is a less extreme policy that provides significant protection for sources and recognizes that their samples may have been collected without adequate disclosure, yet which does so without cutting them off—without their consent—from the possibly life-saving benefits of future research. Where an existing sample is identifiable and it is reasonable to assume that there was not adequate informed consent at the time of collection (which is probably the case for most existing samples at this time), the individual can be offered the choice of either having her sample destroyed, having it rendered nonidentifiable, or giving a blanket consent to identifiable uses of the sample in the future, with a written pledge that 1) every reasonable effort will be made to ensure the source and her physician will be advised of research results that may affect her well-being and that 2) appropriate measures will be taken to ensure appropriate confidentiality regarding the sample. ("Appropriate confidentiality" here might, for example, include the provision of certificates of confidentiality that make records immune to subpoena.) If this proposal were implemented it would be crucial to inform sources who chose the option of rendering their samples nonidentifiable that they would thereby be cutting themselves off from the possibility that future uses might reveal information from which they or their relatives might benefit.

The rationale for including the option of blanket consent in the case of existing samples rather than mere disclosure that the sample may be used for a wide range of purposes is that in most cases existing samples will have been collected without disclosure, and hence without treating the source with sufficient respect. Allowing persons whose previously collected samples are identifiable to choose either to give blanket consent to all lawful future uses or to have their samples rendered nonidentifiable for future uses can be viewed as an effort to repair this deficiency. Even if blanket consent bears only a remote resemblance to genuine informed consent, it can serve as a special expression of respect for persons in the context of proposed uses for existing samples. Simply to disclose to a person *now* that the sample *already* taken from him may be used for purposes of which he had no inkling at the time of collection may not be adequate. (As we saw earlier, in the case of samples collected in the future, disclosure, as opposed to blanket consent, may suffice.)

This more moderate policy for existing samples should be supplemented with the same "special scrutiny" selective consent approach recommended above for future samples. In other words, if the source of an identifiable existing sample chose the option of not rendering the sample nonidentifiable and giving blanket consent to future identifiable uses, he would enjoy the additional protection afforded by the requirement of specific consent for those uses of his sample that fall into the "special scrutiny" category. The same reasons that speak in favor of selective consent for "special scrutiny" uses in the case of future samples also apply to the identifiable uses of existing samples. Because it gives weight both to the source's interest in confidentiality and to her interest in being able to benefit from future research findings, this proposal better reflects a fair balancing of the relevant interests than a policy of requiring that all future uses must be specifically consented to or conducted on nonidentifiable samples.

At this point, it might be objected that in many cases it will either be prohibitively costly or impossible to re-contact all living sources of previously collected identifiable samples to give them the option of blanket consent for all identifiable uses or of having the samples rendered nonidentifiable. The objection contains more than a grain of truth: To require that every possible effort be made to re-contact every source, without regard to costs, seems unreasonable. However, this is not to say that reasonable efforts to re-contact sources should not

be made and that reasonable efforts may entail significant costs. It is not a matter of either spending without limit until every source is re-contacted or making no effort to re-contact them. A third, more attractive alternative, is to require a *reasonable* (or "good faith") effort to re-contact sources.

Recall that the point of attempting to re-contact identifiable sources of existing samples was to respond to a dignatory harm that is likely to have occurred in many cases, namely, a failure to disclose to the source that her sample will be used for a wide range of purposes unrelated to the medical intervention or particular research project in which the sample was collected. To recognize that the original failure to disclose that the sample would be used for a wide range of purposes was an instance of not treating persons respectfully is not to say that there is no limit to the costs that ought to be borne to redress this wrong. Instead, a requirement of making "reasonable" or "good faith" efforts to re-contact sources will generally be an adequate recognition of the fact that in many cases samples were collected in a manner that failed to accord the samples due respect. What counts as reasonable efforts would have to be operationalized so that compliance with this requirement could be effectively monitored, and in such a way as to provide adequate assurance that those charged with the search actually made meaningful efforts to re-contact sources, rather than simply generating a "paper trail" to give the appearance of significant efforts without actually undertaking them. If reasonable efforts to re-contact the source fail, then in general the appropriate course of action will be to render the sample nonidentifiable in all future uses. Doing so would of course eliminate any possibility that the source might benefit from future discoveries, but this possibility will already be foreclosed, unless there is some reason to believe that at some time in the future it will become possible to re-contact the individual even though it is not possible to do so at present.

Samples tainted by violations of human rights. It was noted earlier that the chief harms that informed consent serves to prevent—unwanted bodily invasions and disrespectful treatment—will already have either been averted or not, depending upon whether informed consent was obtained for the collection of the sample. If there is no reason to believe that the requirement of informed consent was *not* met for the procedure by which the existing nonidentifiable sample was collected, the best course of action on balance is to allow access to the sample. If there is reason to believe that informed consent was lacking, the matter is less clear. For in such a case one might argue that it would be wrong to use a sample that was improperly obtained. And there can be little doubt that at least some of the older stored samples in various tissue archives meet this description.

Here it is important to distinguish between two different types of cases in which the informed consent requirement was not met for the procedure that produced the sample. In the first, there was no informed consent, but there was no *further* wrong to the source. In the second, not only was informed consent lacking, but also the individual was seriously wronged in some other way. (To take an extreme example for purposes of clarity, suppose the source was an unwilling human subject in cruel experiments conducted by Japanese or German doctors during World War II.) The argument for not using the sample is much stronger in the latter case than in the former.

Fortunately, most of the stored samples that currently exist in this country do not fall into the second category. However, if there is reason to believe that some particular stored samples were collected as a result of serious violations of persons' basic rights beyond the possible absence of informed consent, a case might be made for not allowing access to these for any purpose. (One might argue, for example, that tissue from the victims of the Tuskegee Syphilis Experiment ought not be used, even for the most benign purposes.) Apart from such special cases, however, we may conclude that respect for the individual's right to control over his body does not require a prohibition on the use of nonidentifiable existing tissue samples, even though many of those uses could not have been anticipated at the time of collection.

In summary, a strong case can be made for the proposal that in general existing samples that are not linkable to individual sources may be used for various research purposes, subject to the usual restrictions on

research with human subjects. None of the interests that might be adversely affected by such uses, either individually or cumulatively, seems to weigh heavily enough to warrant the loss of so much potentially valuable information, except, perhaps, when the circumstances in which the samples were taken involved violations of basic human rights other than the right to informed consent. There are only two exceptions to this generalization: The first is where ascriptive-group harms are a serious possibility because the source's ethnic or racial identity can be determined despite individual nonidentifiability; the second is where the process that generated the sample involved a clear violation of basic human rights. Changes in existing regulations governing IRB scrutiny of protocols to require special scrutiny for these types of cases may be called for.

Proposals for "community consent" or "community consultation." By a community here is meant roughly a group that is more than a "mere association"—one which figures in an individual's conception of who she is, what she values, and what is valuable about her. Thus an individual may at the same time belong to a religious community, an ethnic community, a national community, and a community based on the type of career she pursues, etc.[22]

Some parties to the debate over the uses of biological samples have suggested that in some cases community consent or at least community consultation, in addition to or instead of individual consent, may be appropriate for some or all research uses of biological samples. Three quite different rationales for this proposal must be distinguished.

The first and more radical of the three is that at least for certain types of communities, the assumption of individual agency upon which the doctrine of informed consent is erected is inapplicable or profoundly misleading. According to this view, in some communities (in particular some indigenous peoples) individuals are so deeply embedded in the collective that to rely exclusively on individual informed consent or perhaps to require it at all is to impose an alien value scheme that assaults the very identity of the group. In its most extreme form, this first rationale amounts to the claim that the group has a right to control what happens to the bodies of its members and that individual members are not competent to decide for themselves whether to allow the collection of biological samples from their own persons.

The second, less radical rationale is that some individuals, especially those in "traditional" societies, customarily rely upon collective decisionmaking practices or at least upon consultation with those who occupy certain important roles in the community or who are recognized representatives of the community's values. According to the second rationale, the group does not have a right to control what is done to the individual's body, but it may be important nonetheless to enable the individual to rely upon the community, or certain representatives of the community, in making his decision.[23]

A third rationale for community consultation is based on the interest in avoiding group-based harms. Like the second rationale, and unlike the extreme version of the first, the third rationale does not assert that the group has a right to control the individual member's body. Instead, the idea is that where there is a significant risk of group-based harms, the other members of the group have a legitimate interest in avoiding such harms since they will suffer them.

The first rationale ought to be rejected. Showing proper respect for the value that community plays in the lives of many people, indigenous and otherwise, does not require denying that individuals are moral agents or that they have the right to control what is done to their bodies. If individuals of certain groups wish to allow others to decide for them, they can do so within the framework of law and ethics that the ordinary model of informed consent provides, they can simply follow the guidance of the elders or the council, etc., or they can even in some circumstances formally delegate decision making authority to them.[24]

The second rationale can provide a plausible justification for facilitating the individual's consultation with the group (or certain members of it). This may require modifying the customary ways in which researchers enlist subjects and secure informed consent. However, the second rationale does not provide a justification for requiring consent by the community or its putative representatives.

Where the risk of group-based harm is substantial, the third rationale can justify community consultation and perhaps community participation in the design and implementation of a research protocol. Like the second rationale, it does not justify a community veto on individual participation.

Although the second and third rationales have their attractions, it is important to note that the concept of community consultation has several inherent drawbacks. First of all, there is the problem of determining what the relevant "community" is. In the modern world, most individuals are members of a number of different, sometimes overlapping communities. Even if consulting with all the communities which contribute to the individual's identity were feasible, it cannot be assumed that the distinctive values of the various communities to which the same individual belongs would yield the same conclusion when applied to the question of whether a sample may be taken, how it may be used, or who should decide about whether or how it is to be used. Persons' various communitarian identities are not always harmonious.

Second, there is the problem that consultation may become coercion—that once a community (or the self-styled leader of the community) is mobilized it may exert undue pressure on the individual to conform. Given that individuals in almost all cases belong to more than one community, there seems to be only one morally defensible way of determining which community, if any, ought to be consulted: by letting the individual herself decide. No other approach is compatible with respect for the basic rights to freedom of association and religion that are essential to a liberal democratic political order. But if this is the case, then a proper consideration for "community consultation" ought to be regarded as one possible form the process of individual informed consent may take, not as an alternative to it.

Third, it is a profound mistake to think that either a community's values or who speaks for those values can be readily and uncontroversially identified. Especially in our multicultural world where virtually no community is impervious to a multitude of influences from without, there is no such thing as unanimity of values within a community on any issue of consequence.

Furthermore, there are ongoing and sometimes quite subtle contests among members of the community to determine what the communities' "authentic" values are and who is to be regarded as voicing them. Because until recently outsiders have wrongly assumed that "primitive" or indigenous societies are not only homogeneous in values but *unchanging*, contests over what the group's values are have gone largely unnoticed.

Just as important, it is almost never the case that what are blithely called community decisions are in fact collective decisions of all members. Instead, they are the decisions of political elites whose interests may diverge significantly from those whom they claim to represent. To put the point most bluntly, indigenous or "non-Western" societies are frequently not only much less homogeneous but also much-less egalitarian in their decision-making than what has been called "the myth of primitive harmony" suggests.[25]

Once these facts are appreciated, it becomes clear that the enterprise of "community consultation" is a very complicated matter, and not without risks. Whether these risks are worth taking will depend largely on three factors: 1) whether there is a significant risk of group-based harms (rather than a mere possibility of them); 2) whether other protections against the group-based harms in question are likely to be adequate; and 3) whether a process of consultation can be devised that is not likely to reinforce oppressive inequalities within the group or to become an arena for political entrepreneurship by would-be leaders of the group.[26]

It is also important to distinguish between groups that constitute legitimate polities and those that do not. For example, most American Indian tribes are polities, groups with their own governments, which are recognized as such by federal and state laws. Moreover, such governments are presumed to be representative (since they are required by federal law to operate under democratic constitutions), just as the governments of various municipalities, counties, and states are. At present, the federal government limits the freedom of individuals to participate in experiments by regulating human subjects research, chiefly through institutional review oversight. Whether, or if so, in what manner, it would be Constitutional for state or local governments, or tribal

governments to regulate the participation of those within their jurisdictions so as to impose additional or different conditions on research participation, such as some form of community consent or consultation, is at present unclear. What is clear is that whether a demand for community consultation or consent for research participation is valid may depend in part upon whether those making the demand are the representatives of a duly constituted government, operating within the scope of their legitimate authority, as opposed to self-appointed moral spokespersons for a group. However, even if it should turn out that it is constitutional and otherwise legally unexceptionable for a tribal or a local government to require community consultation or consent for collection of samples, or to otherwise restrict research participation, it is quite another question as to whether this would be morally justifiable. Whether or not it would be will depend upon whether a sound moral justification can be given for allowing the government in question to limit individuals' options for donating samples in that way.

VI. Summary of Main Conclusions

The aim of this study has been to provide an ethical framework for deliberations about policy for stored biological samples. The task has been to articulate in a systematic way the various kinds of moral considerations that policy makers ought to take into account, not to frame model statutes for regulations.

Although it is not feasible to repeat all the arguments for them here, the main conclusions of the analysis can be summarized.

1) An ethically sound policy for stored biological samples must reflect a proper balance of the chief legitimate interests that weigh in favor of greater control over uses of samples and stronger protections for confidentiality and privacy on the one hand, and those that weigh in favor of greater access to samples for purposes of research and clinical interventions, on the other. To frame the issue initially as a conflict between the right to privacy and confidentiality and the value of freedom of scientific inquiry is unilluminating, especially since the content and limits of rights to privacy and confidentiality cannot be determined prior to identifying and judiciously weighing all the relevant morally legitimate interests at stake.

2) The chief legitimate interests that weigh in favor of greater control by sources and more rigorous safeguards for confidentiality and privacy are the interests in a) avoiding insurance and employment discrimination; b) avoiding stigmatization; c) avoiding negative stereotyping (that is, group identity-based harms); d) avoiding familial conflicts; e) avoiding uses of biological samples that the source regards as impermissible per se; f) interests persons have that survive their deaths; and g) the interest in control per se, that is, in having more rather than fewer choices.

3) The chief interests that weigh in favor of wider access to samples and hence in favor of less restrictive safeguards for privacy and confidentiality are a) the societal interest in the growth of scientific knowledge and medical progress; b) the preference or commitment some individuals have for contributing to scientific or medical progress; c) the interest in enhancing valued human characteristics; d) the interest in reproductive freedoms; e) the interests of researchers and clinicians in freedom of inquiry; and f) various commercial interests that can be served by freer access to samples.

4) Given that there are important and morally legitimate interests that weigh in favor of less restricted access to samples, it is a mistake to proceed on the assumption that the goal is to develop policies that reduce the risk of discrimination, stigma, or other harms to the sample source or others to zero, as if risk-reduction were costless—as if the costs of risk-reduction did not include set-backs to important and morally legitimate interests, including the interests in preventing serious harms and improving human health.

5) Not all of the interests that weigh in favor of more stringent restrictions on access to samples are of equal weight, and some are of questionable significance. For example, the interest in control per se, in having more

rather than fewer choices, and the interest in determining who shall profit from various uses of the sample, are generally less weighty than the interest in not being treated as a mere means and the interest in avoiding nonconsensual invasions of the body. Moreover, not all potential harms are of equal probability and some are highly improbable.

6) In addition to the various interests that weigh in favor of less constrained access, both society and individuals have obligations to prevent harm. A policy that requires or allows all or most samples to be rendered nonidentifiable would be an unacceptable impediment to the fulfillment of obligations to prevent harm.

7) Requirements of informed consent can play a useful role in serving some of the legitimate interests concerned, but it is important not to overestimate the resources of informed consent in this context. The requirement of informed consent chiefly serves to protect persons from unwanted invasions of their bodies and to prevent the dignatory harm of being treated disrespectfully. If the requirement of informed consent is met for the procedures by which samples are taken and if the fact that samples may be used for a wide range of purposes in the future is disclosed to the source, the main goals of informed consent have already been achieved. Additional consent requirements for each future use of samples are excessively costly and overly restrictive of opportunities for research and beneficial clinical interventions.

8) In exceptional cases, as when there is a significant risk that the research in question may reinforce racial stereotypes or cause other harms to groups that are already vulnerable or have been treated disrespectfully by researchers or medical authorities in the past, specific consent may be necessary. New regulations may be needed to require IRBs to accord "special scrutiny" to such cases and to determine whether specific consent is required.

9) Blanket consent may be a way of reducing the risk of dignatory harms, but it is only very distantly related to informed consent and should not be expected to perform the functions of informed consent. In most cases of blanket consent to unspecified future uses of samples, key features of informed consent, including disclosure and comprehension of relevant risks and benefits, will not be present due to ignorance of the possible uses to which samples may be put in the future and because of the source's inability to predict how he would evaluate various possible uses that might occur.

10) At present, the ability to diagnose genetically based diseases and susceptibilities to disease far outstrips the ability to cure or prevent these conditions. In the future, however, we can expect the diagnosis/therapy gap to narrow for a number of serious conditions. Policy recommendations concerning the use of stored biological samples must be crafted in such a way as to protect future opportunities for preventing harm. More specifically, whatever safeguards for privacy and confidentiality are devised must not preclude the ability to contact the source or her relatives in cases where serious harms can be prevented.

11) For samples to be collected in the future, sound policy would include a mechanism for "selective consent" in cases where the proposed research uses fall into the "special scrutiny" category, combined with either a blanket consent requirement or a disclosure requirement. In general, there should be a presumption that samples to be collected in the future will not be rendered nonidentifiable, in order to keep open possibilities for preventing harm to the source and others in the future. This presumption against nonidentifiability is only plausible, however, if rigorous safeguards, including appropriate encryption of the source's identity, and perhaps other measures such as certificates of confidentiality to render identities immune from subpoena, are also provided.

12) In the case of samples that have already been collected and are currently being stored, it is neither necessary nor desirable to render them nonidentifiable as a general policy. If, as is likely to be the case, they were collected under circumstances in which the sources were not treated with due respect (in particular, not having been informed that the samples would be stored and used for multiple purposes), a good faith effort to remedy the failure to disclose will suffice, except, perhaps in "special scrutiny" cases. Where the source is identifiable and it is likely that adequate informed consent was not obtained at the time of collection, the source should be

given the option of having the sample destroyed, having it rendered nonidentifiable, or giving blanket consent for future uses, subject to the provision that selective specific consent may be required for uses that fall in the "special scrutiny" category.

13) With regard to previously collected samples, it is important to distinguish between cases in which the source was not treated with due respect (as when there was no disclosure of multiple future uses) and cases where the taking of the sample involved violations of basic human rights. The latter type of case constitutes a far graver breach of ethics and an argument can be made that such samples should not be available for any uses.

14) In some cultural contexts, it will be appropriate to expand the process of informed consent so that an individual can allow family members or trusted advisors to participate. It may also be appropriate to provide opportunities for community consultation regarding collection of samples from especially vulnerable minority groups. However, generally speaking, community consultation should not deprive the individual of the opportunity to participate or refuse to participate in the collection of samples. And when community consultation is considered it is important to recognize that the community in question may be divided on relevant issues and that a decision to recognize some persons as proper representatives of the group's values can be very problematic.

Notes

1 See Elisa Eiseman's paper, "Stored Tissue Samples: An Inventory of Sources in the United States," in *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, v. 2., 1999. Rockville, MD: U.S. Government Printing Office.

2 Ibid.

3 See Joel Feinberg, 1984, *Harm to Others: The Moral Limits of the Criminal Law*, v. 1., Oxford: Oxford University Press.

4 Ibid., 37.

5 Ibid., 51–55.

6 The term *discrimination*, it can be argued, is prejudicial, because it begs the question to assume that when insurers risk-rate they are engaging in unjustified or inequitable treatment, not just treating different cases differently.

7 See, for example, Paul R. Billings et al., 1992, "Discrimination as a Consequence of Genetic Testing," *American Journal of Human Genetics*, 50:476–482.

8 See Kathy L. Hudson et al., 1995, "Genetic Discrimination and Health Insurance: An Urgent Need for Reform," *Science*, 270:391–393.

9 *Moore v. The Regents of the University of California* et al., 793 P.2d 479 (Cal. 1990).

10 See, for example, Jeremy Waldron, 1998, *The Right to Private Property*, Oxford: Clarendon Press.

11 See Gerald Dworkin, 1988, *The Theory and Practice of Autonomy*, New York: Cambridge University Press.

12 President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research, 1983, *Securing Access to Health Care: Commission Report*, v. 1., Washington, D.C.: U.S. Government Printing Office.

13 For an excellent survey of such benefits, see David Korn, "Contribution of the Human Tissue Archive to the Advancement of Medical Knowledge and the Public Health," in *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, v. 2., 1999. Rockville, MD: U.S. Government Printing Office.

14 For an in-depth examination of the ethical issues concerning genetic enhancement, see Allen Buchanan, Dan W. Brock, Norman Daniels, and Daniel I. Wikler, 1999, *Genes and the Just Society: Genetic Intervention in the Shadow of Eugenics*, New York: Cambridge University Press, especially chapter four.

15 See *Genes and the Just Society*, especially chapter five.

16 Perhaps most important, a robust obligation to prevent harm, unlike a robust obligation not to cause harm, would be excessively demanding. A conscientious effort to fulfill it would in effect make one a slave to the well-being of others, including those others who irresponsibly and repeatedly endanger themselves by their imprudent or self-destructive behavior.

17 Allen Buchanan, 1987, "Justice and Charity," *Ethics*, 97:558–575.

18 It is important to note that the lack of a name on a sample or on the record noting the existence of the sample does not guarantee that the source cannot be identified. A combination of demographic characteristics, plus seemingly trivial information such as the date and time at which the sample was collected may make it possible to identify the individual.

19 See, for example, Ellen Wright Clayton et al., 1995, "Consensus Statement: Informed Consent for Genetic Research on Stored Tissue Samples," *Journal of the American Medical Association*, 274:1786–1792.

20 Ruth Faden and Tom L. Beauchamp, 1986, *A History and Theory of Informed Consent*, Oxford: Oxford University Press, 26–28.

21 Allen Buchanan, 1998, "Ethical Responsibilities of Patients and Clinicians," *Journal of Health Care Law and Policy*, 1:391–420.

22 For an analysis of the notion of community, see Allen Buchanan, 1989, "Assessing the Communitarian Critique of Liberalism," *Ethics*, 99:852–882.

23 Although there is some ambiguity in the article on this point, this seems to be the position of Morris W. Foster, Ann J. Eisenbraun, and Thomas H. Carter, 1997, "Communal Discourse as a Supplement for Informed Consent for Genetic Research," *Nature Genetics*, 17:3:277–280. While these authors do not explicitly attribute a group right to control individual members' tissues, they do talk in very misleading ways that suggest unwarranted assumptions about the cohesion or indeed the unanimity of group members as to values. Consider, for example, the following passage: "Two native American Communities we studied treated individual health care decisions as occasions for consultation within extended families. Both asserted that individual illnesses (and actions taken to care for them) can have consequences for other members of the family and community."

Notice that the phrase "both [communities] asserted" is a reifying description that conveys the almost certainly false impression that there is unanimity and complete homogeneity of values within the group. In the past decade, anthropologists have given up the myth that "primitive" communities are lacking in dissent and disagreement and that the values of such groups are fixed and not contested. Foster, Eisenbraun, and Carter show no awareness of this important insight.

24 For a critical evaluation of various conceptions of group rights, see Allen Buchanan, 1993, "Liberalism and Group Rights," in *In Harm's Way*, Jules L. Coleman and Allen Buchanan, eds., Cambridge: Cambridge University Press.

25 See, for example, Robert G. Edgerton, 1992, *Sick Societies: Challenging the Myth of Primitive Harmony*, Toronto: The Free Press. See also Stephanie Lawson, 1997, "The Tyranny of Tradition: Critical Reflections on Nationalist Narratives in the South Pacific," in *Narratives of Nation in the South Pacific*, Nicholas Thomas and Ton Otto, eds., Amsterdam: Harwood Academic Publishers.

26 I am deeply indebted to Norman Fost, Adele Franks, Eric Meslin, Thomas Murray, and Lance K. Stell for their comments on an earlier draft of this paper.

RESEARCH ON HUMAN TISSUE: RELIGIOUS PERSPECTIVES

Commissioned Paper
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Introduction

The retrieval and use of human tissue samples for diagnostic, therapeutic, research, and educational purposes represents a further development in scientific study of the human body as a source of medical information. The central question examined in this report is whether tissue banking for purposes of *research* presents any distinctive theological issues or prompts objections from religious communities or scholars. Since religious discussion of human organs and tissues has largely focused on *donation for therapeutic* purposes (what I describe below as the "donation paradigm"), there is very little direct religious discussion of *nontherapeutic research* uses of human tissue. It is possible, however, to describe implications and suggest inferences by considering religious attitudes to the human body and to organs, tissues, and cells removed from the body and religious discussion of modes of transfer of body parts, such as donations, offerings, sales, and abandonment. By and large, this discussion will reflect themes that emerge from the central Western religious traditions, with some attention given to Eastern and Native perspectives. The first section of the report will conclude by identifying some practical policy recommendations on research on human tissue consonant with religious values about the human body. The second section of the report will describe the views of specific religious traditions on use of bodily organs and tissues.

Section 1

The Body: Religious Holism, Scientific Reductionism, Private Property

The human body as an organic totality has long been the subject of theological reflection and a symbol of religious communities. However, much less attention has been devoted to the religious status of organs, tissues, cells, and DNA. The reflection of religious scholars and communities on the status of body parts has been prompted by the necessity to confront practical questions in personal and public health and in communal life, such as justifications for surgery, autopsies, organ donation, or burial. Scientific and research interest in *parts* of the body can sometimes conflict with religious values about *bodily integrity*. Indeed, E. Richard Gold cites the "disparate claims of scientific investigation and religious belief on the body" as the exemplary case of incommensurate values regarding the body. According to Gold, "The body, from a scientific viewpoint, is a source of knowledge of physical development, aging, and disease. From a religious perspective, the body is understood as a sacred object, being created in the image of God....The scientist values the body instrumentally, as a means to acquire knowledge; the believer values the body intrinsically, for being an image of God."[1]

Theological holism is here posed in fundamental conflict with scientific reductionism. In the Western faith traditions (primarily Judaism, Christianity, and Islam), theological holism takes as its starting part an assessment about the body in its organic totality and in its fundamental integration with the person. This assessment is perhaps best characterized as an expression of "awe" or "reverence" towards the person, who is theologically portrayed as an embodied self in the "image of God" (*imago Dei*).[2] This theological understanding entails that the body is intrinsic to personal identity and is invested with an aura of sacrality: the metaphors of "temple," "sacrament," "tabernacle," and "sanctuary" are prominent in religious language about the body. This profound commitment to the inherent value of the body is acknowledged, even when, as upon death, the self-body interrelationship is severed. The religious traditions of the West nonetheless require respectful treatment and disposal of the corpse, which in practical terms has often meant a presumption in favor of burial following rituals of remembrance.

Body parts, organs, and tissues can also shape a sense of self. Empirical studies suggest that visible parts of the body, such as skin, genitals, fingers, hands, legs, and eyes, as well as the heart, have a strong correlation with a sense of self. With the exception of the heart, nonvisible organs and tissues are not as strongly incorporated into a sense of self. Thus, not all body parts possess equal status, or are equally important to self-identity.

Moreover, men and women may value specific organs and tissues differently; males apparently value the liver as part of self-hood, while females place greater emphasis on eyes, hair, skin, and tears.[3] It is possible, as Russell W. Belk suggests, that the less an organ or tissue is connected with a sense of self-identity, the more willing a person will be to donate it for use by others.

By contrast, the dis-integrating body, or a body that is "dis-incorporated" in the sense that tissues or organs have been removed in isolation from the bodily totality may summon a sentiment not of awe, but of revulsion. The emphasis on bodily integrity in the Western religious faiths has culminated in the development of stigmas and taboos regarding certain bodily tissues when they are *external* rather than internal to the body. Characteristically, the dis-incorporation of bodily tissues is assessed by religious thought with reference to issues of purity and cleanliness. A very prominent historical illustration of this issue of purity, which has permeated secular culture and has not been entirely overcome in contemporary religious communities, is the stigmas and taboos surrounding menstruation.[4]

This distinction between the status of organs, tissues, and fluids when they reside in and are integrated within the body rather than outside and separate from the body is displayed as well in an illustration by Gordon Allport: "Think first of swallowing the saliva in your mouth, or do so. Then imagine expectorating it into a tumbler and drinking it! What seemed natural and 'mine' suddenly becomes disgusting and alien.... What I perceive as separate from my body becomes, in the twinkling of an eye, cold and foreign."[5]

There are then different ways of assessing the theological and moral status of the body and of body organs and tissues depending on the "place" of the organs or tissues, that is 1) intrinsic to self-identity (e.g., heart) or incidental; 2) visible (eyes, skin) or hidden (kidney); and 3) integrated (circulating blood) or dis-incorporated (bodily excretions). In general, it may be claimed that the more an organ, tissue, or fluid possesses the former of these characteristics, the more its retrieval and use for biomedical research purposes may present theological and ethical questions. Put another way, Western religious thought on the body begins with a strong presumption that the status of the body as a whole is greater than the sum of its parts. Body organs and tissues, moreover, contain potent symbolic significance when considered as part of the bodily whole.[6] Yet, as noted above, organs and tissues when considered in isolation from the rest of the body seem a source of revulsion and stigma. The relevant question is what religious significance should be attributed in particular to body tissue that may be stored and used for purposes of medical science.

This question is complicated because the approach of medical science to the human body begins from a different starting point, that of "reductionism." The interest of medical science in the body stems from the prospect of gaining information about human character traits and behaviors, including susceptibilities to illness and bodily responses to disease, through study, analysis and understanding of the basic components of life, such as genes. DNA constitutes the building blocks of life, with cells, tissues, organs, etc., viewed as more complex, functional entities of the basic genetic materials. The scientific value of the body as a totality is instrumental to the goal of deciphering the codes, messages, and functions of the fundamental components of parts of the body that contain valuable information. In this respect, the whole is reduced to the sum of its parts in two respects: 1) genes are more scientifically significant than the body totality; and 2) the value of an organ, tissue, or cell resides primarily in the information it provides researchers, rather than, for example, its significance as a symbol of life.

An illustrative example of scientific reductionism is presented in scientific discourse about the Human Genome Project. Rosner and Johnson have identified three basic metaphors of science discourse about the genome project, interpretation of a "book" or "library," repairing a flawed "machine," or the mapping of a mysterious "wilderness," each of which places the scientist in a dominant and exploitative role.[7] These understandings of a scientific research project involving body organisms contrast significantly with the religious metaphors of the body as "temple" or "sacrament." Thus, while the diagnostic and therapeutic prospects of the genome project are generally viewed with great promise by religious communities, issues may emerge over the

reductionist account of the body embedded in genomic research. If, for example, to develop the wilderness metaphor along the linguistic lines common in any issue of *Science* or *Nature*, the human body is understood as *merely* a "natural resource" for "gene prospectors" to "map," "mine," and make "claims" to establish property rights, patents, and commercial products, then some religious objections may emerge that focus not on the long-term social consequences of the research, but on the intrinsic value of present studies. When the human body of the late 20th century is portrayed in terms analogous to the land of the 19th century, that is, as an exploitable natural resource whose contents are of more interest than the integrity of the whole, then the theological question to modern science is whether the body is only the sum of its constitutive biological materials without remainder.

A prominent model of the body in legal and policy discourse is compatible with the scientific account but potentially in conflict with theological holism. This is the model of the body as "property."[8] The property understanding stems from a claim of self-ownership and seeks to authorize the individual person with control over the use and disposition of their body and of body parts. This view tends to treat the body as incidental rather than intrinsic to personal identity; the body as a totality is distinct from the self, and body organs and tissues can be transferred or alienated to others without compromising the nature of the self. These features make the property model very conducive to the scientific interest in body tissue, with the proviso that informed consent is obtained from the person. However, conflict can arise when, for example, a patient and a researcher assert competing claims or "property rights" to excised body tissues.[9]

These three models ask somewhat different questions about the possibility of using stored tissue samples for research purposes. The question for the scientific and property understandings of the body is what kinds of *limits* may be placed on research on tissue and transfers of bodily property. That is, the scientific and property perspectives assume the legitimacy of the *use* of body tissue and direct attention to the avoidance of *abuse*. By contrast, the theological emphasis on the embodied self and bodily integrity entail the need to articulate an argument that *justifies* use of the body. The most common justifying argument in religious thought is that the presumption in favor of bodily integrity and wholeness may be overridden for the purposes of facilitating therapy. I will refer to this justifying argument as the "donation paradigm."

The Donation Paradigm

With very few exceptions, religious thought on the body and its use within medicine has presupposed a context within which organs and tissues are donated for therapeutic purposes of healing, restoring or saving life. This moral presumption in Western religious discourse is emphasized through the language of "gift," "altruism," "sacrifice," etc., on the part of the donor and that of "benefits" for recipients. The donation paradigm seems constructed by four principal features:

1) *Altruistic intent.* The intent of the donor of an organ or tissue is structured by gift-giving to specific beneficiaries or recipients, such as persons on a waiting list for a transplant (although the identity of such persons may be veiled from the donor).

2) *Therapeutic expectation.* The expectation for the gift of the body is that it will offer a pronounced therapeutic prospect for the recipient. The provision of a needed organ or tissue should offer substantial benefits to the individual beneficiary, whether as enhanced quality of life, or the preserving of life itself. A clear articulation of this therapeutic expectation is found in Jewish thought, where a general presumption in favor of bodily integrity can be overridden by the paramount imperative of *pikkuah nefesh*, the saving of human life.

3) *Re-incorporation.* Body tissue that has been retrieved from the donor, or dis-incorporated, should in most circumstances be "re-incorporated" within the body of the recipient. As noted above, tissue that remains dis-incorporated may evoke sentiments of revulsion and practices of stigma and taboo. Some religious practices and rituals require burial of removed body parts, or re-incorporation in the earth. This is particularly the case with body parts that have an identifiable human form: In Jewish thought body parts composed of "flesh, sinew,

and bones," such as limbs, should under most circumstances be buried. Roman Catholic tradition distinguishes major from minor parts of the body in a manner similar to Jewish thought. Major parts of the body are those that retain their "human quality" following excision (a limb) and should be buried.[10] Such concerns may reflect the importance of these visible body parts for self-identity.

Re-incorporation of body organs or tissues in a human recipient has a generative power in that it offers the prospect of new or renewed life to the recipient. In general, then, the donation paradigm prioritizes practices in which body tissue remains with a body (even if transferred and transplanted to the body of another person) and thus symbolizes the significance of bodily integrity and theological holism.

4) *Recipient Responsibilities.* The gift of the body carries with it certain responsibilities on the part of the recipient, responsibilities that are embedded in everyday practices of sharing and gift-giving.[11] These include a sentiment of gratitude towards the gift-giver, or towards the institutional structure that mediates the gift transfer. Gratitude should also be enacted in the actions and conduct of the recipient by which he or she makes grateful use of the gift. In addition, a gift induces a responsibility of reciprocity. Reciprocity does not necessarily mean the continuation of the gift relationship between the initial giver and recipient; rather, a recipient of donated blood, for example, may at some time in the future become a blood donor for other strangers.

The donation paradigm as delineated above thus provides a religious ground or justification for medical use of human body tissue. It is limited, however, for the most part to medical practices of transplantation or transfusion, that is, those practices that promise some form of therapeutic outcome from the gift. Two questions emerge at this point: 1) To what extent is the donation paradigm compatible with the scientific or property understandings of the body; and 2) Can the donation paradigm accommodate nontherapeutic uses of body tissue, namely, uses of tissue for research purposes? I will examine these two questions in turn, using the four-fold schema above for comparative purposes.

The Resource Paradigm

The different understandings of the body in the scientific and property perspectives carry over into perceptions of the status of body tissue. Following the analogy delineated above, body tissue is a "resource" for scientific study and exploitation; this reflects what I will designate as the "resource paradigm." The donative intent of the source of the tissue is attenuated because the tissue may be acquired through surgical procedures, in which case the tissue assumes the status of "surplus" that has been discarded or abandoned, or it may be acquired through a transfer of "property" rights over bodily tissue. In either case, the resource paradigm downplays or neglects the meaning of "gifts" of the body.

Body tissue is a resource because it contains *information*. The purpose of procuring tissues for research is to generate generalizable knowledge, advancing researchers' understanding of human disease, for example, without necessarily promising therapeutic benefits to individuals, at least in the short-term. This marks out two important distinctions between the resource paradigm and the donation paradigm. First, the recipient of body tissue is different, a member of the scientific research community, rather than the human community in general. In addition, research on body tissue may generate important information in the short-term while deferring therapeutic potential to the long term. This disparity between research that enhances diagnostic capabilities yet defers therapeutic benefits has played an important role in theological assessments of genetics research, including the ethical implications of the genome project.[12]

Moreover, what is of primary importance in the resource paradigm is not the re-incorporation of bodily tissue, but rather the extraction of information from the tissue. This implies that bodily tissue has no distinctive moral status, and that the information that is retrieved should be treated in a manner equivalent to other forms of medical information. Thus, while the tissue may remain dis-incorporated in perpetuity, safeguards such as privacy and confidentiality are placed around the information.

The notion of recipient responsibilities seems no less attenuated on the resource paradigm for several reasons. The researcher is not bound by responsibilities of gratitude or reciprocity because it is the work of the scientific community that has made possible the retrieval of the tissue in the first place. There would be no gifts of the body to give were it not for the initial labor of researchers and physicians. This reiterates the paradigm's attribution of "surplus" or "property" to human body tissue. The main responsibility of the researcher-recipient appears to be ensuring that informed consent takes place. However, in the nature of the case, the research process may lead to inadvertent and serendipitous discoveries, so it can be very difficult to anticipate possible research uses of tissue, and thereby disclosure of relevant information by the researcher may be very limited.

Although these contrasts between the donation and the resource paradigms may be somewhat overdrawn, such simplifications should not hide the general point that the paradigms are not easily reconcilable. Indeed, if they were completely compatible, there would not likely be much in the way of distinctive *ethical* issues in research on tissue samples. The ethical issues emerge because of the conflict between fundamental values embedded in the paradigms, e.g., a personalized gift given for the specific purpose of benefiting another, and depersonalized surplus or property retrieved in order to generate information that may not be therapeutic. This conflict in turn is rooted in the differing approaches of holism of the body, which places the moral burden of proof on those who seek to *justify uses* of the body, and reductionism of the body, which places the moral burden on those who seek to *impose limits* on uses and *prevent abuses* of body tissue that will be used in research. The question is whether there is another paradigm that, on one hand, retains the aspects of gift, benefit, and responsibility embedded in the donation paradigm, and on the other, retains the importance of biomedical research and permits pursuing research in the case of human tissue samples, features vital to the resource paradigm.

The Contribution Paradigm

The use of human body tissue for research poses a problem for the donation paradigm, which is central to religious understandings of the body and of moral life, because it is not structured by personalized gifts of the body for therapeutic purposes. I want to suggest a different paradigm that seeks to bridge the gap between the donation and resource paradigms. I will refer to this as the "offering" or "contribution" paradigm. This paradigm aims to retain the morally valuable features of the donation paradigm, while providing a justification for biomedical research undertaken without therapeutic intent. The paradigm also acknowledges the importance of medical research to generate generalizable knowledge, but works to impose some limits on the scope and extent of research on human tissues. Again, the four-fold features of the donation paradigm will be used to illuminate distinctions and comparisons.

An analogy may be useful to illustrate the moral context of this paradigm. Following Belk's suggestion that "the house is a symbolic body for the family,"[13] in this analogy household goods take the place of human tissue samples. Household goods can be discarded in several ways, but I will here focus on three ways. One method is to donate certain goods, for example, clothing, to a community goodwill program. This presents an example of a gift or an altruistic action designed to benefit others and to enhance a recipient's quality of life. A different set of household materials are those goods that have been used completely and are now discarded through a community service agency, for example, a trash collection service. Household refuse has no personal meaning to the discarder, who is typically quite willing to pay a fee to have the items removed. This does not, of course, pre-empt the possibility that this refuse might have value to someone else who is willing to take the time to sort through the materials. A third form of disposal consists of those household materials whose designed use has been depleted by members of the household, for example, food products that come in plastic or cardboard containers, but may subsequently undergo "recycling" by those organizations that have the knowledge and expertise to convert these materials into something beneficial for the community.

This analogy underscores the claim that not all body organs and tissues have equal status.[14] Some body parts, such as the heart, eyes, or blood, may have such symbolic significance and connection to personal identity that their donation is the moral equivalent of a gift of self. Other body tissues, for example, urine or cut hair, may have such minimal value to the sense of self that they are routinely discarded. Still other organs and tissues, such as a pancreas, liver, spleen, marrow, etc., fall in between these examples, not as central to personal identity as the heart or eyes, but not as incidental as urine either. And, as indicated above, the status of human tissues is shaped not only by issues of personal identity, but also of visibility and hiddenness, and location relative to the bodily totality. In this context, it is possible to think of human tissue samples procured for research purposes as falling in this middle category and thus as analogous to domestic recyclables. The features of this analogy form the basis for the offering or contribution paradigm.

Contributor intent. An individual who places their recyclable materials at the curbside is not necessarily making a personalized gift, but rather is *contributing to a cause* that is larger than oneself and the benefits one might provide in a direct relationship with another person in need. The cause in the domestic case may be "environmental preservation;" in the case of body tissue, it may be designated as "scientific discovery" or "medical progress." The contribution in both cases is one of *nonspecific generosity*, "nonspecific" in that the recipient is a "cause" rather than having a person as the intended beneficiary; it is also a generous act in that a person is participating in the advancement of the larger cause when they could just as easily place the recyclable material in the refuse bin without moral blame.

Beneficial expectation. The contribution does not bring benefits to a specific or designated individual, but the expectation of the contributor is that benefits will over time accrue to the larger whole of society, or least those persons with a stake in the justifying cause. In most instances of contributions, the beneficiary will be future patients, persons, or generations.

One's contribution of either domestic or bodily recyclables provides the raw materials from which persons and institutions with the requisite knowledge can apply their technical skills and expertise. Unlike the resource paradigm, however, the willingness to contribute does not imply that the contribution has minimal or no value to the contributor. A plastic milk jug that can be recycled is equally serviceable as a water jug, and newspaper can be a fire starter. Similarly, a person may attribute value to many tissue specimens, including blood, reproductive tissues, skin or hair that have been retrieved or excised from the body. Rather, the difference between the resource and contribution paradigms lies in the fact that in the latter, something of value is contributed to a person or organization through whose work the society realizes an increased benefit than had the contributor retained the material. The contribution paradigm thereby intends a benefit for the common good of all.

Symbolic Re-incorporation. The religious understanding of the body that prevails in the West commonly requires some practices or rituals that re-incorporate those tissues that are removed from the body into another body, whether an organ transplant or blood transfusion into a person, or burial in the earth. The contribution paradigm can meet this condition through symbolic re-incorporation. Just as recycling contributes to the good of the communal body, the contribution of body tissues for research can provide information that can then be integrated within a larger, symbolic body, namely, the "body of scientific knowledge."

Recipient Responsibilities. Contributions in general are acknowledged in some form by recipients; it thereby seems important for contributions of bodily tissue to be acknowledged with some expression of gratitude. This might occur through the informed consent ritual, in which a researcher should not presume that the contributor should simply "sign off" to any and all uses made of retrieved body tissues, but instead might directly thank the person for their contribution to the advancement of scientific research. The researcher-recipient also has a responsibility to use the contribution of body tissue for the common good. At a minimum, this requires treating the information generated by tissue research with safeguards that ensure protection against discrimination or harm. The appeal to the "common good" also does not necessarily preclude recourse to the private

sector to carry out research; in some cases, as with domestic recyclables, the good of all can be more efficiently and effectively achieved through private sector initiatives. However, any profit interests must be subordinated to and limited by the common good and the greater cause that the contribution is designed to advance. In short, retrieved body tissue cannot be viewed as *merely* an economic asset.

The contribution paradigm thus provides a *justification for research* uses of human body tissue, a justification that was absent in the donation paradigm due to its focus on direct therapeutic prospects. It also imposes *limitations on research*, such as the importance of the common good, re-incorporation, and informed consent, that seem absent in the resource paradigm due to its focus on using the body merely as a means to generate generalizable information. The chart below summarizes the overlaps and similarities of the three paradigms:

Table 1. Paradigms

Characteristics	*Donation*	*Resource*	*Offering/Contribution*
Intention	Gifts of the body	Research on body "surplus"	Participation in "larger" cause
Expectation	Therapy for recipient	Generate information	Benefit to larger whole
Outcome of Body Tissue	Re-incorporation in body and "new life"	Safeguard information	Re-incorporation in symbolic body (e.g., scientific knowledge)
Recipient Responsibilities	Gratitude, reciprocity	Informed consent	Acknowledgment, informed consent, safeguards, common good

The question now is the extent to which a contribution paradigm is compatible with specific religious attitudes towards the human body and body tissues.

Implications of Embodiment

The analysis to this point has situated ethical issues in research on human tissue within the broad framework of the Western religious tradition. The issues and conflicts may be different when consideration is given to the pluralism present in religious thought on the status of the body, the body's relationship to self, and the status of body parts. Protestant theologian William F. May has distinguished five "religious" attitudes on the status of the body and its parts that are useful to review in the context of retrieval of human tissue.[15]

Dualism—Gnosticism—Embodiment—Materialism—Idealism

This typology relies on distinctions over whether the body has a phenomenal reality, is ontologically good, and is intrinsic or incidental to personal identity.

Dualism affirms the phenomenal reality of the body but denies its goodness because of the body's association with flesh and matter. Dualism portrays the body as "at war" with the self, its literal mortal enemy. Parts of the body, disposal of the body, and persons who come into contact with the corpse are denigrated, stigmatized and considered taboo and sources of pollution or uncleanness.

At the opposite end of the continuum, idealism denies that bodily life has any ultimate significance. The body, disease, and death are constructs of the mind that can be transcended through identification with a separate realm of the spiritual. The self seeks its true home in this spiritual realm, and relies on spiritual healing rather than on medical ministrations to achieve this goal. Body parts, or study of the body, are not denigrated as much as seen as existentially indifferent.

The gnostic attitude seeks liberation of the true self from the body, which is understood as a prison of the soul. The true self resides in a disembodied mind or consciousness. Knowledge is the means to liberation, which entails overcoming the burdens of mortality, including finitude, disease and death. Body parts have no significant value.

Hindu and Buddhist teachings about life's purpose reflect a similar appraisal of the secondary status of the body and the necessity of liberation from the bodily world. The body is incidental to personal identity—indeed, a self may be incarnated in several bodies—and the true self resides in a realm of trans-bodily consciousness.

In the West, May argues that the gnostic attitude lives on in the form of philosophical Cartesianism. The Cartesian separation of self (mind) and body (matter) is embedded within the ideology of biomedical research; as exemplified above, the body is perceived merely as a "resource" for obtaining raw biological materials that can, through study and application, be converted into drugs that offer mastery over nature.[16] The Cartesian separation of self and body has a further consequence, namely, that there is no moral necessity for informed consent to the removal of bodily tissue, or subsequent research and manipulation. Since a body is incidental to personal identity, the retrieval of an organ, tissue, or cell cannot be said to violate the person and their integrity, even if their bodily space is violated. In this respect, informed consent appears to be a rule without a rationale. Its use under the resource paradigm may be a signal of the general inadequacy of that paradigm with respect to human tissue research.

In contrast to an approach that seeks to master nature, the materialistic attitude to the body is shaped by an ideology that human life is at the mercy of powers in nature that are arbitrary, abusive, and destructive. This can lead to two different, and conflicting, perspectives, both of which are present in Western cultures: avoidance and denial (of aging, death, etc.), or resistance. The latter belief is enacted primarily through the practice of medicine and its war on death and human disease. In this perspective, the body assumes the role of primary "battleground." Patients may well give consent to invasive procedures, but the patient is principally a passive observer to the battle plan carried out by physicians and researchers. A successful waging of the war often requires excision of body parts or removal of tissue; such parts thereby possess instrumental value but no intrinsic value.

Within this typology, the dualistic, gnostic, and materialistic perspectives can be construed as compatible with the resource paradigm of biomedical research. The idealistic attitude, by contrast, finds in medical research a misguided attempt at medicalization of the metaphysical. This implies that scientific proposals for research on human tissue samples become an *ethical* issue only in those traditions that understand embodiment—that is, the intrinsic relationship of body and self—as a fundamental given of human life. Such attitudes are embedded in the monotheistic religious traditions of Judaism, Christianity, and Islam. These traditions affirm the ontological reality of the body as well as its intrinsic moral goodness, in contrast to the instrumental value embedded in Cartesian and materialist thought. Moreover, the Western traditions affirm the intrinsic nature of the body to personal identity: Human beings are embodied selves, not simply souls or minds housed within corporeal prisons.

These features provide a religious and moral validation for medical interventions in the body. The reality and goodness of the body entail the use of medical procedures to restore and heal. The fundamental connection of body and self makes consent of the person a moral mandate with respect to invasive medical procedures and removal of bodily tissue, healthy or diseased. However, the rationale for consent does not necessarily presume personal ownership of the body. Instead, control over the body and its disposition is rather a responsibility often portrayed as "trusteeship" or "stewardship" from the Creator.[17] Responsible stewardship involves accountability for uses of the body and an orientation of such uses toward the common good. Ethical positions and liturgical rituals, for example, can justify sharing of the body as a form of altruistic service to others. The

trusteeship understanding thereby rules out viewing the body *merely* as property or *merely* as a resource for economic gain.

Within these traditions, it is clear that the donation paradigm is prominent with respect to organ transplants or transfusions of vital tissues (blood, bone marrow). Discussion of use of body tissues retrieved for research or educational purposes is minimal. It is possible to begin, however, by considering theological perspectives on issues raised by donation of the whole body to medical schools for research or teaching purposes and by requests for autopsies. These provide some examples of uses of the body in medicine without direct therapeutic benefit, and thus may illuminate important theological principles and precedents.

Body Donation and Dissection

Within Judaism, some debate exists about the moral status of donating the whole body to medical school for educating prospective physicians. This dispute reflects differences over the priorities given to two primary obligations in Jewish law. There is a presumptive obligation, *kavod ha'met*, that supports preserving the integrity of the corpse as a symbol of the person and as a requirement of care for God's creation; this precludes desecration of the corpse. However, this presumption can be overridden (as can all commandments in Jewish law, save for prohibitions against murder, idolatry, and illicit sexual relations) by the requirement of *pikkuah nefesh*, the saving of human life.

Within the moral framework set by these two principles, some Orthodox rabbis object to body donation unless it has an immediate practical benefit to a needy patient. Other rabbis permit body donation in principle because it contributes to medical education and future patients can benefit through the anatomical studies carried out by present researchers. The principal proviso in this understanding is that the body parts dissected for study be preserved and eventually receive a respectful burial in conformity with Jewish law.[18] The emphasis on burial and re-incorporation of the body in Judaism is also illustrated by the practices of ultra-Orthodox Jews in Israel, who, following a terrorist bombing, seek to locate dismembered body parts so that they will receive a proper burial.

While Jewish thought appears to permit donation of the body to medical science in principle, Jewish scholars have cited a surplus of cadavers available for research and training at medical institutions to contend there is no practical imperative within the tradition.

The Islamic understanding of the human body also stresses the importance of body wholeness at death. Islam affirms a general presumption against donation of the body for anatomical dissection that reflects the principles of the dignity of the human body and a prohibition on mutilation of the body. Anatomical research in Islamic medical schools is instead frequently performed on animals.[19]

Autopsy

The Jewish approach to autopsy again invokes the two basic principles of nondesecration and the preservation of life. Within this moral structure, autopsies may be permitted under certain limited conditions: when legally required; when the cause of death cannot be determined; when an autopsy may help save the lives of persons suffering from an illness similar to the cause of death of the deceased; or when relatives might be protected by learning of hereditary illness.[20] In the rare circumstances in which an autopsy is performed, only small blood, fluid, and tissue specimens can be removed for analysis; organs must be examined intact within the body, and the body must be buried whole.[21]

In the Roman Catholic tradition, Pius XII declared that autopsy can be morally permitted so long as two conditions are satisfied: (1) the body must be treated with respect and not objectified or treated as a "thing," and (2) the family of the deceased person gives consent to the procedure.[22]

The strong presumption in Islamic thought on bodily wholeness at the time of death limits the scope of acceptable autopsies. Autopsy is therefore not a routine medical procedure, but the presumption can be

overridden and accommodate request for autopsies in cases where death occurs from suspicious causes.[23] This precludes use of human tissue for research purposes.

Other religious traditions that have articulated objections to autopsies include Orthodox Christianity, Hinduism, and Shinto (the indigenous religion of Japan). It is also common for Native Americans to refuse to give permission for autopsy, unless it is an absolute legal requirement.[24] Protestant perspectives on autopsy, by contrast, generally reflect deference to familial autonomy. Autopsy is a permissible procedure if the family of the deceased consents.

Fetal Tissue

Another context for religious discussions of research on bodily tissue is that of fetal tissue research, although this is not as clear an illustration because procurement of fetal tissue is complicated by its moral proximity to abortion. In discussion before the National Institutes of Health Human Fetal Tissue Transplantation Research Panel, rabbinic arguments invoked the principle of *pikkuah nefesh*, that is, therapy to a specified individual, as a condition of justification. Research on fetal tissue, by contrast, was portrayed as "*research* protocols with undetermined and remote benefits for future patients, rather than therapeutic protocols with high probabilities of immediate benefits for current patients."[25]

Roman Catholic teaching holds that a fetal cadaver should receive the same respect as the corpse of any human being and that obtaining fetal tissue for research purposes from direct abortion constitutes complicity in moral evil. Other religious objections have focused on the possible commercial exploitation of fetal tissue.[26]

These few examples of religious discussion regarding use of the human body and human tissue for purposes of research and education reiterate the importance that religious traditions attach to the integrity and totality of the body. Even under the circumstances in which body donation or autopsy is deemed permissible (or legally required), researchers and teachers have an obligation to maintain respect for the corpse as a symbol of the person. Beyond these rather limited examples, there seems to be minimal religious discussion of use of human tissue for research purposes that are acquired from living persons through routine medical procedures, e.g., a blood draw, postpartum retrieval of a placenta or umbilical cord blood, or surgical excisions. A recent study on ethical issues in the banking of umbilical cord blood, for example, recommended sensitivity to "the variety of beliefs held regarding the placenta and umbilical cord" of individual patients, but acknowledged a general "dearth of information" with respect to more general cultural attitudes.[27] Yet, in many indigenous cultures, include Native American, the placenta, umbilical cord, and umbilical cord blood have sacred symbolic value associated with the creation of life and personal identity.[28] This disparity between the meaning of body tissue to researchers and its meaning to members of religious cultural traditions should be a central concern of public policy.

Policy Issues and Recommendations

Recommendation 1: Public education on human tissue banking is vital.

It is difficult to interpret the meaning of silence of religious traditions on medical issues. In some cases, ecclesiastical silence may reflect a particular tradition's commitment to personal autonomy and conscience in making health care decisions. In other traditions, silence may indicate the question at stake is morally indifferent, in which case a decision is deferred to the individual. Given the strong convictions about the body present in most religious traditions, however, the absence of religious discussion on tissue banking for research purposes may also reflect widespread lack of awareness. It seems education of the public, including citizens who are members of religious communities, is an essential part of concerted public policy on use of human tissue for research. The National Bioethics Advisory Commission (NBAC) would be well served by reiterating its concluding recommendations from *Cloning Human Beings* concerning "widespread and continuing deliberation"

and the provision of "information and education to the public in the areas of genetics, and on other developments in the biomedical sciences, especially where these affect important cultural practices, values, and beliefs."[29] This prior recommendation certainly encompasses the kinds of issues raised by tissue banking and the implications of such research on important value systems, including religious values. Moreover, as it is the research community that seeks access to human tissue, for policy purposes a moral burden should fall on researchers to elicit from prospective tissue contributors, both individual and communal, the values and meaning they attach to the requested tissue. In addition, public forums should be developed, perhaps in conjunction with the American Association for the Advancement of Science Program on Dialogue between Science and Religion, to ensure that these recommendations are carried out.

One important rationale for public forums that provide a clear account of ongoing or proposed research is that they can pre-empt religious objections to research on human tissues that are based on fuzzy understandings of science and muddled theology. The most prominent recent example of conflict over the status of human tissues and genes occurred in May 1995, when a coalition of some 200 religious leaders encompassing over 80 different religious bodies made a public call for a moratorium on the patenting of any human and animal life forms.[30] While theological arguments were offered for the moratorium, some of which seemed misdirected, behind the call for a moratorium is a valid concern over the public accountability of biomedical and genetics research (and its commercial development), including the need to consider the implications of research for important religious values.

Recommendation 2: The informed consent process for obtaining authorization to use human tissue for research should be specific, substantive, and sensitive to religious values about the body, both personal and communal.

"Religious" beliefs, such as belief in an afterlife or in bodily resurrection, have been commonly cited as grounds for refusal to sign organ donor cards; in the absence of general public awareness, it is likely that similar objections may surface when requests are made to use retrieved tissue for research purposes. The NBAC Genetics Subcommittee meeting of 5 March 1997 identified several different reasons for patient dissent to research on tissue samples. These included a) general distrust of science (underscoring the importance of the initial recommendation for public education and accountability); b) the alteration of scientific purposes from the rationale when informed consent was first obtained; c) concerns about personal, familial, or communal identity; d) the potential for research results to be used in such a way as to risk social stigma and discrimination; and e) religious reasons (which could encompass concerns about both identity and stigmas). The religious status of informed consent thereby seems an important consideration in formulating practical public policy.

Informed consent was described by the Protestant ethicist Paul Ramsey as the "cardinal canon of loyalty" between patient and professional in medicine, whether physician or researcher.[31] Informed consent was the tangible expression of an implicit covenantal bond between the patient (as person) and professional in a *joint* enterprise of developing medically-useful knowledge. This influential understanding of the meaning of informed consent requires a version of "thick" or specific consent to use of human tissue samples, rather than a general or implicit consent to any research and educational uses a research protocol might develop for analysis of tissue. Specific consent is compatible with and extends the values underlying the contribution paradigm and makes it possible for persons to understand themselves as contributing partners in the scientific enterprise of generating important knowledge.

Moreover, in some religious traditions, the informed consent process may be viewed as reflecting respectful or cavalier attitudes to the body. Roman Catholic teaching emphasizes that informed consent should protect the dignity of the human person, but it can only do this when physicians or researchers adopt a holistic rather than reductionistic view of the patient as person. John Paul II stated that "in the body and through the body, one touches the person himself in his concrete reality." Thus, even though physicians and researchers may have a scientific interest in specific body tissues, the informed consent process should inform and respect the embodied self rather than proceed as though the self is a disembodied will.[32]

In the process of information disclosure and descriptions of benefits and risks, professionals should be cognizant of the significance of "symbolic" harms for members of religious communities. The language of biomedical description can hinder understanding and comprehension within some communities, as revealed in studies on information disclosure among the Navajo culture.[33] Researchers thus need to be familiar with, and sensitive to, the communicative processes within a religious or cultural tradition.[34]

The idea of symbolic harm is often placed at the boundaries of bioethical controversies, portrayed as a mere "sentimental" or "speculative" concern rather than as a tangible substantive harm equivalent to the direct injury of the person. Yet, religious traditions are very centrally organized around symbol-systems; indeed, "symbolism is the language of religion generally; it is to religion what numbers are to science."[35] Issues of symbolic harm should be not be dismissed in the research setting. As described above, the body is a symbol of the divine in much religious thought. Symbolic harms inform religious restrictions on, for example, appropriate treatment of the corpse, such as the prohibition of desecration found in Judaism, thus placing off-limits body tissue that might otherwise provide important medical knowledge through dissection or autopsy. The study and subsequent disposal of body parts, rather than conforming to the contributor expectation of burial, also constitutes harm of a symbolic nature.

Recommendation 3: The patient should be regarded as possessing dispositional authority over his or her body, and over the specific research uses of retrieved human tissue for which informed consent is sought.

The concept of ownership is comprised of a "bundle of rights," including rights to use, transfer (via donation or sale) or dispose of a thing one owns.[36] It has been argued that, since religious traditions generally recognize the liberty of a person to donate organs or tissues, this constitutes an implicit property right of the person to their body parts. This interpretation seems to contravene the basic theological conviction of the Western traditions that any "ownership" rights to the human body reside in the Creator, and that persons are trustees or stewards over their bodies, not owners.

There are two different approaches to resolve this potential conflict. A first approach might accept the validity of the ownership-property model, but still seek to distinguish between God's creation (the body) and human intervention (retrieval of body parts). A second approach claims that concepts of ownership and property are misguided ways to think about the human body and its parts. Property discourse, which is shaped in large part by market values, effectively preempts other discourses of value about the human body, including religious discourse.[37] Property discourse emphasizes a relationship with "things;" the theologies of the body outlined in this report consider the body so intrinsic to personal identity and invest the body with such symbolic significance, as conveyed in rich imagery as "temple" or "sanctuary," that attribution of status of "thing" to the body is simply inadequate.

This function of property discourse about the body is no different than the historical role of property discourse: "Property" is the language of power. Property discourse empowers an agent with decision-making authority about use, transfer, and disposal, whether it be land or ideas ("intellectual property"). It seems possible, and from a religious understanding, desirable, to refer to the person whose body tissues might be donated or retrieved as holding dispositional authority over the body without presuming that this authority implies ownership or property rights. Since trustees and stewards can be authorized to share the goods entrusted to them for the benefit of others, this distinction between dispositional authority and property rights does not impugn the ultimate sovereignty or ownership of the Creator over the body.

Recommendation 4: Contributions of human body tissue for purposes of advancing scientific research and knowledge are ethically preferable to other modes of acquisition of tissue, such as sales or abandonment. Any compensation to individuals for their contribution should not presuppose or encourage an organized and regulated market in human tissue.

The donation paradigm and contribution paradigm are strongly supported in Western religious discourse by discourse and symbols of "gifts," "sacrifice," and "altruism." This emphasis presents important questions

regarding the prospects of acquiring bodily tissue sales. The latter approach seems more compatible with the resource and property understandings of the body. The Protestant ethicist William May is especially critical of proposals for commerce in the body, arguing that they reflect "no religious view but rather...a wholly secularized marketplace that permits one to reduce any and all things to assets for sale."[38] The claim that the religious status of the body is incompatible with a market in body tissues and cells resonates even with nonreligious writers, who nonetheless appeal to religious language of "reverence," "sacred" and "image of God" to express criticism of property and market models of the body and of human biological materials.[39] It seems fair to state that religious thought, in addition to objecting to scientific reductionism of the body, also would find economic reductionism morally problematic.

Roman Catholic teaching has expressed some openness to compensation of donors, though not to a full-scale organ or tissue market. Pius XII expressed concern about the "grave abuses" that may ensue from routine market transactions in bodily parts, but qualified his reservations by stating, "it would be going too far to declare immoral every acceptance or every demand or payment. It is commendable for the donor to refuse recompense: it is not necessarily a fault to accept it."[40] The donation and contribution paradigms are perhaps best embodied and facilitated by altruism, but compensation—which is morally and institutionally different than a system of commerce in body parts—may be ethically acceptable for some religious traditions, although not ethically ideal or preferable.

In the case of abandoned tissue, Childress has argued that the central issue turns on the understanding component of informed consent: "The fundamental question is whether the original possessor of the biological materials in question understood when he or she relinquished control over those materials that they would be used in research rather than destroyed." Indeed, "it is ethically unacceptable for researchers simply to take putatively abandoned or unclaimed tissues and use them in research projects without informing patients about that use."[41] This assessment seems compatible with the religious claims advanced above, in which it is insufficient for researchers interested in studying bodily tissue to rely on a general consent, or on tacit or implicit consent. The patient should express explicit consent and should clearly understand the implications and meaning of this consent. A consent to contribution of body tissue does not constitute a transfer of property, but rather involves the transfer of dispositional authority.

Recommendation 5: Procedures for retrieving, storage and research use of human tissue should incorporate provisions of protection of confidentiality. Such procedures should also provide protections for communities.

The preceding analysis has emphasized the importance in religious thought of the body as partly constitutive of personal identity. While the retrieval of tissue from the dis-incorporated body may diminish the intrinsic connection of self and body in many circumstances, the prospects of genetic analysis of tissue samples and research constructions of a person's genotype can reaffirm this connection in important and potentially risky ways. The concern here is not an expression of theological reductionism, that is, a view that personal identity is derived from genetic make-up. Rather, the issue is that, in a society in which genetic information may be highly valued to parties outside the contributor-researcher relationship, disclosure of this information to such parties may have a significant impact on a person's social self. The religious understandings of the body therefore establish a strong presumption in favor of the protection of this information as confidential.

The justification for confidentiality is embedded in the features of the contribution paradigm. The moral intent of the contribution is to facilitate the advance of biomedical research through the generating of generalizable knowledge. Research that discovers and discloses specific, identifying information, by contrast, risks violating the moral intent of the contribution. Moreover, a contribution entails recipient responsibilities, including a responsibility to prevent harm or discrimination from befalling tissue contributors. These features present presumptive arguments in favor of protection information as confidential. It is possible in some research studies

that study samples taken from members of a larger community, for the community to experience harms and stigmas due to information disclosure, even if the particular individuals from whom tissues are retrieved are anonymous. These protections do not preclude contributors from waiving claims of confidentiality.

Within these justifications and limitations, it seems possible to both respect and acknowledge the sacral role of the body in religious discourse and practice, and promote promising directions in research on human tissue.

Section II

This section briefly explores the views of specific religious traditions on uses of body parts within medicine. As previously discussed, in large measure these positions have evolved in response to therapeutic uses of the body, either for oneself or for others, rather than research uses contemplated in human tissue sampling.

Western Attitudes

Jewish Themes

Rabbinic writings give high esteem to the body as the "masterpiece" of creation. God is worshiped through the body: The positive precepts of the Torah (248) are said to correspond to the number of body parts, and the body is compared to a Torah scroll in its sanctity.[42] Moreover, rights of "ownership" pertaining to the body belong to God, who allows human beings to use the body during the "lease of their lifetimes."[43] Even though the connection between self and body may be severed through, for example, death, there remains an obligation of respectful care for the corpse (*kavod ha'met*) as a creation in the divine image.

Jewish tradition therefore presents a strong presumption in favor of respecting bodily integrity both before and after death. However, the obligation of *pikkuah nefesh*—the duty to preserve life—permits retrieval of bodily organs and tissue if such action occurs when there is 1) an immediate prospect of saving human life and 2) a high probability of achieving a specific benefit. Interpretative issues surround the concepts of "immediate," "probability," and "benefit." Dorff, for example, contends that retrieval of organs for transplant is permitted if it is "known that the body part will *eventually, but definitely*, be used for purposes of transplantation."[44] This reasoning would also seem to validate tissue storage (e.g., blood banking) for therapeutic purposes.

Jewish tradition, then, is likely to give a different appraisal to the need of a prospective recipient of a kidney who can benefit immediately from a transplant and the needs of researchers for human tissue to conduct studies that seem to offer undetermined and remote benefits to future patients. Retrieval of body tissue for general medical knowledge or to establish epidemiological data through tissue banking do not in general satisfy the criteria of providing an immediate practical benefit to another person. While cornea banking is legitimated because the number of prospective recipients indicates a high probability of immediate use, Childress contends that Jewish thought would need to "subordinat[e] the criterion of immediacy to the criterion of the probability of significantly benefiting human beings through the research...." in order to permit biomedical research on human biological materials.[45]

The question with respect to human tissue banking for purposes of research and genetic analysis within Jewish thought, then, is whether such testing a) promises a probable benefit, rather than an exploration that succeeds by serendipity; b) will benefit patients (and not simply provide scientists with general knowledge of genetics); and c) will provide benefits to present or to future patients. Thus, guidelines for policy on tissue research likely to issue from Jewish thought would limit scientific autonomy on grounds of respect for persons as embodied selves; beneficence, especially specific benefits to patients; and justice with respect to the distribution of benefits between present and future patients.

Roman Catholic Themes

Roman Catholic thought affirms the intrinsic nature of the body to both personal and religious identity. Bodily life is incarnational and "sacramental," that is, a revelation of the divine in corporeal form. The sacramental nature of the body is reaffirmed in central doctrinal teachings (the incarnation of Jesus, the resurrection of the physical body), liturgical rituals (baptism, the Eucharist), and ecclesiastical identity, the Church as *corpus Christi* or "body of Christ."

Like Judaism, Roman Catholic discussion about the religious status of the body and body parts has often emerged from such contexts as cadaver dissection, surgery, and organ transplants. The major theological principle invoked in moral deliberation is that of *totality*, which presumes background commitments to bodily integrity and functions and a correlative prohibition against mutilation. The principle of totality historically justified the removal of a diseased part of the body (such as by amputation) for the benefit of the totality of the whole body. The interpretation of totality has subsequently been expanded to encompass benefits to the well-being of the person, and not only the body (that is, psychological and physiological benefit), or to refer to natural body functions (primarily procreative) rather than body parts. However, Pope Pius XII maintained that totality does not extend to justifying communal claims on the body through an appeal to collective or social benefits.[46]

Roman Catholic thought does not require the medical use of body parts to meet conditions of immediacy and specific benefit. It therefore seems more open to the possibility of human tissue banking than does Judaism, although magisterial teaching usually presumes a therapeutic potential. It is possible to donate some body tissues (such as blood) to institutions (such as a blood bank) for storage and eventual use, or to specific persons with immediate needs. Such acts are *donative*—that is, nonobligatory acts of charity offered as a bodily gift rather than a sale—and they are constrained by the principle of proportionality, which requires the benefits to outweigh the burdens for both donor and recipient. This donative context has been reiterated by John Paul II: "[T]he medical act of transplantation makes possible the donor's act of self-giving, that sincere gift of self which expresses our constitutive calling to love and communion."[47]

Protestant Perspectives

Protestants are united on the embodied nature of human life, but disagree over the implications of that commitment. The norm of stewardship requires careful keeping of one's own body and health as a form of reverence for the bodily temple. The integrity of the body on some accounts sets limits on what otherwise is an overarching Protestant theme in both theology and medical ethics, the principle of autonomy. Paul Ramsey, a leading Protestant theologian in medical ethics, was quite critical of both Protestant and "liberal" Catholic acceptance of organ donation because, he maintained, such views reflected a form of Cartesian self/body dualism. Ramsey instead commended "traditional" Jewish and Catholic ethics as a model by which to ground Protestant understandings of the religious significance of the body and of organ donation.[48] In this view, autonomy of the will is constrained by respect for the person as an embodied self.

Protestantism lacks a unifying principle, such as *pikkuah nefesh* or totality, to ground removal of body parts and tissues. Some arguments have appealed to the Protestant vocation to discern the workings of the divine order through the natural world. Critics have maintained that this view supplants the sovereignty of the Creator with the sovereignty of creation and, in the modern context, gives primacy of place over to science and technology rather than worship. The Protestant affirmation of personal autonomy confronts counter-claims that this reduces the image of God to a disembodied will. Although each of these positions gives a theological warrant for medical interventions and uses of the human body, both seem unable to set limits on autonomy, either scientific or personal, with respect to uses of body parts.

William F. May's argument for the donation of body parts, primarily organs and tissues for transplants, appeals to a still different strand of Protestant thought that emphasizes love of neighbor. The central Christian ritual of the eucharist, patterned after the passion of Jesus, exemplifies love of neighbor through sharing one's body to serve others. This provides a profound religious motivation for organ and tissue donation that, because of its altruistic expression, is not susceptible to the critiques directed against autonomy. Moreover, love of neighbor provides a standard against which to assess noncommunal motives for body and tissue removal, such as personal financial gain.[49]

Islamic Concepts

Islam both perpetuates and differs from attitudes to the body displayed in its predecessor Western traditions. The Qu'ran does not use the language of "image of God" to refer to human beings; nonetheless, the body is a divine trust given to persons for the purpose of serving God. Moreover, bodily parts possess a religious significance that parallels the Jewish correspondence between body parts and God's commandments: In Qu'ranic teaching, God will require of each part of the human body to "account for the actions of the person whose bodily organs they formed."[50]

The principal doctrine in Islamic thought that bears on uses of the body is not creation, as in many Jewish and Christian views, but rather the themes of judgment and bodily resurrection. While Allah has power to summon dispersed body parts into an organic whole, Islamic views of bodily resurrection have typically supported immediate burial of an intact cadaver. Dismembered remains, especially those composed of flesh, sinew, and bone, should also be buried out of respect for bodily sanctity.

Similarly, bodily resurrection and respectful treatment for the dead have made organ transplantation and donation a contentious issue among Islamic scholars. Sachedina has interpreted conflicting Muslim juridical opinions on transplantation to presuppose two relevant norms, discretion on the part of a potential donor (or proxy) and the saving of human life. Sachedina concludes that donation of an organ is a permissible, but optional, act within Islamic thought.

Non-Western Attitudes

While Hindu, Buddhist, and Native American understandings of the body can be represented within the broad typology of religious views developed by May, that does not necessarily mean they are more amenable to scientific research involving the body. Each of these traditions is critical of the worldview and values presumed by Western biomedical science, particularly in its more reductionistic forms. The following presents bare outlines of very rich and complex communal traditions and practices to enable a contrast with the Western religious faiths.

Hinduism

Hindu thought on the body more closely reflects a form of gnosticism than the traditions of the West. The ultimate goal of Hinduism is "moksha," or liberation from the confines of the world, including the body, and unification of the self ("atman") with the universal ground of existence ("Brahman"). Hinduism proposes different paths or "yogas" by which this unity is achieved, each of which seek to give the self complete control over every bodily function; the "jnana-yoga," for example, proposes a series of steps in meditation and discipline by which the adherent gains knowledge about and gradually transcends the body, then consciousness, then sub-consciousness, and then ultimately achieves "samadhi," a state of superconsciousness and unity with all life.

Hinduism thus presents a sharp separation of body and self. While body-mind are understood as integrated to some degree, the true self is, in important respects, untouched by medical interventions on the body; it is "eternal, free from disease, free from old age, deathless, free from decay; it cannot be pierced, cut or agitated."[51] Moreover, a prominent Hindu creation narrative describes the sacrifice and dismemberment of the lord of

immortality, out of which life is given to human beings, the world, and the cosmos. This narrative could provide the same religious motivation within Hinduism for donation of the body and body tissues that May attributes to the Christian narrative of the sacrificial death of Jesus.

It should not be concluded from the body/self separation or illustrative narratives embedded in Hindu thought that there are no limits on retrieving human body tissue. Hindu world views offer a holistic understanding of bodily identity and integrity and thereby find themselves in opposition to the reductionist approach of western science and biomedicine. Indeed, some Hindu scholars have seen in the recent reception given to popularized versions of Vedic teaching (e.g., the writings of Deepak Chopra) a generalized resonance with Eastern holism and a shallowness to Western reductionism.[52]

Buddhism

Buddhism also sees as the ultimate purpose of human life to bring to an end the continual suffering experienced in mortality; the primary source of suffering (*dukkha*) is the body or attachment to bodily life. Although Buddhism rejects the concept of self, and instead affirms the "no-self" (*an-atman*), it parallels Hinduism in instituting rules, meditative practices, and rituals designed to culminate in detachment from the body and its desires, and in enlightenment (*nirvana*) about the way things really are. Buddhist understandings of karma give the body a very impermanent and instrumental ontological status. Embodiment is "a patterned heap of a collective of material elements."[53] and this patterning, determined by the workings out of karma, may take the shape of human, animal, or plant form. This, while the body is not accidental to the person, in the sense that it is governed by karma, it is co-incidental.

The body itself is no more than the sum of its constituent parts, the five aggregates or "skandhas." Buddhist writings portray the body as "just a collection of feet and toes, legs, chest, loins, belly, navel, backbone, heart, ribs and flanks, hands, forearms, upper-arms, shoulder, neck, jaw, forehead, head, skull, accumulation by the action that causes existence [karma], the abode of sundry passions, ideas and fancies."[54] The body just "happens," so to speak; it possesses no intrinsic integrity or value. Such an understanding has led major traditions in Buddhist thought to emphasize the instrumental value and dis-value of the body. On one hand, for persons just beginning in the path of the Buddha, Buddhist teachings emphasize renunciation of the body as an "enemy" and encourage meditation on repulsive bodily functions as a path to enlightenment. Once a person has achieved detachment from the body, however, it then can be used as a means for teaching others detachment and the way of enlightenment.

The practical context in bioethics in which these understandings of the body confront medical science and therapy is organ transplantation. As is well known, Japan has recently had contentious debates about changing the standard of death in order to permit transplants, and opposition to such changes has frequently invoked Shinto and Buddhist traditions and values. Buddhism affirms the integrity of the dying process, which is very critical to the prospects of rebirth or even escape from rebirth, and inquiries for bodily organs may be seen as disruptive to this process.

However, since the body in Buddhist teaching is composed of coincidental aggregates, there is no strong claim to the necessity of postmortem bodily integrity. At death, the body begins the process of dis-aggregation. Given that the "self" from whose body organs are removed cannot be affected by transplantation, Buddhist scholars may describe transplantation as "merely an act of technology, much like replacing a carburetor in a car, and not of religiosity."[55]

However, as with Hinduism, Buddhism could not be construed as condoning routine salvage of the body, and reservations are present even with respect to donation. If the requests of recipients, whether patients or researchers, for body organs or tissues reflect an undue attachment to bodily life, they become problematic for Buddhism, because such practices will increase rather than alleviate suffering in the world. Thus, the motives and purposes for organ and tissue retrieval are very closely scrutinized by Buddhist scholars.

Native American

The diversity of Native cultures and their practices regarding the body are just beginning to be probed by bioethics. In the most general terms, Native traditions emphasize a holistic understanding of the relationship between human beings and the natural world, in which balance is sought between the "lifeways." The self, the body, and nature are intimately united; the body in an ultimate sense is integrally intertwined with the earth and its material composition, to which the body will return following death through practices of burial or rituals of exposure. Bodily remains are sacred for Native Americans; disturbance of a gravesite is a sacrilege. Cultural insensitivity to Native values about the body and ancestral bones led to the passage in 1990 of the Grave Protection and Repatriation Act.

Native American practices are also oriented by the primacy of the whole over the part, and the moral priority of the community over the individual. As Freeman argues, this emphasis has important implications for research studies, including research on human tissue. It suggests that the informed consent of individual patients may not be morally sufficient; rather communal consent and perhaps communal participation in the development of a research protocol is more consonant with Native values. This also entails that the community can experience harm, for example, through studies that seek to determine a genetic predisposition to alcohol among the Native population, even if individual participants receive protections of confidentiality and anonymity.[56]

Conclusion

This study has sought to situate the ethical dilemmas posed by biomedical research on human tissue within a context of various religious understandings of embodiment and the centrality of the body to personal identity. If there is one common theme amongst this theological diversity it is the affirmation of the moral significance of the body in its organic totality and a concern that biomedical research may encourage a reductionist attitude towards the body. In so doing, the awe demanded by the presence of an embodied person will be diminished as the self is seen primarily as a disembodied will. The central theological concern is that the sacral role of the body be acknowledged in order to justify biomedical research on bodily tissue.

Notes

1 E. Richard Gold, *Body Parts: Property Rights and the Ownership of Human Biological Materials* (Washington, D.C.: Georgetown University Press, 1996), 149.

2 While Islamic thought clearly affirms the sacrality of the body, the tradition's proscription against images of the divine (e.g., Allah cannot be portrayed in Islamic art) does not allow for use of the language of "image of God" to describe the self.

3 Russell M. Belk, "Me and Thee Versus Mine and Thine," in *Organ Donation and Transplantation: Psychological and Behavioral Factors*, James Shanteau, Richard Jackson Harris, eds. (Washington, D.C.: American Psychological Association, 1990), 139–149, at 144.

4 Janet Lee, Jennifer Sasser-Coen, *Blood Stories* (New York: Routledge), 1996.

5 Gordon Allport, *Becoming* (New Haven, CT: Yale University Press, 1955), 43.

6 Olivia Vlahos, *The Body: The Ultimate Symbol* (New York: J.B. Lippincott Company), 1979.

7 Mary Rosner, T.R. Johnson, "Telling Stories: Metaphors of the Human Genome Project," *Hypatia* 10:4 (Fall 1995):104–129.

8 Russell Scott, *The Body as Property* (New York: Viking Press), 1981; Lori Andrews, "My Body, My Property," *Hastings Center Report* 16:5 (October 1986):28–38.

9 *Moore v. Regents of University of California*, 51 Cal. 3d 120 (1990).

10 James F. Childress, “Attitudes of Major Western Religious Traditions Toward Uses of the Human Body and Its Parts,” in *Justice and the Holy*, Douglas A. Knight, Peter J. Paris, eds. (Atlanta: Scholars Press, 1989), 215–240, at 220, 224; Childress, “Ethical and Legal Issues Regarding Cadavers,” in *Encyclopedia of Bioethics*, 2nd ed, Warren T. Reich, ed. (New York: Simon & Schuster Macmillan, 1995), 1857–1865.

11 Paul Camenisch, “Gift and Gratitude in Ethics,” *Journal of Religious Ethics* 9 (1981), 1–34; Thomas H. Murray, “Gifts of the Body and the Needs of Strangers,” *Hastings Center Report* 17:2 (April 1987):30–38.

12 Hessel Bouma III, et al., *Christian Faith, Health & Medical Practice* (Grand Rapids, MI: Wm B. Eerdmans Publishing Co., 1989), 243–266.

13 Russell M. Belk, “Possessions and the Extended Self,” *Journal of Consumer Research* 15 (September 1988):139–168, at 152.

14 Russell M. Belk, “Possessions and the Extended Self,” at 157.

15 William F. May, *The Patient's Ordeal* (Bloomington, IN: Indiana University Press, 1991), 187–191; May, “Religious Justifications for Donating Body Parts,” *Hastings Center Report* 15:1 (February 1985):38–42.

16 Courtney S. Campbell, “Marks of the Body: Embodiment and Diminishment,” in *Embodiment, Morality, and Medicine*, L. Sowle Cahill, M.A. Farley, eds. (Dordrecht: The Netherlands: Kluwer Academic Publishers, 1995), 169–183.

17 Courtney S. Campbell, “Body, Self, and the Property Paradigm,” *Hastings Center Report* 22, no. 5 (1992):34–42.

18 Eliott N. Dorff, *The Jewish Tradition: Religious Beliefs and Health Care Decisions* (Chicago: Park Ridge Center, 1996), 16–18.

19 Fazlur Rahman, *Health and Medicine in the Islamic Tradition* (New York: Crossroads Publishing, 1989), 106.

20 Immanuel Jakobovits, *Jewish Medical Ethics* (New York: Bloch Publishing Co, 1959), 150.

21 Kenneth V. Iserson, *Death to Dust: What Happens to Dead Bodies?* (Tucson, AZ: Galen Press, Ltd., 1994), 157,158.

22 Ronald P. Hamel, ed. *The Roman Catholic Tradition: Religious Beliefs and Health Care Decisions* (Chicago: Park Ridge Center, 1996), 17.

23 Abdul-Aziz Sachedina, “Islamic Views on Organ Transplantation,” *Transplantation Proceedings* 20:1, Suppl. 1 (February 1988):1084–1088.

24 Christine Quigley, *The Corpse: A History* (Jefferson, NC: MacFarland and Company, Publishers, 1996), 115–120.

25 James F. Childress, *Practical Reasoning in Bioethics* (Bloomington: Indiana University Press, 1997), 301–328.

26 Edwin R. DuBose, ed. *The Episcopal Tradition: Religious Beliefs and Health Care Decisions* (Chicago: The Park Ridge Center, 1996), 7.

27 Jeremy Sugarman, et. al., “Ethical Issues in Umbilical Cord Blood Banking,” *Journal of the American Medical Association* 278:11 (September 17, 1997):938–943.

28 Aroha Te Pareake Mead, “Genealogy, Sacredness, and the Commodities Market,” *Cultural Survival Quarterly* 20 (Summer 1996):46–51.

29 National Bioethics Advisory Commission, *Cloning Human Beings* (Rockville, MD: U.S. Government Printing Office, 1997), iv, v, 110.

30 R. David Saperstein, “Jewish Leader Urges Moratorium on Commercial Patents on Life,” Religious Action Center of Reform Judaism, Washington, D.C., 18 May 1995; Richard Stone, “Religious Leaders Oppose Patenting Genes and Animals,” *Science* 268 (26 May 1995):1126; Ronald Cole-Turner, “Religion and Gene Patenting,” *Science* 270 (6 October 1995):52.

31 Paul Ramsey, *The Patient as Person* (New Haven, CT: Yale University Press, 1970), 5.

32 Ronald P. Hamel, ed. *The Roman Catholic Tradition: Religious Beliefs and Health Care Decisions* (Chicago: Park Ridge Center, 1996), 6–7.

33 Joseph A. Carrese, Lorna A Rhodes, “Western Bioethics on the Navajo Reservation: Benefit or Harm?,” *Journal of the American Medical Association* 274 (1995):826–829.

34 William L. Freeman, “The Role of Community in Research with Stored Tissue Samples,” (unpublished ms).

35 Huston Smith, *The World's Religions* (Harper Collins: San Francisco, 1991), 262.

36 A.M. Honoré, “Ownership,” in *Oxford Essays in Jurisprudence*, A.G. Guest, ed. (London: Oxford University Press, 1961), 118–119.

37 E. Richard Gold, *Body Parts: Property Rights and the Ownership of Human Biological Materials* (Washington, D.C.: Georgetown University Press, 1996), 125–143, 164–177.

38 William F. May, *The Patient's Ordeal* (Bloomington, IN: Indiana University Press, 1991), 187–191; May, "Religious Justifications for Donating Body Parts," *Hastings Center Report* 15:1 (February 1985):38–42.

39 Andrew Kimbrell, *The Human Body Shop: The Engineering and Marketing of Life* (New York: HarperCollins Publishers), 1993; Gold, *Body Parts: Property Rights and the Ownership of Human Biological Materials*, at 35–37.

40 Pope Pius XII, as cited in James F. Childress, "Attitudes of Major Western Religious Traditions Toward Uses of the Human Body and Its Parts," 236.

41 James F. Childress, "Attitudes of Major Western Religious Traditions Toward Uses of the Human Body and Its Parts," 238.

42 Louis Jacobs, "The Body in Jewish Worship: Three Rituals Examined," in *Religion and the Body*, Sarah Coakley, ed. (Cambridge: Cambridge University Press, 1997), 71–89.

43 Eliott N. Dorff, "Choosing Life: Aspects of Judaism Affecting Organ Transplantation," in *Organ Transplantation: Meanings and Realities*, Stuart J. Youngner, Renee C. Fox, Laurence J. O'Connell, eds. (Madison, WI: University of Wisconsin Press, 1996), 168–193, at 171; Abraham Twerski, Michael Gold, Walter Jacob, "Jewish Perspectives," in *The New Harvest*, C.D. Keyes, ed. (Clifton, NJ: The Humana Press, Inc., 1991), 187–197, at 190.

44 Eliott N. Dorff, "Choosing Life: Aspects of Judaism Affecting Organ Transplantation," at 170–171.

45 James F. Childress, "Attitudes of Major Western Religious Traditions Toward Uses of the Human Body and Its Parts," 223, 224; Cf. U.S. Congress, Office of Technology Assessment, *New Developments in Biotechnology: Ownership of Human Tissues and Cells—Special Report*, OTA-BA-337 (Washington, D.C.: U.S. Government Printing Office, 1987), 138–144.

46 John Gallagher, "The Principle of Totality: Man's Stewardship of His Body," *Moral Theology Today: Certitudes and Doubts* (1984), pp. 217–242; Charles E. Curran, "Roman Catholicism," in *Encyclopedia of Bioethics*, 2d ed, Warren T. Reich, ed. (New York: Simon and Schuster Macmillan, 1995), 2321–2331; David Kelly, Walter E. Wiest, "Christian Perspectives," in *The New Harvest*, C.D. Keyes, ed. (Clifton, NJ: The Humana Press, Inc., 1991), 199–221.

47 Pope John Paul II, as cited in Ronald P. Hamel, ed. *The Roman Catholic Tradition: Religious Beliefs and Health Care Decisions*, 13.

48 Paul Ramsey, *The Patient as Person* (New Haven, CT: Yale University Press, 1970) 187–188.

49 William F. May, *The Patient's Ordeal* (Bloomington, IN: Indiana University Press, 1991), 187-191; May, "Religious Justifications for Donating Body Parts," *Hastings Center Report* 15:1 (February 1985), 38–42.

50 Abdul-Aziz Sachedina, "Islamic Views on Organ Transplantation," *Transplantation Proceedings* 20:1, Suppl. 1 (February 1988):1084–1088.

51 Julius J. Lipner, "The Classical Hindu View on Abortion and the Moral Status of the Unborn," in *Hindu Ethics: Purity, Abortion and Euthanasia*, Harold G. Coward, Julius J. Lipner, Katherine K. Young, eds. (Albany, NY: SUNY Press, 1989), 41–70.

52 Cromwell Crawford, "Hindu Developments in Bioethics," *Bioethics Yearbook, v. 5*, B. Andrew Lustig, ed. (Dordrecht, The Netherlands: Kluwer Academic Publishers, 1997), 55–74.

53 Paul Williams, "Some Mahayana Perspectives on the Body," in *Religion and the Body*, Sarah Coakley, ed. (Cambridge: Cambridge University Press, 1997), 205–230, at 207.

54 Steven Collins, "The Body in Theravada Buddhist Monasticism," in *Religion and the Body*, Sarah Coakley, ed. (Cambridge: Cambridge University Press, 1997), 185–204.

55 S.H.J. Sugunasiri, "The Buddhist View Concerning the Dead Body," *Transplantation Proceedings* 22 (1990), 947–949.

56 William L. Freeman, "The Role of Community in Research with Stored Tissue Samples," (unpublished ms).

STORED TISSUE SAMPLES: AN INVENTORY OF SOURCES IN THE UNITED STATES

Commissioned Paper
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Preface

One aspect of the recent and rapid advances in biological and medical research is that human tissue is being used in an increasing variety of new ways. Now that techniques exist to extract DNA from miniscule archival samples, including frozen blood or tissue samples, and even paraffin-embedded tissue blocks, genetic tests could potentially be performed on virtually any stored tissue sample. These technological advances, which have been so instrumental in recent biomedical discoveries, also raise several legal, ethical, and societal issues, including concerns about privacy and informed consent.

To assist in its examination of the issues associated with the use of stored tissue samples, the National Bioethics Advisory Commission (NBAC) requested information about the magnitude of the existing archives of tissues. This report represents the first inventory of stored tissue sample repositories in the United States. Although it is not meant to be a comprehensive inventory, this report does identify the major sources of stored tissue. It also provides information about several aspects of stored tissue samples, such as how many tissue samples there are in the United States, where they are, who has access to them, and for what purposes they are used. This report should also be of interest to science policymakers as well as a large segment of the research and biomedical communities, including research facilities within the federal government such as the National Institutes of Health and the Department of Energy; university-based research laboratories and pathology departments; and research and development divisions of pharmaceutical and biotechnology companies.

This report was prepared by RAND's Critical Technologies Institute (CTI) in response to a request from the Genetics Subcommittee of NBAC and is intended for inclusion in the NBAC's report to the President on stored tissue samples. The author, Dr. Elisa Eiseman, is an American Association for the Advancement of Science Fellow at CTI.

CTI was created in 1991 by an act of Congress. It is a federally funded research and development center sponsored by the National Science Foundation and managed by RAND, a nonprofit corporation created for the purpose of improving public policy. CTI's mission is to help improve public policy by conducting objective, independent research and analysis on policy issues that involve science and technology in order to

- support the Office of Science and Technology Policy and other Executive Branch agencies, offices and councils,
- help science and technology decisionmakers understand the likely consequences of their decisions and choose among alternative policies, and
- improve understanding in both the public and private sectors of the ways in which science and technology can better serve national objectives.

CTI research focuses on problems of science and technology policy that involve multiple agencies. In carrying out its mission, CTI consults broadly with representatives from private industry, institutions of higher education, and other nonprofit institutions.

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the chairs of pathology at the Universities Associated for Research and Education in Pathology; Ginny Levin from George Washington University for providing useful information and informed consent forms from the Women's Health Initiative longitudinal study, as well as general consent forms for diagnostic and therapeutic obstetrical and gynecological procedures; Jayne Hart Chambers, Cathy O'Donaghue, and Dr. Travers from the College of American Pathologists (CAP) for providing documents about the types of laboratories that CAP accredits and the CAP statement on laboratory regulation to the Task Force on Genetic Testing; Philippe Bishop from the National Cancer Institute (NCI) who engaged in substantive discussions and critically reviewed this document; Tom Moore, the CEO of Cord Blood Registry, for valuable information about umbilical cord blood banking; Sheila Taube and Marianna Bledsoe from the NCI for useful information about NCI-funded tissue banks; Michael Peterson from the Armed Forces Institute of Pathology (AFIP) who supplied detailed information about the AFIP National Pathology Repository; Lynn Agostini, Ianve Clark, and Janice Smith from the American Red Cross who provided information about American Red Cross blood banking and tissue services; Brett Fritz from the Eastern Cooperative Oncology Group (ECOG) who supplied information about ECOG tissue banking; Gladys White from the National Advisory Board on Ethics in Reproduction for information on assisted reproduction technologies and fertility clinics; Captain Wurzel, a pathologist at the Bureau of Medicine and Surgery, United States Navy, who supplied information and contact names for Navy pathology and blood banking services; Jean McEwen from Boston College School of Law who suggested people to contact for information on DNA banking; Gregory Curt from the NCI for examples of informed consent forms for clinical trials and diagnostic procedures at the NCI; Ken Goodman, the director of the Forum for Bioethics and Philosophy at the University of Miami for examples of informed consent for genetic research on biological samples; Richard A. Rettig from RAND for critically reviewing this document; Donna Fossum and David Trinkle from RAND for guidance on the use of the RaDiUS database; Birthe Wenzel from RAND for her computer expertise; and everyone who provided valuable information about sources of stored tissue samples described in this report.

1. Introduction

Human tissues have been stored for many decades. 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 diseases such 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 have made it possible to analyze DNA from almost any miniscule sample of human tissue, concerns about privacy and informed consent also are raised. Complicating these issues is the paucity of information addressing tissue acquisition, use, and storage.

To date, no central database captures information about stored tissue samples. Therefore, the National Bioethics Advisory Commission (NBAC) requested information about stored tissue samples in the United States to obtain a better understanding of the magnitude of existing archives. The purpose of this report is to bring together for the first time, in a single document, information about tissue storage in the United States. Although it is not meant to be a comprehensive inventory, this report does identify the major sources of stored tissue and will attempt 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)

In this report, human tissue is defined as including everything from subcellular structures such as DNA, to cells, tissue (bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, placenta). The most common source of tissue is from patients following diagnostic or therapeutic procedures. Tissue specimens may also be taken during autopsies that are performed to establish 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 may be stored in multiple forms, such as slides, paraffin blocks, formalin-fixed, frozen, tissue culture, or extracted DNA.

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 where biological evidence is available for comparison.

Tissue collections vary considerably, ranging from formal repositories to the informal storage of blood or tissue specimens in a researcher's freezer. Other 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 nonprofit organizations.

This report classifies these tissue collections into the following categories: large tissue banks, repositories and core facilities; longitudinal studies; research that simultaneously creates tissue collections or contributes to a tissue bank; pathology specimens; newborn screening laboratories; forensic DNA banks; sperm, ovum, and embryo banks; stem cell blood banks; organ banks; and blood banks. The report also contains two appendices: Appendix 1 contains a list of organ banks in the United States, and Appendix 2 provides a listing of Internet websites referenced in this report.

2. Methods

Definitions

Several terms used in this report require further definition:

1) In this report, *human tissue* is defined as including everything from subcellular structures such as DNA, to cells, tissue (bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, placenta).

2) This report attempts to count both the number of *cases* from which stored tissues are derived as well as the number of *specimens* generated from each case. For example, when a patient enters the hospital for a biopsy, the resulting tissue is accessioned in the pathology department as a single case. However, that single biopsy may generate several specimens, including a number of slides, a paraffin block, and a frozen sample.

3) In this report, the term *DNA Bank* refers to a facility that stores extracted DNA, transformed cell lines, frozen blood or tissue, or biological samples for future DNA analysis. Specimens are usually stored with some form of individual identification for later retrieval. *DNA Databanks* are repositories of genetic information obtained from the analysis of DNA samples, sometimes referred to as *DNA profiles*. The genetic information is usually stored in computerized form with individual identifiers.

4) *Graduate Medical Education (GME) programs* are the primary means of medical education beyond the four-year medical school training received by all physicians. Usually called residency programs, they are based in hospitals or other health care institutions, some of which do and some of which do not have formal relationships with medical schools. *GME Teaching Institutions* include medical schools; the Armed Forces hospitals; Veterans Affairs medical centers; the Public Health Service (PHS); state, county, and city hospitals; nonprofit institutions; and health maintenance organizations.

Data Collection

For this report, collections of stored tissue samples were identified through several sources: 1) a literature review of papers about tissue and DNA banks; 2) searches of the World Wide Web; 3) searches of RAND's RaDiUS database to identify federally funded sources of stored tissue; and 4) personal communications and consultation with experts. Several papers served as valuable sources of information on DNA banks and DNA databanks, including Forensic DNA Banks and the Department of Defense (DoD) DNA Specimen Repository for Remains Identification. Information contained in numerous Internet websites for several tissue banks, organ banks, umbilical cord blood banks, sperm and embryo banks, and longitudinal studies was also used in this report. Relevant websites appear in Appendix 2 of this report. In addition, RAND's RaDiUS database provided information about government, university, nonprofit, and commercially based tissue repositories. Finally, a substantial amount of information was obtained through personal communications with various people, including pathologists, relevant people at several tissue banks, and experts who have published several papers on the subject of stored tissue samples.

RaDiUS

RAND's RaDiUS (Research and Development in the United States) database is a comprehensive, real-time accounting of federal research and development (R&D) activities and spending. RaDiUS allows users to see the total R&D investment by all federal agencies, to compare the level of R&D investment in specific areas of science and technology across all federal agencies, or to examine the details of research investments within a specific agency. RaDiUS was searched using proximity and wildcard searches for combinations of six different search terms: tissue(s), bank(s), repository(ies), blood, DNA, and cell(s). The following searches yielded 203 unique hits: 1) tissue(s) near bank(s); 2) tissue(s) near repository; 3) blood near bank(s); 4) DNA near bank(s); and 5) cell(s) near repository(ies).

Estimate of Cases Accessioned at GME Teaching Institutions

Two techniques were used to estimate the total number of cases accessioned per year at all GME institutions and the number of tissues stored at each institution. The first estimate used information found in the American Medical Association's *Graduate Medical Education Directory 1997–1998* about residency programs in pathology at GME institutions (American Medical Association, 1997). However, information was not available about all pathology specialties. Therefore, a second estimate was made from information obtained from several chairs of pathology departments attending the Universities Associated for Research and Education in Pathology (UAREP) at the Federation of American Societies for Experimental Biology (FASEB).

An analysis was performed to estimate the total number of cases accessioned per year at all GME teaching institutions in the pathology specialties of anatomic and clinical pathology, dermatopathology, forensic pathology, neuropathology, and pediatric pathology. This calculation was based on 1) the number of GME pathology programs in each specialty; 2) the number of resident positions open in these programs for the academic year; 3) the recommended number of cases per program to meet the training requirements of the residents; and 4) the duration of the program in years. An estimate of the number of cases/specimens accessioned in cytopathology and hematopathology programs was obtained by averaging the number of cases/specimens reported on various GME teaching institutions' Internet websites.

Chairs of pathology departments attending the UAREP meeting were asked several questions about the pathology departments at their institutions. Information from ten pathology chairs was obtained about the size of their institutions, the number of cases accessioned per year, the age of the oldest tissues archived, how long the tissue samples are stored, what identifying information is kept with the tissues, and who has access to the samples. This information was used to calculate ranges and averages of hospital size and number of cases accessioned.

3. Large Tissue Banks, Repositories, and Core Facilities

Large tissue banks and repositories exist in almost every sector of the scientific and medical communities, including the military, the federal government, universities and academic medical centers, commercial enterprises, and nonprofit organizations. In addition, several universities have established core tissue banking facilities to support both their own research as well as collaborations with other universities. These large tissue banks, repositories, and core facilities are a major source of human tissue for biomedical research.

Military Facilities

The military maintains two of the largest tissue repositories in the world. The National Pathology Repository and the DoD DNA Specimen Repository for Remains Identification are both housed within the Armed Forces Institute of Pathology (AFIP). The AFIP is responsible for maintaining a central laboratory of pathology for consultation and diagnosis of pathologic tissue for DoD, other federal agencies, and civilian pathologists. The AFIP also conducts research in pathology, trains enlisted personnel in histopathology and related techniques, and offers more than 50 pathology education courses for medical, dental, and veterinary personnel.

National Pathology Repository. The National Pathology Repository, located at the AFIP, is the largest and most comprehensive collection of pathology material in the world. Since 1917, the Pathology Repository has collected more than 2.5 million cases comprising more than 50 million microscopic slides, 30 million paraffin tissue blocks, 12 million preserved wet-tissue specimens, and associated written records. The Pathology Repository accessions approximately 50,000 cases annually, with 53,384 cases accessioned in the fiscal year (FY) 1996, and 51,908 in 1997. In addition, approximately 40,000 cytology cases are sent for primary diagnosis annually, but are not accessioned. (Only cytology cases sent for second opinions are accessioned.) During 1993, approximately 10,000 of the cases were cancers and 8,000 were benign neoplasms, with the balance representing the entire spectrum of human disease. Material is stored permanently unless there is a specific request by the contributor or other authorized individual to return or release the material.

The AFIP accepts cases from all Army, Navy, and Air Force medical facilities and investigative agencies. The AFIP also serves as the central laboratory of pathology for the DoD and certain other federal agencies, such as the PHS and the Justice Department. In addition, the AFIP serves as a Veterans Affairs Special Reference Laboratory for Pathology and maintains a special registry of former prisoners of war. Civilian and foreign contributions are accepted from pathologists (or clinicians who are functioning as pathologists) through

the Civilian Consultation Program. Cases represent both sexes, all races/ethnicities, and all ages and come from contributors worldwide.

Cases are sent to the AFIP for a variety of reasons. The majority of cases are submitted to the AFIP because the contributor wants a second opinion regarding the diagnosis. Some are forwarded as part of established peer-review and quality assurance programs. Some military cases are required to be forwarded by DoD regulation, such as forensic cases and cases subject to litigation. Other cases are submitted because they are unusual or rare and may be able to be used by the AFIP in research and education missions. In addition, cases have been submitted over the years for specific purposes, such as to study particular diseases or to answer current and future research questions (e.g., serum from Gulf War veterans).

All submitted case material is coded by pathological diagnosis and is identified by an AFIP accession number. The source name, Social Security number, date of birth, age, sex, and race are stored if provided by the contributing pathologist. Any medical history provided is stored in the case folder and on an optical disk imaging system. The source address is not routinely provided or stored but is obtained on occasion for follow-up studies. Likewise, the original consent is a matter between the patient and the clinician and is not routinely provided to AFIP by the contributing pathologist. The submitting pathologist's name and address and the source's surgical identification numbers are also stored.

All research protocols using Pathology Repository stored material or data are reviewed by the AFIP's Institutional Review Board (IRB). Research involving patient follow-up, and thus requiring identifying information, is reviewed at a full meeting of the IRB prior to approval. Other than for research involving follow-up, original sources of material are not notified. If an unexpected disease or abnormality is discovered, the contributing pathologist is notified, and it is then up to the pathologist to contact the patient. Otherwise, current AFIP policy requires that material be anonymized before release to outside investigators.

The main functions of the Pathology Repository are consultation, education, and research in pathology. The Pathology Repository also loans pathologic material to assist in patient treatment, for research, or for litigation. Requests for loan of material or provision of data for research purposes require submission and approval of a research protocol. Requests from individuals or organizations other than the original contributor must be accompanied by a properly executed authorization signed by the patient or designated representative. Pathologic specimens stored at the Pathology Repository can be used to study unusual tumors or as part of a public health surveillance system to study emerging infectious diseases or trends in disease progression. For example, samples in the Pathology Repository have been used to identify and date tissues harboring genomic material of the human immunodeficiency virus (HIV) that were obtained before the availability of HIV testing and before the spread of the HIV infection.

DoD DNA Specimen Repository for Remains Identification. The DoD DNA Specimen Repository for Remains Identification is the world's largest DNA bank. As of September 1997, the DNA Repository has received approximately 2 million DNA specimens. Specimens come into the DNA Repository at a rate of 10,000 per day, and the tally (database) is updated every seven seconds. It is estimated that by year 2001, the DNA Repository will contain approximately 3.5 million samples. All DNA specimens will be maintained for 50 years before being destroyed. However, donors may request that their specimens be destroyed following the conclusion of their military service obligation or other applicable relationship to DoD.

Since June 1992, the DoD has required all military inductees and all active duty and reserve personnel to provide blood and saliva samples for its DNA Specimen Repository at the time of enlistment, re-enlistment, annual physical, or preparation for operational deployment (McEwen, 1997). The DNA Repository also contains samples from civilians and foreign nationals who work with the United States military in arenas of conflict. A total of three DNA specimens are collected from each person: one bloodstain card is stored in a pouch in the service member's medical record; another bloodstain card and a buccal swab are stored at the

DNA Specimen Repository. The blood is placed on special cards with the service member's Social Security number, date of birth, and branch of service designated on the front side of the card, and a fingerprint, a bar code, and signature attesting to the validity of the sample on the reverse side. The bloodstain card stored at the DNA Repository is placed in a vacuum-sealed bag and frozen at -20°C. The buccal swab is fixed in isopropanol and stored at room temperature. DNA will be extracted from the specimens in the Repository only when it is needed for the purpose of remains identification.

The DNA Repository, along with the Armed Forces DNA Identification Laboratory, make up the DoD DNA Registry. The purpose of the DNA Registry is to identify the remains of soldiers killed in combat or missing in action. High velocity weapons often destroy any chances of using fingerprints or dental records, but DNA can almost always be used to identify remains. Most times, the armed forces can identify the dead based on rosters, but DNA identification provides closure for the family and biological proof of death required by life insurance companies. The military's policy ensures that specimens can be used only for remains identification and routine quality control except when subpoenaed for the investigation or prosecution of a felony. The specimens cannot be used without consent for any other purpose, such as paternity suits or genetic testing. In addition, the specimens are considered confidential medical information, and military regulations and federal law exist to cover any privacy concerns.

National Institutes of Health

The National Institutes of Health (NIH), founded in 1930, consists of 24 separate institutes, centers, and divisions. The NIH is the principal health research agency of the federal government. It is one of the eight health agencies of the PHS, which is part of the United States Department of Health and Human Services (DHHS). The mission of the NIH is to protect and improve human health. To accomplish its mission, the NIH conducts and supports basic, applied, and clinical and health services research aimed at understanding the processes underlying human health and acquiring new knowledge to help prevent, diagnose, and treat human diseases and disabilities. In 1997, the NIH budget was more than $12.7 billion. The extramural program, which accounts for approximately 80–85 percent of NIH's total budget, awards grants to researchers at universities, medical schools, hospitals, small businesses, and research institutions across the country, while the intramural program, which represents approximately 11 percent of the budget, supports research and training of scientists at the NIH. NIH is probably the single highest funder of extramural tissue and data resources for basic, applied, and clinical research. Some of the institutes at NIH that support tissue banks include the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Mental Health (NIMH), and the National Institute on Aging (NIA).

The NCI, the largest of NIH's biomedical research institutes and centers, has coordinated the government's cancer research program since 1937. Through both its extramural and intramural programs, the NCI supports research on all aspects of cancer prevention, detection, diagnosis, and treatment. In addition, the NCI supports several tissue and data resources for cancer research, including the NCI Cooperative Human Tissue Network, the Gynecologic Oncology Group Tissue Bank, the NCI Cooperative Breast Cancer Tissue Resource, the NCI-NAPBC (National Action Plan on Breast Cancer) Breast Cancer Specimen and Data Information System, the NCI Cooperative Family Registry for Breast Cancer Studies and NCI Cooperative Family Registry for Colorectal Cancer Studies, and the NCI AIDS Malignancy Bank .

NCI Cooperative Human Tissue Network. The Cooperative Human Tissue Network (CHTN), supported by the NCI since 1987, provides biomedical researchers with access to fresh surgical or biopsy specimens of normal, benign, precancerous and cancerous human tissues (see Table 1). The CHTN is a tissue collection system and not a tissue bank. Only very rare specimens that are difficult to obtain are stored to anticipate

future requests. Except for a collection of frozen tissue from rare pediatric tumors, banked specimens are generally not stored for longer than one year. Normally, the specimens are obtained prospectively to fill specific researcher requests. Five member institutions[1] coordinate the collection and distribution of tissues across the United States and Canada. Tissues are provided by the CHTN only for research purposes and cannot be sold or used for commercial purposes. The intent of the CHTN is to encourage research using human tissue for the good of the public rather than for private gain.

During the first nine years of operation, the CHTN supplied more than 100,000 specimens to approximately 600 investigators. CHTN tissues have been used in many areas of cancer research for a wide variety of basic and developmental studies, including molecular biology, immunology, and genetics. Researchers have used these tissues to study mutations of protooncogenes in human tumors and the role of growth factors in cancer and to isolate new cancer genes. More than 2,000 publications have resulted from studies using CHTN tissues.

The CHTN obtains tissues from routine surgical resections and autopsies. Tissues are from both adult and pediatric patients and represent all organ systems, as well as blood and other body fluids. Specimens are collected according to the individual investigator's protocol and may be preserved as fresh, fixed or frozen tissue, slides, or paraffin blocks. The CHTN was designed for basic research studies not requiring clinical follow-up information. Each specimen is given a unique identifier. A link is kept by the parent institution for quality control purposes. Only minimal demographic data is provided with the specimen. Other information routinely provided with the specimens includes pathology reports and histological characterization.

NCI-NAPBC Breast Cancer Specimen and Data Information System. The NCI is developing a national information database of breast cancer resources to fulfill one of the six priorities of the NAPBC. The NCI-NAPBC Breast Cancer Specimen and Data Information System contains information about 14 breast tissue banks. This database does not represent an exhaustive national listing of all facilities holding breast cancer tissue. However, by centralizing information on biological specimens, this database promotes access to breast tissue specimens and facilitates collaboration among basic, clinical, and epidemiologic researchers. Table 1 summarizes the information contained in the NCI-NAPBC Breast Cancer Specimen and Data Information System.

Table 1. NCI-NAPBC Breast Cancer Specimen and Data Information System

Resource	Number of Specimens	Tissue Type(s)	Other Data	Limitations
Dana Farber Cancer Institute	225 invasive breast cancer cases	- cell lines - DNA - plasma - frozen cells	- demographic - clinical - other	no identifying information provided
Duke University	> 1,400 blood and tissue samples in inventory (50 fresh and 140 frozen tissues per year)	- blood or blood products - fresh and frozen malignant, benign, and normal tissue	- demographic - clinical - outcome	collaboration required
Georgetown University Medical Center and Lombardi Cancer Center and SPORE	~ 200 cases per year of paraffin-embedded tissue since the mid-1970s (each case has from 3–30 tissue blocks)	- blood or blood products - frozen and paraffin-embedded malignant, benign, and normal tissue	- demographic - clinical - outcome	collaboration required
National Cancer Institute of Canada-Manitoba Breast Tumor Bank	malignant: 2,000+ cases normal: 100 cases (each case has matching frozen and paraffin-embedded blocks)	frozen and paraffin-embedded malignant and normal tissue	- demographic - clinical - outcome	acknowledge bank in publications; only use samples for studies proposed

Table 1. NCI-NAPBC Breast Cancer Specimen and Data Information System *continued*

Resource	Number of Specimens	Tissue Type(s)	Other Data	Limitations
National Surgical Adjuvant Breast and Bowel Project (NSABP)[a]	10,000 specimens of malignant tissue from breast cancer patients enrolled in NSABP clinical trials	paraffin-embedded malignant tissue	- demographic - clinical - outcome	use limited to nongenetic studies only
NCI Cooperative Breast Cancer Tissue Resource (CBCTR)[b]	8,289 primary breast cancer tissues	formalin-fixed, paraffin-embedded primary breast cancer tissues	- demographic - clinical - outcome - other	must document IRB approval for use of human subjects
NCI Cooperative Human Tissue Network (CHTN)[c]	specimens collected to meet researcher requests; only rare specimens banked to meet future requests	neoplastic and associated normal tissue, blood, and body fluids from routine resections and autopsies	- demographic - clinical - outcome	cannot be used to produce a commercial product
NCI Surveillance, Epidemiology, and End Results Program (SEER)[d]	not applicable	this is a source of breast cancer-related data, not actual specimens	- demographic - clinical - outcome	must sign confidentiality statement
New York University Medical Center[e]	- 300 malignant samples - 500 benign and precancerous samples (10 slides per case) - 500 serum and blood samples	- blood or blood products - frozen and paraffin-embedded malignant, benign, and normal tissue	- demographic - clinical	none specified
North Central Cancer Treatment Group Research Base at Mayo Clinic	800 specimens from breast cancer patients entered in clinical trials over the past 10 years	paraffin embedded malignant tissue	- demographic - clinical - outcome	peer reviewed, scientifically meritorious uses
San Antonio SPORE - Familial Breast Cancer Registry and Gene Bank	6 frozen and 42 paraffin-embedded malignant breast cancer specimens	- blood or blood products - frozen and paraffin-embedded malignant tissue	- demographic - clinical - outcome	collaboration required
San Antonio SPORE - National Breast Cancer Tissue Resource	151,320 biopsy specimens from about 101,000 cases of breast cancer	frozen malignant tissue	- demographic - clinical - outcome	collaboration required
University of Michigan[f]	- malignant: 5–10 fresh/month, >100 frozen, several hundred paraffin-embedded - normal: 1–2 fresh/month, ~20 frozen, >100 paraffin-embedded	- fresh, frozen, and paraffin-embedded normal and malignant tissue - blood or blood products - cells and cell lines	- demographic - clinical - outcome	none specified
University of Pennsylvania[g]	- frozen: 200 malignant, 30 benign, and 100 normal - paraffin-embedded: >1,000 malignant, >1,000 benign, >1,000 normal - >500 lymphoblastoid cell lines	- fresh, frozen, and paraffin-embedded normal, benign and malignant tissue - blood or blood products - lymphoblastoid cell lines	- demographic - clinical - outcome	results reported back for inclusion in University of Pennsylvania database

[a]National Surgical Adjuvant Breast and Bowel Project, www-cbctr.ims.nci.nih.gov
[b]NCI Cooperative Breast Cancer Tissue Resource, www-chtn.ims.nci.nih.gov
[c]NCI Cooperative Human Tissue Network, www.nsabp.pitt.edu
[d]NCI Surveillance, Epidemiology, and End Results Program, www-seer.ims.nci.nih.gov
[e]New York University Medical Center, www.med.nyu.edu
[f]University of Michigan, www.cancer.med.umich.edu/umbnkdb.html
[g]University of Pennsylvania, www.upenn.edu

Cumulatively, the 14 breast tissue banks in the NCI-NAPBC database contain more than 130,000 cases of breast cancer-related specimens and data, with banks ranging in size from 48 cases to approximately 101,000 cases (see Table 1). Three of the 14 banks are accruing as many as 200 new cases per year. A specimen from a single case may generate several samples. For example, a specimen from a single case may be split into 3–30 paraffin-embedded blocks, ten slides, or matched frozen and paraffin-embedded tissue blocks (i.e., one frozen and one paraffin-embedded sample from the same case). A conservative estimate is that there are approximately 240,000 samples in the database. Samples available to the research and clinical communities include breast tissue, serum, urine, cells, and DNA from patients diagnosed with breast cancer, those at high risk, and unaffected individuals. Information on demographics (age, sex, race, ethnicity, family history of cancer), clinical findings (pathologic diagnosis, stage, initial therapy), and outcome (subsequent breast cancer, vital status) is also available from some institutions.

NCI Cooperative Breast Cancer Tissue Resource. The Cooperative Breast Cancer Tissue Resource (CBCTR), supported by the NCI, provides researchers with access to more than 8,200 cases of formalin-fixed, paraffin-embedded primary breast cancer tissues (see Table 1). The current specimens represent cases accessioned starting in 1974 through the present. Each case is given a unique identifier. Since the block is currently part of the pathology archives, a link is kept at the collecting institution. The link provides a one-way flow of information for research purposes but is not part of the research database. Associated pathology and clinical data, such as demographic data, diagnosis, extent of disease, treatment, follow-up, recurrence, survival, and vital status are available. However, patient identification or information about other family members will not be provided. Cases representing all stages of disease from both sexes, all ages, and all races/ethnicities are available for study. Four collaborating institutions contribute tissue and data from patients treated at their hospitals: Fox Chase Cancer Center, Philadelphia, Pennsylvania; Kaiser Foundation Research Institute, Portland, Oregon; University of Miami, Miami, Florida; and Washington University, St. Louis, Missouri. The resource was designed for large studies to validate promising diagnostic and prognostic markers for breast cancer.

NCI Cooperative Family Registry for Breast Cancer Studies and NCI Cooperative Family Registry for Colorectal Cancer Studies. The Cooperative Family Registry for Breast Cancer Studies (CFRBCS), initiated by the NCI in 1995, contains biological specimens from patients with a family history of breast cancer, breast/ovarian cancer, or Li-Fraumeni syndrome, and their relatives. Six CFRBCS sites collaborate to ascertain families at high and intermediate risk for breast cancer.[2] Specimens are in the form of tissue sections from paraffin-embedded breast and ovarian cancers, peripheral blood lymphocytes, serum, fresh frozen tissue, and other biological fluids. The CFRBCS provides related family history (pedigrees), and clinical, demographic, and epidemiologic data on risk factors exposures, but will not provide patient identification. In addition, the CFRBCS will provide follow-up epidemiologic data as well as data on recurrence, new morbidity, and mortality in the participating families. The CFRBCS repository and related databases are available to the research community to provide a resource for interdisciplinary and translational breast cancer research. The Cooperative Family Registry for Colorectal Cancer Studies, a similar resource for colorectal cancer, was recently established and is expected to be available to the research community in early 1998.

Gynecologic Oncology Group Tissue Bank. The Gynecologic Oncology Group (GOG) Tissue Bank, supported by the NCI, provides malignant, benign, and normal ovarian and cervical tissue from more than 3,176 patients for molecular biology studies of gynecologic tumors. The specimens are stored as snap-frozen specimens, formalin-fixed sections, OCT embedded primary tumor, touch imprint slides, and patient serum collected prior to surgery. Currently, specimens are stored dating back five years. Each case is given a unique identifier, and a link is kept at the GOG Tissue Bank. The link provides a one-way flow of information for research purposes. Clinical information is provided with each case and may include patient age and race in addition to the institutional pathology and operative reports.

Specimens are obtained from patients on clinical trials at approximately 76 participating institutions and are stored centrally at the Children's Hospital Research Foundation in Columbus, Ohio. The GOG Tissue Bank is ideal for clinical correlative studies to identify those factors that place patients with ovarian carcinoma at high risk for treatment failure independent of traditional variables such as stage, grade, and cell type. A total of 52 projects, focusing mainly on the molecular genetics underlying gynecologic malignancies, have utilized this resource.

Cooperative Central Nervous System Consortium Tissue Bank. The Central Nervous System Consortium (CNSC) is funded by the Cancer Therapy Evaluation Program and the Radiation Research Program of the Division of Cancer Treatment Diagnosis and Centers at the NCI. The CNSC conducts laboratory and clinical phase I and phase II research trials to study central nervous system tumor biology and to discover new treatments for adult patients with malignant brain tumors. The Cooperative CNSC Tissue Bank provides the consortium with a mechanism for sharing human brain tumor specimens among investigators conducting research on the biology, clinical behavior, or therapy of central nervous system tumors.

Eastern Cooperative Oncology Group. The Eastern Cooperative Oncology Group (ECOG), established in 1955, is supported by the NCI. ECOG is an international organization with more than 365 university- and community-based hospitals and practices and more than 4,000 participating scientists and health care professionals, including physicians, statisticians, nurses, clinical research associates, and pharmacists. ECOG's primary function is to conduct clinical trials that compare new therapeutic approaches to standard therapies, assess dosing and toxicity, or determine response rates of experimental therapies. In addition to clinical trials, ECOG conducts studies in cancer control and prevention and performs translational research. ECOG's overall goal is to improve the care of patients with cancer.

Tissue banking is an integral part of the laboratory science effort of ECOG. ECOG maintains four tissue banking facilities, a solid tumor tissue bank, a myeloma tissue bank, a leukemia cell bank, and an immunologic tumor repository. In January 1997, ECOG moved the solid tumor tissue bank and disbursement facility from the ECOG Operations Office in Boston, Massachusetts, to the Pathology Coordinating Office (PCO) in Evanston, Illinois. The new facility consists of 750 square feet of space, a 500 square foot laboratory, a specially designed 250 square foot walk-in cold room for storage of paraffin-embedded tissue blocks and slides, and a -80ºC freezer for storage of bone marrow and DNA. The ECOG-PCO is responsible for acquisition, storage, data entry, tissue processing, and quality assurance of solid tumors and lymphomas. The ECOG-PCO stores both retrospective, archived fixed tissues (blocks and slides) and prospectively collected tissues (blocks, slides, frozen tissues, etc.). Tissue samples will never be discarded from the bank, and great efforts will be made to always maintain at least a portion of all samples. Tissues will be returned to their home institutions for storage if the ECOG-PCO bank ever closes. In 1995, the solid tumor bank contained 3,000 paraffin-embedded blocks and 15,000 slides with an estimated accrual rate of 3,000 blocks per year. The ECOG-PCO bank also stores specimens for three other Cancer Cooperative Groups, the Southwest Oncology Group (SWOG), the Cancer and Leukemia Group B (CALGB), and some specimens from the Radiation Therapy Oncology Group (RTOG) (see below).

Radiation Therapy Oncology Group. The Radiation Therapy Oncology Group (RTOG), established in 1968, has had funding from the NCI since 1971. RTOG is a national cooperative cancer study group that conducts multicenter clinical trials that integrate surgical, radiotherapeutic, and chemotherapeutic treatments. Since its inception, the RTOG has activated 271 protocols and has accrued a total of about 56,000 patients to cooperative group studies. More than 250 radiation oncology departments in North America are members of the RTOG, which has its headquarters at the American College of Radiology in Philadelphia, Pennsylvania. In 1996, RTOG created the Translational Research Program, which coordinates RTOG's basic science committees, including the Tumor Repository.

In 1993, a frozen tumor tissue repository was established at Fox Chase Cancer Center to provide access to frozen tissue for use in correlative and translational studies. The frozen tumor repository collects three to five frozen tissue fragments per case from phase III protocols of cervical, lung, head and neck, esophageal, and anal cancers. Currently, the frozen tumor repository contains more than 290 specimens from approximately 70 different tumors (cases). Approximately two-thirds of the specimens are from cervical cancer, and the next most abundant specimens are from head and neck tumors.

Because of technological advances allowing the analysis of tumor markers in paraffinized tissue removed from tumors, the RTOG began archiving paraffin blocks and tissues from all RTOG phase III trials in 1995. Phase III protocols for cancer of the prostate, bladder, lung, head and neck, esophagus, and malignant glioma were modified to contain a request for blocks or unstained slides on each patient. The patient consent form was modified to allow tissues to be stored and used for future research. These tissues are used for population-based studies, not patient-related issues, and investigators performing the research do not have access to clinical information that might allow patient identification or linkage to treatment and demographics. A central processing site for all blocks and unstained slides was established in February 1996 and funded by NCI in November 1996. The fixed tissue repository was moved to Latter Day Saints Hospital in March 1997. Currently, the RTOG has approximately 4,400 cases stored at a central repository in Salt Lake City, Utah, and is accruing about 1,500 cases per year.

NCI AIDS Malignancy Bank. The NCI AIDS Malignancy Bank (AMB), established by the NCI in 1994, consists of five "banks" located in San Francisco and Los Angeles, California, Washington D.C., Ohio, and New York. Each bank is actually a multi-institutional consortium. The San Francisco consortium is centered at the University of California-San Francisco and is coordinated by the AIDS Immunobiology Research Laboratory at San Francisco General Hospital. It consists of investigators at the major hospitals in San Francisco, New England Deaconess Medical Center in Boston, Memorial Sloan-Kettering Hospital in New York, and the Duke University Oncology Consortium of eight hospitals in the southeastern United States. The Washington, D.C., bank is a consortium operated by the Department of Pathology at George Washington University Medical Center with participation by the Children's National Medical Center, Fairfax Hospital, Howard University Hospital, the University of Miami, the Veterans Affairs Medical Center, and Washington Hospital Center. The Ohio State AIDS Malignancy Bank is in consortium with the University of Texas Southwestern Medical Center in Dallas, Texas. The participating institutions in New York are the State University of New York Health Science Center at Brooklyn, King's County Hospital Center, and Woodhull Medical and Mental Health Center. The University of California-Los Angeles AIDS Malignancy Bank consortium includes the University of Southern California.

The AMB is a collection of tissues and biological fluids with an associated clinical database from patients with HIV-related malignancies. As of May 1997, the AMB contained 8,847 samples from 3,134 cases of HIV-related malignancies. The AMB contains formalin-fixed paraffin-embedded tissues, fresh frozen tissues, malignant cell suspensions, fine needle aspirates, and cell lines from patients with HIV-related malignancies. The bank also contains serum, plasma, urine, bone marrow, cervical and anal specimens, saliva, semen, and multisite autopsy tissues from patients with HIV-related malignancies, including those who have participated in clinical trials. The bank has an associated database that contains prognostic, staging, outcome, and treatment data on patients from whom tissues were obtained. Follow-up clinical information will be requested every six months. The specimens and clinical data are available to qualified investigators in the United States for research studies, particularly those that translate basic research findings to clinical applications. Access to these specimens should encourage and facilitate research in HIV-related malignancies.

National Institute of Allergy and Infectious Diseases. The NIH AIDS Research and Reference Reagent Program (Repository), established by NIAID in 1988, is a unique resource. The Repository is an AIDS

Collaborating Center of the World Health Organization. It acquires critically needed reagents for AIDS-related research and provides these reagents free of charge to qualified investigators worldwide. The Repository contains samples of cell lines, HIV and related viruses, opportunistic infectious agents associated with HIV infections, DNA libraries, DNA clones, antibodies, purified proteins, synthetic peptides, body fluids, and reference standards.

The Repository encourages collaborative research aimed at standardizing reagents and laboratory techniques. Most of the reagents in the Repository are used by and donated by scientists from the NIH, academic and nonprofit institutions, and the private sector. Any commercial use of reagents requires written permission and compensation of reagent donor(s) and notification of the Repository. Currently, the Repository has 500 registered users of its services. During the past five years, the Repository has provided more than 17,000 reagents to AIDS investigators worldwide.

National Heart, Lung, and Blood Institute. The Transfusion Medicine Branch of the NHLBI has a Blood Specimen Repository that is available for use by the research community for research related to transfusion-transmitted diseases, other blood disorders, or diseases of the cardiovascular system. The repository is operated by McKesson Bioservices, Corp., located in Maryland, through an extramural contract with NHLBI. The repository, established in 1974, contains approximately 1.5 million well-characterized specimens of serum, plasma, and cells from NHLBI-sponsored studies. Since 1991, the Blood Specimen Repository has been storing an average of approximately 300,000 samples per year (NHLBI, 1996). (See Figure 1.) In 1995, the demand for specimens greatly increased. From 1991 to 1993, approximately 1,000 specimens per year were distributed to researchers, in 1994 approximately 4,000 specimens were distributed, while in 1995 approximately 20,000 specimens were distributed (NHLBI, 1996). (See Figure 2.)

National Institute of Mental Health. NIMH has awarded funds to three universities: the University of Alabama at Birmingham, Harvard Medical School, and Johns Hopkins University, to establish a national resource to study both early and late-onset Alzheimer's disease. A collection of 400 pairs of relatives, primarily pairs of siblings, is available for finding susceptibility genes linked to Alzheimer's disease. This resource provides a large enough sample of families, obtained through a common protocol and diagnosed by a consensus procedure, to be useful for identifying clinical and genetic subtypes of Alzheimer's disease. NIMH also maintains a Brain Bank.

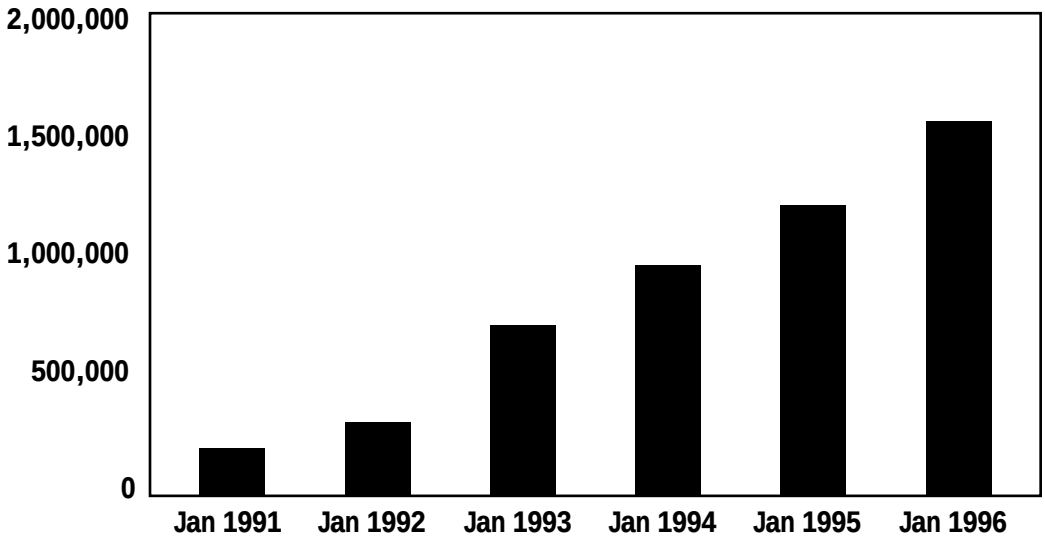
National Institute on Aging. NIA supports research on the general biology of aging and age-associated diseases and disabilities. The specific areas of research on the general biology of aging include the characterization of normal aging, cell cycle regulation and programmed cell death, stress response, and DNA damage and repair. Age-associated disease and disabilities research include the study of Alzheimer's disease, cancer, cardiovascular disease and hypertension, diabetes, and osteoporosis, osteoarthritis, and frailty. The NIA also supports the development of different intervention strategies to treat many of these age-associated diseases, such as pharmacotherapy, gene therapy, and behavioral or lifestyle changes. To provide appropriate tissue for neuropathological studies in Alzheimer's disease, the NIA maintains a brain bank.

As part of the NIA Research Resources Branch, the Central Laboratory Services Section (CLSS) collects, analyzes, and prepares for long-term storage of blood and tissue samples. Other services provided by CLSS include phlebotomy, tissue handling and preservation, DNA extraction, cell transformations to create renewable cell lines, and inventory management of stored samples.

National Institute of Standards and Technology and the United States Environmental Protection Agency

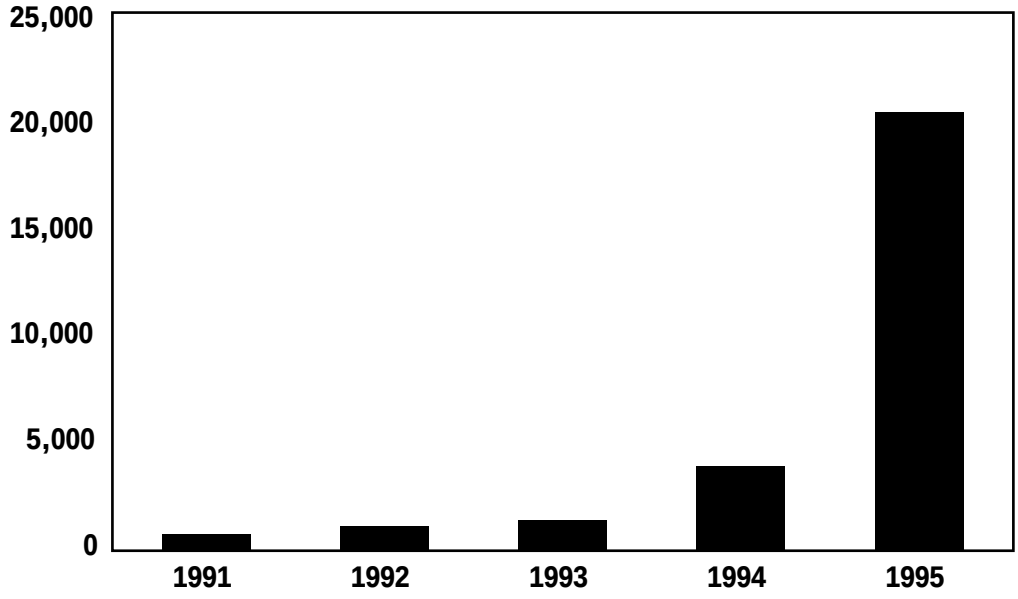
Two other agencies within the federal government have tissue banks, the National Institute of Standards and Technology (NIST) and the United States Environmental Protection Agency (EPA). These tissue banks were established primarily to determine human exposure to pollutants and pesticides and to follow long-term trends.

Figure 1. Number of Vials Stored at the NHLBI Blood Specimen Repository*



*Source: National Heart, Lung, and Blood Institute. Blood Specimen Repository: 1996 Catalog

Figure 2. Number of Vials Distributed from the NHLBI Blood Specimen Repository*



*Source: National Heart, Lung, and Blood Institute. Blood Specimen Repository: 1996 Catalog

National Biomonitoring Specimen Bank. The National Biomonitoring Specimen Bank (NBSB) at the NIST was established in 1979 in conjunction with the EPA to determine the feasibility of long-term storage of environmental samples (Wise and Koster, 1995). In addition to human liver specimens contained in the human liver specimen bank supported by the EPA, the NBSB consists of three other projects supported by various government agencies that bank marine specimens and total human diet specimens. The EPA human liver specimen bank has collected and archived 632 human liver specimens since 1980 and is currently collecting approximately 25 specimens per year. The goals of the EPA human liver project are 1) to develop procedures for the collection, processing, and long-term storage of biologic specimens; 2) to improve analytical methods for the determination of inorganic and organic contaminants in human tissue; 3) to evaluate the long-term storage stability of biologic specimens; and 4) to provide an archive of well-documented specimens of human liver for retrospective studies to determine long-term pollution trends and document the appearance of new pollutants (Wise and Koster, 1995). This archive of human liver specimens is an invaluable resource for the investigation of environmental pollution trends in human population.

National Human Monitoring Program. The National Human Monitoring Program (NHMP) was established in 1967 and continued through 1993. The NHMP was designed to study changes in pesticide residues in the population of the United States. Originally part of the United States PHS, the NHMP was transferred to the EPA in 1970. One of the primary activities of the NHMP was the National Human Adipose Tissue Survey (NHATS), a program developed to measure residues of chemicals in human adipose tissue. Through 1991, the NHATS had collected approximately 12,000 samples of adipose tissue from autopsied cadavers and surgical patients. The NHATS documented widespread exposure to pesticides in the United States and showed that reduced use of polycholorinated biphenyls (PCBs), DDT, and dieldrin resulted in lower tissue concentrations of these compounds (Bailar, 1995).

Research Universities and Academic Medical Centers

Research universities and academic medical centers maintain both formal tissue banks for distribution throughout the research community as well as core facilities to support their own research. Examples of both types of tissue collections are described below.

Specialized Programs of Research Excellence. The Specialized Programs of Research Excellence (SPOREs) are highly interactive, mutlidisciplinary programs of translational research directed at reducing the incidence, morbidity, and mortality of cancer. SPOREs are NCI-funded, NIH-designated Clinical Research Centers at research universities and consist of cancer-specific research programs supported by core resources, including administration, tissue and serum banks, and biostatistics. SPOREs are designed to develop areas of basic science with potential impact on cancer and to move these promising areas into clinical trials. SPOREs are also designed to communicate important findings rapidly into the research community to stimulate investigation and to bring validated translational findings into the medical community where the research can ultimately reduce incidence and mortality of cancer. Several of the SPOREs have core tissue banking facilities that support both their own research as well as collaborations with other SPOREs and researchers worldwide.

The SPORE in Gastrointestinal Cancer at Johns Hopkins is a translational research program aimed at reducing the incidence of and mortality from colorectal and pancreatic cancer. The SPORE includes four research programs involving six projects supported by four core resources. All programs in this SPORE use human specimens. The Human Tissue Resource and Logistics Core, built on an existing bank established in 1986 for the Bowel Tumor Working Group, banks a wide range of tissues from resection specimens of colorectal and pancreatic cancers. By the end of 1992, the bank contained 716 colorectal cancer resections, 142 colorectal

adenoma resections, 398 colorectal polypectomy specimens, 47 hepatic resections for metastatic colorectal cancer, 80 pancreatic cancer resections, 107 fecal specimens, and 1,338 blood specimens. This core also includes family histories and food frequency questionnaires for patients with specimens in the bank.

The Prostate SPORE at Johns Hopkins is a multidisciplinary approach to reduce the incidence, morbidity, and mortality of prostate cancer through prevention, genetics, early detection and diagnosis, morbidity reduction, and treatment. Research in early detection and diagnosis will be correlated with cancer risk in the Baltimore Longitudinal Study of Aging, the world's largest and longest longitudinal aging study. A large core tissue bank was established to accelerate translation of human prostate research to clinical medicine. This is an interactive clinical and basic research team dedicated to translate new discoveries into the control of prostate cancer.

Harvard Brain Tissue Resource Center. The Harvard Brain Tissue Resource Center (the Brain Bank), located at McLean Hospital in Massachusetts, is a centralized repository for the collection and distribution of postmortem human brain specimens from both diseased and other donors for use in research on the brain and nervous system. The Brain Bank is supported by NIMH, the National Institutes of Neurological Disease and Stroke, the Alzheimer Disease Association of Indiana, the Hereditary Disease Foundation, the Tourette Syndrome Association, and the Wills Foundation. Research on brain tissue has contributed to the understanding of severe mental illness, the development of a genetic test for Huntington's disease, and a treatment for Parkinson's disease. Since the majority of research only requires very small amounts of tissue, each donated brain provides a large number of samples for many researchers. Brain tissue donations are accepted by the Brain Bank from individuals or the parents, siblings, and offspring of individuals with severe neurological disorders such as Huntington's, Parkinson's, and Alzheimer's, with a serious psychiatric diagnosis, and various other disorders. The Brain Bank also accepts brain tissue from normal individuals with no neurological or neuropsychiatric disorders for research that needs to make comparisons between normal and diseased tissue. Prospective brain tissue donors must be 18 years of age or older. Donors should discuss their wishes with their families and register with the Brain Bank by completing the "Brain Donation Questionnaire."

University of California-San Francisco AIDS Specimen Bank. The University of California-San Francisco (UCSF) AIDS Specimen Bank has been in existence since 1982 and has banked more than 76,000 specimens and sent out more than 82,000 specimens to researchers worldwide. Specimens include serum, tissue, saliva, cells, and cerebrospinal fluid from HIV-infected individuals. Specimen data are archived on a computerized database. The Bank provides investigators with specimens for basic, epidemiological, and clinical research.

Commercial Enterprises

Some commercial enterprises maintain tissue banks for their own proprietary use, while others establish banks for storage and distribution purposes. OncorMed and LifeSpan are examples of companies that maintain proprietary tissue banks, while PathServe collects human tissues and organs to market them to the research community.

OncorMed. OncorMed is a medical services company whose mission is to "improve cancer patient outcomes by rapidly translating new genetic discoveries into clinically useful, cost-effective services." OncorMed provides genetic testing and information services for the early detection and management of cancer. OncorMed offers cancer predisposition counseling, genetic susceptibility testing, early diagnosis, and analysis of tumors. OncorMed's Hereditary Cancer Consulting Service, offered at sites all over the country, determines a patient's risk for developing cancer by analyzing family history information. OncorMed also offers genetic testing for cancer susceptibility genes, including BRCA1 and BRCA2 for breast and ovarian cancer, hereditary nonpolyposis colorectal cancer, inherited melanoma, and hereditary thyroid cancer. OncorMed is also developing a test that

analyzes DNA in a urine sample for the early diagnosis of bladder cancer. OncorMed has a laboratory service called TumorCheck that looks for a specific mutation in the p53 gene that may help physicians choose more effective treatments.

OncorMed has an IRB for review and approval of protocols and has developed physician guidelines that closely parallel the American Society of Clinical Oncology guidelines. These guidelines require that genetic testing is linked with counseling and informed consent. OncorMed requires both pre- and post-testing genetic counseling. The informed consent includes information on the possible benefits, limitations, and risks of genetic testing, such as the benefits of early detection and prevention of cancer, the technical accuracy of the test, and the risk of discrimination by insurers and employers. In addition to genetic testing, OncorMed has established a proprietary biorepository.

LifeSpan BioSciences, Inc. LifeSpan BioSciences, Inc., founded in 1995, is a genomics company focused on discovering and licensing genes that play a role in the aging process and identifying disease-associated genes for use as therapeutic or diagnostic targets. Because highly characterized samples of normal and diseased tissues are critical in localizing disease-associated genes, LifeSpan has an on-site tissue bank. LifeSpan's Tissue and Disease Bank contains 250,000 normal and diseased human samples. The tissue bank has more than 175 different types of tissues from virtually every organ in the body, covering all ages. The tissue bank also includes more than 500 different pathologic disease categories such as autoimmune diseases, infectious diseases, degenerative diseases, cancer and benign proliferative diseases, and genetic diseases.

PathServe. PathServe Human Tissue Bank, established in 1990 and commercial since 1996, is a major supplier of human tissue to biotechnology and neuropathological research institutions. PathServe also serves as a main training facility of autopsy technicians for private pathologists and local hospitals. PathServe collects all types of organs and tissues including specimens from placental and fetal origin. Tissues are obtained through postmortem examinations, referrals from transplant banks of nontransplantable organs, and donations by next of kin. PathServe has distributed approximately 30,000 specimens in the last year. Consent for donation is obtained from the family. PathServe does not maintain a centralized storage facility. Instead, specimens are stored in the morgues of different hospitals.

Nonprofit Organizations (Noneducational)

There are many nonprofit institutions that bank tissues for purposes of storage and distribution. Nonprofit institutions such as the American Type Culture Collection (ATCC), Coriell Institute for Medical Research, the Research Foundation for Mental Hygiene, the Rocky Mountain Multiple Sclerosis Center (RMMSC), the National Psoriasis Tissue Bank (NPTB), the Kaiser Permanente Center for Health Research (CHR), and the Hereditary Disease Foundation receive millions of dollars in federal funding. Descriptions of these nonprofit centers that bank tissue are provided below.

American Type Culture Collection. Since its establishment in 1925, the ATCC has served as an archive of living cultures and genetic materials for researchers in the biological sciences. The mission of the ATCC is to acquire, authenticate, and maintain reference cultures, related biological materials, and associated data, and to distribute these to qualified scientists in government, industry, and education. The ATCC has approximately 2,300 human cell lines. However, all of the human cell lines are immortalized cultures, and the genetic material is mainly the products of recombinant DNA research, both of which are outside the scope of this report.

Coriell Institute for Medical Research. The Coriell Institute for Medical Research is a basic biomedical research institution that conducts research on the causes of genetic diseases, including cancer. The Coriell Institute's three missions are research, cell banking, and public education. The largest collection of human cells for research is maintained at the Coriell Institute, and these cells are available to the general scientific community.

Seminal research on the genes associated with Huntington's disease, cystic fibrosis, Alzheimer's disease, ataxia telangiectasia, and manic depression have utilized cells from the Coriell collection. The Coriell Cell Repositories also support the human genome project. More than 35,000 cell lines are currently stored, representing approximately 1,000 of the 4,000 known genetic diseases, and more than 60,000 cell lines have been distributed to more than 40 nations, resulting in more than 8,000 research publications. Cultures are established from both blood and skin, and the cells are stored frozen at the Institute. There are 750,000 vials of cells in 37 giant tanks containing liquid nitrogen. In 1990, the NIMH awarded the Coriell Institute a $5.7 million contract to establish a cell repository for the study of the genetic basis of Alzheimer's, manic depression, and schizophrenia. New repositories have recently been set up for the study of diabetes.

Rocky Mountain Multiple Sclerosis Center Tissue Bank. The RMMSC Tissue Bank, one of the largest multiple sclerosis tissue banks in the world, was established in 1976 to procure, process, preserve, and distribute multiple sclerosis brain tissue to research laboratories from all over the world involved in finding the cause of and cure for multiple sclerosis. More than 170 central nervous system samples have been banked at RMMSC, representing material from a well-defined patient population. The stored tissue has led to several key discoveries in the pathogenesis of multiple sclerosis. The bank is funded by the National Multiple Sclerosis Society.

National Psoriasis Tissue Bank. The NPTB is the only international public source of genetic material for psoriasis research. The NPTB is dedicated to finding the genetic causes of psoriasis and psoriatic arthritis. The stored tissue is available for use by international experts. The NPTB is supported by private donations through the National Psoriasis Foundation, a voluntary nonprofit national health agency. The NPTB consists of nearly 300 Epstein Barr Virus-transformed cell lines, isolated DNA, and fibroblasts from families with psoriasis and psoriatic arthritis. Blood samples from sibling pairs will add 1,000 DNA samples by the end of 1997. Researchers can obtain the cell line, DNA, family history, and medical history of any individual with samples in the bank; however, names and locations of contributors remain anonymous. There is a small fee for the service. Blood and skin samples are obtained by a medical team at the Baylor Psoriasis Center, a regional referral center at the Baylor University Medical Center in Dallas, Texas.

Kaiser Permanente Center for Health Research. The Kaiser Permanente Center for Health Research (CHR) is a nonprofit health care research institute started in 1964. Currently, more than 40 studies are under way, and some involve stored tissue. For example, the CHR started the Benign Breast Disease Registry (BBDR), funded by the NCI-NAPBC. The BBDR includes data on nearly 10,000 women diagnosed with breast cancer between 1970 and 1994. The BBDR provides both benign and malignant archived tissue to researchers. In another NCI-sponsored breast cancer study, almost 16,000 breast cancer cases and associated archived tissue will be made available for research. This tissue will be made available to qualified researchers for molecular studies. In the last 20 years, more than 25,000 people in the Portland-Vancouver area have voluntarily participated in the research at the CHR. Clinical trials involving archived tissue are also undertaken. For instance, the Fracture Intervention Trial is an 11-center double-blind, placebo-controlled, randomized clinical trial to determine the efficacy of alendronate in preventing fractures secondary to osteoporosis. The CHR has received more than $96 million in grants from federal and state agencies and private foundations.

Hereditary Disease Foundation. The Hereditary Disease Foundation of Santa Monica, California, is studying the genes involved in Huntington's disease in a Venezuelan kindred of more than 14,000 people. Through studying this kindred, the gene for Huntington's disease was localized to chromosome 4p. This kindred is a valuable resource enabling researchers to study members that share background genes and a common environment. The Hereditary Disease Foundation will study the unstable trinucleotide repeat in the Huntington's disease gene. In order to study this protein, the Hereditary Disease Foundation will collect tissue samples including lymphoblast lines and sperm samples to examine the effect of age, disease duration, birth order, or

environmental factors on sperm. Brain and other postmortem tissues from genetically and clinically well-characterized members of the kindred will be collected to understand how the Huntington protein specifically devastates striatal neurons.

4. Longitudinal Studies

Longitudinal studies, in which the same group of individuals is studied at intervals over a period of time, often collect large numbers of specimens that can be used for both retrospective and prospective research. Several well-known longitudinal studies have been conducted over the years including the Physicians' Health Study, the Nurses' Health Study, and the Framingham Heart Study. Other large longitudinal studies include the Health Professionals Follow-up Study, the Multiple Risk Factor Intervention Trial, the Family Heart Study, and the National Health and Nutrition Examination Surveys. Several longitudinal studies are described below.

The NIH Women's Health Initiative

The NIH Women's Health Initiative (WHI), established in 1991, is the largest preventive study of women's health in the United States. The WHI is a 15-year research program concluding in the year 2005 that focuses on the major causes of death, disability, and impaired quality of life in postmenopausal women. The overall goal of WHI is to reduce coronary heart disease, breast and colorectal cancer, and osteoporosis in post-menopausal women through prevention, intervention, and risk factor identification.

The WHI will involve more than 164,500 women of all races and socioeconomic backgrounds ages 50 to 79. Recruitment began in September of 1993 and will continue through January of 1998. Approximately 64,500 women will be enrolled in a randomized clinical trial with three study groups: hormone replacement therapy, dietary modification, and calcium and vitamin D supplementation. Eligible women can choose to be in one, two, or all three of the study groups. The observational study will track the medical history and health habits of approximately 100,000 women to examine the relationship between lifestyle, health and risk factors, and disease. The clinical trial and observational study are being conducted at 40 clinical centers nationwide. The Fred Hutchinson Cancer Research Center in Seattle, Washington, is the WHI Clinical Coordinating Center for data collection, management, and analysis.

The 164,500 women enrolled in both the clinical trial and the observational study will be followed for 8 to 12 years and will provide multiple blood samples throughout the course of the study. Participants sign a consent form that states that the collection of blood samples is for use in future research, which may include genetic research, and participants will not be informed of any test results. Participants may opt out of having their samples used for genetic research, if they so desire. The clinical trial participants provide a blood sample at their initial visit and at their one-year visit, and a subset of participants have samples drawn at three, six, and nine years. Blood samples are also collected from participants in the observational trial at their initial visit, and again at their three-year visit. Blood samples are divided into serum, plasma, and buffy coat and are stored at a central facility in Rockville, Maryland. Participants' charts contain identifying information, including name, Social Security number, address, and telephone number, and are bar-coded. Blood samples are labeled with matching bar codes to link them back to the charts. Approximately 27,000 women will be enrolled in the hormone replacement therapy trial, some of whom will also undergo an endometrial biopsy to rule out endometrial hyperplasia or cancer.[3] These biopsies are stored at the individual clinical centers within the pathology departments and are labeled with a pathology accession number. In cases in which abnormalities are detected, slides of the biopsy are bar coded and sent to a central laboratory at NIH. Participants and their physicians are informed of any abnormalities found in the endometrial biopsy. All study records will be kept indefinitely for analysis and follow-up.

The third component of the WHI, the community prevention study, is a five-year collaborative effort with the Centers for Disease Control and Prevention (CDC) to study community approaches to developing healthy behaviors. This study will include women of all races and socioeconomic backgrounds ages 40 and over. Eight university-based prevention centers will conduct and evaluate health programs that encourage women to adopt healthy behaviors such as improved diet, nutritional supplementation, smoking cessation, exercise, and early detection of treatable health problems.

Baltimore Longitudinal Study of Aging

The Longitudinal Studies Branch of the NIA is responsible for the operation and management of the Baltimore Longitudinal Study of Aging. The Baltimore Longitudinal Study was initiated in 1958, enrolling only men until 1978, when women were included. The Longitudinal Studies Branch has a research program based primarily on the Baltimore Longitudinal Study because it offers a unique opportunity to study a number of aging-related diseases and disabilities including frailty, Alzheimer's disease, cardiovascular disease, cancer, and osteoporosis.

Storage of samples of blood or blood fractions began in 1963 and has been systematically continued since that time. Serum, plasma, lyophilized erythrocytes, and whole blood plasma (including leukocytes) and aliquots of 24-hour urine collections have all been stored. Over the years, samples have been used for various approved protocols. For example, recently a longitudinal study of prostate-specific antigen (PSA) was retrospectively performed and showed that following PSA levels over time could detect prostatic cancer many years earlier than usual clinical measures.

Bogalusa Heart Study

The Bogalusa Heart Study, ongoing since 1972, is the longest and most detailed study of children in the world. The Bogalusa Heart Study is an NIH-sponsored Specialized Center for Research at Louisiana State University Medical Center run by a multidisciplinary team of anthropologists, biochemists, cardiologists, epidemiologists, geneticists, nurses, nutritionists, psychologists, sociologists, and statisticians. The purpose of the study is to understand the environmental and hereditary aspects of early coronary artery disease, essential hypertension, and cardiovascular risk factors in African American and Caucasian children in the semi-rural community of Bogalusa, Louisiana. In addition, more than 160 substudies have been conducted, including special studies on socioeconomic evaluations, blood pressure, lipid levels, genetics, exercise, heart murmurs, and pathology. Knowledge gained in the Bogalusa Heart Study has been applied to develop, test, and evaluate methods for cardiovascular risk intervention.

The Bogalusa Heart Study has cross-sectional and longitudinal observations on more than 14,000 children and young adults. For example, there is currently a post-high school study that follows individuals until 38 years of age. Blood samples have been sent to Boston, Johns Hopkins in Baltimore, Sweden, and Finland for special analysis. More than 632 publications, 3 textbooks, and numerous monographs have been produced using samples and data from the Bogalusa Heart Study.

National Health and Nutrition Examination Survey

Since 1960, the National Center for Health Statistics (NCHS) of the CDC has conducted seven health examination surveys of the population of the United States, the National Health Examination Surveys (NHES) Cycles 1, 2, and 3, the National Health and Nutrition Examination Surveys (NHANES) I, II, and III, and the Hispanic Health and Nutrition Examination Survey (HHANES). The surveys are designed to periodically assess the health and nutritional status of children and adults in the United States through interviews and direct physical examinations. The surveys employ interviews to obtain information about demographics, socioeconomic status, dietary habits, and health-related issues and physical and dental examinations that include physiologic assessments and laboratory tests. Blood samples are collected as part of the physiologic assessments and are placed in storage banks after laboratory tests are completed.

Cumulatively, all of the health examination surveys have analyzed and banked samples from more than 85,000 participants. The most recent survey, NHANES III, conducted between 1988 and 1994, performed laboratory tests on approximately 29,314 people of all races ages two months and older from 81 counties in 26 states. Some of the 30 topics investigated in the NHANES III included high blood pressure, high cholesterol, obesity, second-hand smoking, lung disease, osteoporosis, HIV/AIDS, hepatitis, *helicobacter pylori*, immunization status, diabetes, allergies, growth and development, anemia, dietary intake (including fats), antioxidants, and nutritional blood measures. The NHANES I analyzed blood and urine samples from 23,808 study participants, and NHANES II analyzed 20,322 samples. The HHANES was a one-time survey conducted from 1982 to 1984 that provided data on 11,653 people of Hispanic origin.

5. Research That Simultaneously Creates Tissue Collections or Contributes to a Tissue Bank

Most research that uses human tissue obtains specimens from pathology laboratories or existing tissue banks. However, some research studies require unique samples and must collect specialized tissue. Therefore, some research will create small tissue collections and may end up contributing these samples to an established tissue bank for storage. A few examples of research that simultaneously creates tissue collections or contributes to a tissue bank are described below.

National Institute of Child Health and Human Development (NICHD). NICHD performs and supports several research projects in pregnancy, delivery, and child development-related issues that involve collection and storage of tissue samples. To fulfill its needs for storage, monitoring, and distribution of existing and yet-to-be-collected specimens, the NICHD contracts with commercial enterprises. For example, the Maternal Fetal Network Project, conducted by the Pregnancy and Perinatology Branch of NICHD, has contracted with Biotech Research Laboratory to establish a repository that will contain frozen plasma and serum samples from patients studied in several clinical protocols. This repository is a valuable source of biological markers for the study of preterm births and preeclampsia. In addition, two NICHD-funded research studies, the Diabetes in Early Pregnancy Study (DIEP) and a Longitudinal Study of Fetal Growth and Perinatal Outcome, have contracted with Biomedical Research, Inc., to provide storage, monitoring, and distribution of serum samples. Both studies involved collecting multiple blood samples throughout the course of the study. Biomedical Research, Inc., also provided storage, monitoring, and distribution of serum, plasma, and urine from a double-blind, randomized clinical trial of supplemental calcium for the prevention of preeclampsia during pregnancy. Five clinical centers, enrolling 4,500 women over a two-year period, contributed samples from study participants at baseline, early and late in the third trimester of pregnancy, and at the time of diagnosis of preeclampsia.

Genetics of Familial Polycystic Ovary Syndrome. The Milton S. Hershey Medical Center is studying polycystic ovary syndrome (PCOS) to find a genetic marker that would be useful in identifying women at risk for developing PCOS before the onset of complications. The study will include a few large, three-generation kindreds of PCOS to reduce genetic heterogeneity. A DNA bank of complete PCOS pedigrees is being assembled for genetic studies. A normative database will be established for age, weight, and ethnicity-matched controls. Previously identified kindreds of familial PCOS will be phenotyped for clinical, biometric, and biochemical abnormalities. All available pedigree members, male and female, will be phenotyped. By identifying women at risk for PCOS, medical resources could be focused on preventing complications.

Molecular Basis of Split Hand/Foot Malformation. The University of North Carolina at Chapel Hill is characterizing the molecular defect responsible for split hand/split foot (SHSF) malformation, a human developmental disorder that results in abnormal hands and feet. A repository of cell lines from individuals with SHSF and related malformations is being established. This resource will facilitate cloning of the SHSF gene as well as future investigations of genotype-phenotype relationships in SHSF. SHSF pedigrees will also be

analyzed. Isolation of the SHSF gene will provide an opportunity to investigate the molecular basis of pattern formation in the human limb.

AIDS-Malignancy Clinical Trials Consortium. The University of Southern California AIDS-Malignancy Clinical Trials Consortium (AM-CTC) helps design, develop, and conduct collaborative, innovative phase I and II clinical trials, employing novel agents and approaches in patients with various AIDS-related malignancies. In addition, the AM-CTC provides tumor tissue and other relevant biologic materials derived from patients accrued onto trials to the NCI-funded Tissue and Biological Fluids Banks of HIV Associated Malignancies. Since 1987, the AIDS Clinical Trials Group has accrued more than 470 patients onto various AIDS-malignancy protocols. The University of Southern California AIDS Malignancy Program has been actively engaged in phase I and II trials related to HIV-related cancers, with participation in 45 such studies resulting in 17 publications and 30 published abstracts.

Exogenous Toxicants and Genetic Susceptibility in Amyotrophic Lateral Sclerosis. Stanford University is investigating the role of environmental toxicants and genetic susceptibility factors in the etiology of Amyotrophic Lateral Sclerosis (ALS) by conducting a case-control study of 175 incident ALS and 550 age- and gender-comparable control subjects. All 175 ALS cases and a subset of 350 control subjects will undergo measurement of bone lead stores using X-ray fluorescence and will have a venous blood sample drawn for copper-zinc superoxide dismutase (SOD1) enzyme genotyping and DNA banking. The collection of detailed information regarding the duration and timing of environmental exposures will enable the evaluation of dose response trends and estimation of latent periods between putative exposure and the development of ALS. It is hoped that the proposed study will advance knowledge of neurotoxic and endogenous susceptibility factors that are important in the etiology of ALS.

6. Pathology Specimens

A large number of tissues are collected for diagnostic or therapeutic reasons. These tissues are usually sent to a clinical, diagnostic, or pathology laboratory for examination. These laboratories may be located at GME teaching institutions, physicians' offices, community hospitals, or independent laboratories. These tissues may sometimes be used for research, educational, and quality control purposes; however, the vast majority of them are not. Most patients sign a general consent stating that after completion of any diagnostic test, some of the sample may be saved/used for research purposes.

To be accredited, laboratories are required to keep pathological specimens for a minimum amount of time. The Clinical Laboratory Improvement Amendments of 1988 (CLIA) set forth the conditions that laboratories must meet to be certified to perform testing on human specimens. CLIA stipulates that laboratories must retain cytology slides for a minimum of five years, histopathology slides for a minimum of ten years, and paraffin blocks for a minimum of two years (CLIA, 1996). In addition, some states have regulations that require retention of pathology specimens for a longer period than that specified in the CLIA regulations. For example, New York, which has some of the most stringent regulations, requires laboratories to retain abnormal cytology slides for 10 years, cytology slides with no abnormalities for 5 years, and histopathology slides and paraffin blocks for 20 years. Once the regulated length of time for storage is met, institutions continue to store pathology specimens based on the room they have for storage, the philosophy of the institution, and several other variables.

Pathology Departments at GME Teaching Institutions

Medical education in the United States can be divided into three major phases. The first phase, medical school, provides instruction in the sciences that underlie medical practice and in the application of those sciences to health care. In 1997, there were 125 medical schools in the United States (including three schools in Puerto Rico) (American Medical Association, 1997). The second phase, GME, prepares physicians for independent practice in a medical specialty. GME programs, usually called residency programs, are based in hospitals or

other health care institutions, some of which do and some of which do not have formal relationships with medical schools. GME teaching institutions include medical schools; the Armed Forces hospitals; Veterans Affairs medical centers; the PHS; state, county, and city hospitals; nonprofit institutions; and health maintenance organizations. In 1997, there were 1,687 accredited GME teaching institutions in the United States (including 22 programs in Puerto Rico) (American Medical Association, 1997). Continuing medical education (CME), the third phase of medical education, continues medical professionals' education throughout their careers.

Collectively, pathology departments at GME teaching institutions constitute the largest and oldest stores of tissue samples in the United States. Two techniques were used to estimate the total number of cases accessioned per year at all GME institutions and the number of tissues stored at each institution. The first estimate used information found in the American Medical Association's *Graduate Medical Education Directory 1997–1998* about residency programs in pathology at GME institutions (American Medical Association, 1997). However, information was not available about all pathology specialties. Therefore, a second estimate was made from information obtained from several chairs of pathology departments attending a meeting of the Universities Associated for Research and Education in Pathology (UAREP) at the Federation of American Societies for Experimental Biology.[4]

The number of pathology residency positions at a GME teaching institution is determined by the caseload of the pathology department. The *Graduate Medical Education Directory* stipulates that programs should have a sufficient number of cases to ensure that residents have a broad exposure to both common and unusual conditions and that the number of resident positions requested by an institution should not exceed the educational resources available in a program (American Medical Association, 1997). The actual number of GME programs and residency positions in 1996–1997 and the number of programs and proposed residency positions for 1997–1998 are shown in Table 2. Table 3 shows the recommended number and types of cases/specimens residents should examine during their training in anatomic and clinical pathology, dermatopathology, forensic pathology, neuropathology, or pediatric pathology. This information was not available for the specialties of cytopathology, chemical pathology, hematology, immunopathology, and microbiology.

An analysis was performed to estimate the total number of cases accessioned per year at all GME teaching institutions in the pathology specialties of anatomic and clinical pathology, dermatopathology, forensic pathology, neuropathology, and pediatric pathology. This calculation was based on 1) the number of GME pathology programs in each specialty; 2) the number of resident positions open in these programs for the academic year; 3) the recommended number of cases per program to meet the training requirements of the residents; and 4) the duration of the program in years. Table 4 contains data for the academic year 1996–1997, and Table 5 contains data for 1997–1998. Information on the recommended number of cases per resident was not available for all pathology specialties. However, an effort was made to obtain information on the average number of cases/specimens accessioned per institution each year for cytopathology and hematopathology, the two other pathology specialties in Tables 4 and 5 with large numbers of residency positions.

Of the pathologic specialties, anatomic and clinical pathology, cytopathology, and hematology specimens probably account for the largest collection of tissues. For the academic year 1996–1997, there were 180 anatomic and clinical pathology programs with 2,675 residents (see Table 2). To have enough cases to fulfill the educational needs of their residents, institutions would have had to accession more than 5 million total cases/specimens, which is an average of 28,050 cases/specimens per program (Table 4). In comparison, in 1997–1998, the 180 anatomic and clinical pathology programs with 2,656 residency positions would have to accession more than 5 million total cases/specimens, which is an average of 27,851 cases/specimens per program (Table 5). Some of the specimens collected by anatomic and clinical pathology may be referred to another specialty, such as dermatopathology, neuropathology, or immunopathology and given a separate accession number within that specialty. Therefore, some specimens listed in Tables 4 and 5, especially for dermatopathology and neuropathology, may already have been accounted for in anatomic and clinical

pathology numbers. Forensic pathology cases are accessioned separate from the other specialties. It is recommended that forensic pathology programs conduct approximately 500 medicolegal autopsies per year and approximately 300 additional autopsies for each additional residency position. Therefore, forensic pathology programs would have to conduct 21,900 autopsies[5] in 1996–1997 and 29,700 in 1997–1998 to provide enough cases for resident training.

Table 2. GME Pathology Programs and Residency Positions

	1996–1997[a]		1997–1998[b]	
Pathology Specialty	**Number of Programs**	**Number of Residents**	**Number of Programs**	**Number of Residents**
Anatomic and Clinical	180	2,675	180	2,656
Cytopathology	68	74	68	101
Chemical Pathology	7	4	7	6
Dermatopathology	41	54	41	72
Forensic Pathology	39	47	39	73
Hematopathology	54	51	54	119
Immunopathology	9	6	9	12
Microbiology	9	5	9	9
Neuropathology	47	37	47	66
Pediatric Pathology	20	12	20	28
Total	**474**	**2,965**	**474**	**3,142**

[a]Graduate Medical Education. 1997. Journal of the American Medical Association 278(9):775–784.
[b]American Medical Association. 1997. Graduate Medical Education Directory 1997–1998. American Medical Association, Chicago.

Table 3. Recommended Specimens for Pathology Residency Programs*

Pathology Specialty	Recommended Cases/Specimens per Resident
Anatomic and Clinical	≥ 75 autopsies ≥ 2,000 surgical pathology specimens ≥ 1,500 cytologic specimens ≥ 200 intraoperative consultations (frozen sections)
Dermatopathology	≥ 5,000 new accessions
Forensic Pathology[a]	250–350 autopsies
Neuropathology[b]	≥ 50 neuromuscular biopsy specimens
Pediatric Pathology	≥ 40 pediatric autopsies ≥ 2,000 pediatric surgical pathology specimens ≥ 50 intraoperative consultations (frozen sections/smears)

*Source: American Medical Association. 1997. Graduate Medical Education Directory 1997–1998. American Medical Association, Chicago.

[a]In addition to the 250–350 autopsies recommended for residents in forensic pathology, it is recommended that forensic pathology programs should conduct approximately 500 medicolegal autopsies per year and approximately 300 additional autopsies for each additional residency position requested.

[b]In addition to the minimum of 50 neuromuscular biopsy specimens recommended for residents in neuropathology, it is recommended that neuropathology programs should conduct at least 200 necropsies and examine at least 100 neurosurgical specimens per year.

Table 4. Specimens and Autopsy Cases Accessioned in 1996–1997

Pathology Specialty	Number of Specimens[a] per Year	Number of Programs	Number of Specimens[a] per Program Each Year
Anatomic and Clinical[b]	5,049,063	180	28,050
Dermatopathology	270,000	41	6,585
Forensic Pathology	21,900	39	562
Neuropathology	14,100	47	300
Pediatric Pathology	25,080	20	1,254

[a]This includes autopsy cases.

[b]Anatomic and clinical pathology programs range in length from 18–24 months. Therefore, the number of specimens per year represents the number of programs multiplied by the number of residents (Table 2) divided by 2 years (24 months) as a minimum estimate.

Table 5. Specimens and Autopsy Cases Accessioned in 1997–1998

Pathology Specialty	Number of Specimens[a] per Year	Number of Programs	Number of Specimens[a] per Program Each Year
Anatomic and Clinical[b]	5,013,200	180	27,851
Dermatopathology	360,000	41	8,780
Forensic Pathology	29,700	39	762
Neuropathology	14,100	47	300
Pediatric Pathology	58,520	20	2,926

[a]This includes autopsy cases.

[b]Anatomic and clinical pathology programs range in length from 18–24 months. Therefore, the number of specimens per year represents the number of programs multiplied by the number of residents (Table 2) divided by 2 years (24 months) as a minimum estimate.

In some institutions, pediatric pathology cases may go directly to the pediatric pathology department; however, in some institutions, they may first be accessioned in anatomic and clinical pathology. The 12 residents in pediatric pathology programs in 1996–1997 would have conducted 480 pediatric autopsies and examined 24,000 pediatric surgical pathology specimens and 600 intraoperative consultations (frozen sections, smears). To support 28 pediatric pathology resident positions in 1997–1998, a total of 58,520 specimens and autopsy cases would have to be accessioned. A conservative estimate is that an average of approximately 30,000 anatomic and clinical, forensic, and pediatric pathology and autopsy cases are seen per GME teaching institution each year.

An estimate of the number of cases/specimens accessioned in cytopathology and hematopathology programs was obtained by averaging the number of cases/specimens reported on various GME teaching institutions Internet websites. Table 6 shows information obtained for cytopathology, and Table 7 shows information about hematopathology. Cytopathology programs accession an average of approximately 50,000 cytology specimens per year (range of 14,000 to 100,000 cases/specimens). Hematopathology programs accession an average of 750 bone marrow aspirations and biopsies and resections of lymph nodes and related tissue.

As an independent method to estimate the average number of pathology cases accessioned per institution each year, chairs of pathology departments attending the UAREP meeting were asked several questions about the pathology departments at their institutions. Information was obtained about the size of their institution, the number of cases accessioned per year, the age of the oldest tissues archived, how long the tissue samples are stored, what identifying information is kept with the tissues, and who has access to the samples. The medical

Table 6. Cytopathology Programs

Program	Specimens per Year
University of North Carolina	>24,000
Emory University	65,500
University of Wisconsin	100,000
University of Michigan	47,500
Georgetown University	14,000
Total	251,000
Average	50,200

Table 7. Hematopathology Programs

Program	Specimens per Year[6]
NYU Medical Center	750
Emory University	1,000
University of Michigan	500
Total	2,250
Average	750

schools represented had facilities that ranged in size from 250 beds to approximately 2,000 beds, and accessioned from approximately 10,000 to approximately 60,000 cases per year. The medical schools accessioned an average of 40 cases per bed with a range of 20–60 cases per bed. Most of the pathology departments stored tissue samples indefinitely, with the oldest tissues archived anywhere from 20 years old to more than 100 years old. Stored specimens are labeled with either a pathology accession number that is linked to the patient's medical record or with the patient's name and medical record number. People who have access to the specimens include pathologists, researchers, other physicians, and others who have a court order. Each institution accessions an average of approximately 30,000 cases per year, with approximately 3.8 million total cases accessioned per year at all 125 medical schools in the United States.

DNA Diagnostic Laboratories

HELIX. HELIX is a national directory of DNA diagnostic laboratories. It includes a fairly comprehensive listing of clinical service and research laboratories performing disease-specific clinical molecular genetic testing for single-gene and contiguous-gene disorders. HELIX is funded by the National Library of Medicine and administered through the National Network of Libraries of Medicine. In January 1994, there were 148 laboratories listed in HELIX, with 131 located in the United States, 16 located in Canada, and 1 in Mexico (McEwen and Reilly, 1995). One hundred and thirty-seven of the laboratories were academically based or within government agencies, and 11 were commercial laboratories (McEwen and Reilly, 1995).

In a 1994 survey of HELIX DNA diagnostic laboratories, 90 percent of the respondents (93 out of 148 laboratories surveyed responded [63 percent]) stated that they banked DNA (McEwen and Reilly, 1995). DNA banks ranged in size from fewer than 100 to more than 1,000 samples in storage (McEwen and Reilly, 1995). Most laboratories banked DNA as a service to referring physicians or for individuals and families at risk for a particular genetic disorder, for research purposes such as gene mapping, and as a service to clinical, forensic, or research laboratories (McEwen and Reilly, 1995). More than 50 percent of the respondents stated that their laboratories had released samples to researchers after stripping them of identifiers (McEwen and Reilly, 1995).

Clinical Service and Diagnostic Laboratories

The majority of clinical service and diagnostic laboratories are not associated with GME teaching institutions. These include laboratories within physicians' offices, community hospitals, as well as independent laboratories. In 1991, there were approximately 640,000 clinical laboratories and other facilities that performed laboratory tests on human specimens (DHHS, 1991). The number of tissues stored at these laboratories varies greatly, but the minimum storage time is determined by the Clinical Laboratory Improvement Amendments and state regulations.

Centers for Disease Control and Prevention

The CDC, located in Atlanta, Georgia, is an agency of DHHS. The CDC's mission is to promote health and quality of life by preventing and controlling disease, injury, and disability. The CDC is made up of eight centers, one institute, and two offices. Several centers have stored tissue samples, including the National Center for Environmental Health (NCEH) and the National Center for Infectious Disease (NCID).

National Center for Environmental Health. NCEH is involved in several areas of research including biomonitoring, breast-cancer related projects, and genetic research. The NCEH has also prepared DNA specimens from approximately 8,000 NHANES participants to be used by researchers around the country.

National Center for Infectious Diseases. NCID plans, directs, and coordinates a national program to improve the identification, investigation, diagnosis, prevention, and control of infectious diseases. The NCID also maintains several tissue banks. The NCID's Scientific Resources Program maintains a bank of serum specimens of epidemiological and special significance to CDC's research and diagnostic activities. The NCID is also responsible for the integrity, security, and maintenance of a computer-inventoried serum bank consisting of 250,000 aliquots of serum from 100,000 Alaskan Natives.

7. Newborn Screening Laboratories

Archives of newborn screening cards for inborn errors of metabolism (Guthrie cards) represent an enormous source of banked DNA. Guthrie cards are used to test newborns for several different diseases, including congenital hypothyroidism, phenylketonuria, glactosemia, hemoglobinopathies (e.g., sickle cell anemia), biotinidase deficiency, homocystinuria, maple syrup urine disease, and cystic fibrosis. These newborn screening tests utilize bacterial inhibition assays and automated enzymatic methods. However, as new genetic screening tests are developed and as the Human Genome Project discovers new disease-related genes, it is likely that newborn screening tests may become DNA based. In addition, interest in using Guthrie cards for population-wide genetic epidemiological studies has grown, given the stability of DNA in dried blood and the ability to analyze the DNA in these samples (McEwen and Reilly, 1994).

A 1994 survey of all newborn screening programs in all 50 states, the District of Columbia, Puerto Rico, and the Virgin Islands revealed that the majority of laboratories have accumulated fewer than 500,000 Guthrie cards over the years; seven have amassed more than 500,000, four reported collections of between 1–5 million cards, and one reported a collection of 6 million (McEwen and Reilly, 1994). The number of cards collected over a one-year period ranged from <10,000 in four laboratories to >500,000 in two especially populous states (McEwen and Reilly, 1994). For example, over 99 percent of the 550,000 children born each year in California are tested for three genetic conditions (Reilly, 1992).

The trend in most states is to save Guthrie cards for longer and longer periods of time. Eleven laboratories indicated that their state departments of public health have issued written regulations on the retention of Guthrie cards, while 29 stated that their laboratories have internal written policies on this matter (McEwen and Reilly, 1994). Forty of the state newborn screening laboratories retain all the Guthrie cards that they receive through their newborn screening programs, including those cards that test negative, at least for a short period of time (McEwen and Reilly, 1994). Twenty-three laboratories indicated that they keep their cards for a year or less, 10 plan to keep their cards for 1–5 years, 13 will keep them for longer than 5 years, 3 save all their cards for 20–25 years, and 4 plan to keep their cards indefinitely (McEwen and Reilly, 1994). Thirteen other respondents discard their cards within several weeks or months (McEwen and Reilly, 1994).

Guthrie cards contain identifying information, such as mother's name and address, hospital of birth, baby's medical records number, and the name and address of the baby's doctor. The conditions under which Guthrie cards are stored vary from state to state. Some store the cards in boxes at room temperature, some keep them

in boxes or folders in a freezer, refrigerator, or climate-controlled room, some keep them in boxes or folders in a basement or warehouse, and some keep them in a cabinet either in folders or biohazard bags (McEwen and Reilly, 1994). Fourteen state laboratories periodically check the condition of their stored cards (McEwen and Reilly, 1994).

All states participate in some form of newborn screening, but few have issued regulations that explicitly define the scope of permissible use of Guthrie card samples (Andrews, 1995). Seven state departments of public health have issued written regulations on third-party access to Guthrie cards, and 10 of the laboratories have internal written policies on this matter (McEwen and Reilly, 1994). Over a 5-year period, 28 laboratories estimated that they had received either no requests or fewer than 6 third-party requests, 7 received 6–20 requests, 2 received 21–100 requests, and 1, from a very large state, received more than 100 requests (McEwen and Reilly, 1994).

8. Forensic DNA Banks

In 1989, the Virginia Division of Forensic Science was the first state laboratory to offer DNA analyses to law enforcement agencies and the first to create a DNA databank of previously convicted sex offenders. By November 1997, 48 states had established forensic DNA data banks from convicted criminals, especially violent sex offenders and other violent felons (Finn, 1997). The two states without forensic DNA banks, Vermont and Rhode Island, are planning legislation to create them (Finn, 1997). In addition, the Federal Bureau of Investigation (FBI) is exploring ways to create a forensic DNA bank for the District of Columbia (Finn, 1997).

The DNA Identification Act of 1994 (Pub. L. No. 103-322, 1994 HR 3355, 108 Stat. 1796, § 210304), a federal law enacted in the fall of 1994 as part of the Omnibus Crime Control Law, created a national oversight committee to develop guidelines for DNA forensics and established a five-year, $40 million grant program to assist state and local crime laboratories in developing or improving forensic DNA testing capabilities. The DNA Identification Act also formally authorized the FBI to establish the Combined DNA Index System (CODIS) for law enforcement identification purposes (TWGDAM, 1989). CODIS is a national computer network containing DNA profiles of convicted offenders, unknown suspects, and population samples (which are used for statistical purposes only). Using CODIS, federal, state, and local law enforcement agencies are able to compare DNA profiles from crime scenes to DNA profiles of felons in the CODIS database.

In addition to collecting specimens from sex offenders and violent felons, a number of states also require samples from juvenile offenders, nonviolent felons, such as drug or white collar offenders, and those convicted of misdemeanors (McEwen, 1997). South Dakota requires samples from people merely arrested (not convicted) for a sex offense (Finn, 1997), with several other states considering similar bills (McEwen, 1997). There is also a proposal to establish a federal DNA databank that would include profiles from people convicted in federal or military courts of offenses similar to those covered by most state laws (McEwen, 1997).

Convicted offenders are required to provide blood, or in some cases saliva, either at sentencing or before release from prison (McEwen, 1997). Some states also require samples from people already incarcerated before laws' effective dates (McEwen, 1997). The DNA from these samples is analyzed for its unique identification characteristics. Nationwide, samples from about 380,000 offenders have been collected, mostly in Virginia and California, and about 116,000 samples (30 percent) have been analyzed (McEwen, 1997). These DNA identification profiles are stored, along with the samples themselves, to help identify suspects by matching biological evidence found at crime scenes to state DNA databases.

DNA profiles prepared from these samples have already proven to be a valuable resource for tracing biological material found at crime scenes to felons with prior convictions. By February 1997, forensic DNA databanks had achieved more than 200 cold hits linking serial rape cases or identifying suspects by matching DNA

extracted from biological evidence found at a crime scene to that of a known offender whose DNA profile was in the databank. For example, Minnesota's DNA databank was used to tie the same individual to 18 separate assaults (McEwen, 1997).

The power of DNA testing is to not only implicate an individual in a crime, but also to exonerate an apparently innocent individual. Recently, a Texas man who had served 12 years in prison for rape was pardoned after he was cleared of the crime by DNA tests (Holmes, 1997). Semen samples kept from 1985 were tested and failed to match his DNA.

9. Sperm, Ovum, and Embryo Banks

Fertility Clinics

In 1995, there were more than 280 fertility clinics in the United States. In 1995, 57,000 assisted reproductive technology (ART) cycles were carried out in the United States. Most of these cycles used fresh embryos using the couple's own egg and sperm. A smaller number of ART cycles used frozen, nondonated embryos that had been thawed and then transferred into a woman's uterus, and fewer still used donated eggs. Most of these cycles did not produce a clinical pregnancy. The Genetics & IVF Institute (GIVF) is an example one of these fertility clinics.

Genetics & IVF Institute. The GIVF, founded in 1984, is one of the largest, fully integrated providers of infertility treatment and genetics services. The GIVF has a main facility in Fairfax, Virginia, and a second facility in Gaithersburg, Maryland. In the Fairfax facility, the GIVF provides medical diagnosis and treatment, genetic and reproductive laboratory testing, including paternity testing, and cryobank services.

The GIVF's Cryopreservation Division, established in 1986, produced the first frozen human embryo twins in the United States. The cryobank services include embryo cryopreservation and storage, sperm banking, and human ovarian tissue cryopreservation. The Institute's embryo cryopreservation program currently freezes 2,300 embryos annually and has produced more than 250 pregnancies.

The sperm bank, the Fairfax Cryobank, was established in 1986 to provide patients at GIVF with anonymous frozen donor semen. Fairfax Cryobank was the first sperm bank in the United States to test for genetic carriers of BRCA1, Gaucher, and Canavan disease in Jewish donors, and cystic fibrosis, alpha-1 antitrypsin, and HIV by polymerase chain reaction in all donors. Fairfax Cryobank also tests for Tay Sachs in Jewish donors, thalassemia in Asian, Middle Eastern, and Mediterranean donors, and sickle cell anemia and other hemoglobinopathies in African American donors.

Sperm, Ovum, and Embryo Banks

California Cryobank. The California Cryobank, founded in 1977, is one of the largest full-service sperm banks. The California Cryobank provides physicians and their patients a comprehensive resource for semen cryopreservation and specialized reproductive services. It is accredited by the American Association of Tissue Banks and licensed by the state departments of health in California, Maryland, Massachusetts, and New York. The California Cryobank offers the following services: 1) freezing and storing human sperm for use in artificial insemination; 2) long-term semen storage for men facing the possibility of sterilization, reduction in fertility potential, or genetic damage due to vasectomy, chemotherapy, radiation therapy or high-risk occupational exposures; 3) long-term storage of pre-implantation embryos; and 4) andrology laboratory services, such as semen analysis, fertility testing, sperm washing, and male sex selection. California Cryobank's staff includes physician medical directors, genetic counselors, donor matching counselors, and technical staff.

The California Cryobank's donor catalog currently contains more than 200 donors. Donors agree to leave semen donations at least once per week for a period of 9 to 12 months. Donors are required to complete a

donor profile that contains a detailed, three-generation medical and genetic history that includes information about the donor's parents, siblings, grandparents, aunts, and uncles. This donor profile is provided to the patient. Donor profiles also include personal information such as the donor's religion, physical characteristics, favorite sports, favorite pets, SAT scores, educational background, and work experience. All donors undergo genetic testing for sickle cell anemia, Tay Sachs disease, and cystic fibrosis carrier status. Donors are also tested for infectious diseases including hepatitis B and C, CMV, sexually transmitted diseases, and HIV/AIDS. All semen specimens are quarantined for at least six months, during which time donors are retested every three months for these infectious diseases. Both donor and patient records are kept indefinitely.

California Cryobank has written standard operating procedures pertaining to the storage and maintenance of reproductive tissue. These procedures require a designated secure area for storage tanks that is locked at all times and has limited access, extensive external and internal security systems, personnel to monitor the liquid nitrogen level daily of each storage tank, and complete records of all tissues stored and all activities pertaining to the stored tissues. Quality control measures include racially color-coded donor specimens and an electronic identification system to identify donors prior to each deposit.

United States Cryobanks of Florida and United States Center for Cord Blood. The United States Cryobanks of Florida is a "cryocenter" that unites parallel technologies of freezing autologous blood, semen, and umbilical cord blood within one facility.

10. Umbilical Cord Blood Banks

Stem cells, progenitor cells that produce all other blood cells, are used to treat patients with blood diseases, certain genetic disorders, and patients receiving chemotherapy and/or radiation treatment for cancer. Until scientists discovered that umbilical cord blood contained hematopoietic stem cells, the only known source of stem cells was from bone marrow. However, retrieval of bone marrow is invasive, may be painful, requires general anesthesia, and is expensive to harvest. In contrast, retrieval of umbilical cord blood is noninvasive, painless, and generally only takes a few minutes to complete. After a baby is delivered and the umbilical cord is cut, blood is withdrawn from the umbilical cord and placenta with a syringe and then cryogenically stored. In addition, bone marrow is difficult to match between donor and recipient, while cord blood is compatible with more people. Cord blood transplants also have a lower incidence of graft versus host disease and are less likely to transmit infectious diseases.

In 1988, the first successful human cord blood transplant was performed in a child with Fanconi anemia using cord blood from a sibling (Gluckman et al., 1989). Since then, more than 500 autologous and allogeneic umbilical cord blood transplants have been performed worldwide, with the majority done in the past two to three years (Perdahl-Wallace, 1997). Approximately two-thirds of the cord blood transplants have been performed for malignant conditions including acute lymphocytic leukemia, acute myelocytic leukemia, chronic myelogenous leukemia, and neuroblastoma (Wagner et al., 1995). The other one-third have been for a variety of genetic disorders including Hurler and Hunter syndromes, adrenoleukodystrophy, osteopetrosis, severe aplastic anemia, severe combined immunodeficiency, and hemoglobinopathies such as beta thalassemia and sickle cell anemia (Wagner et al., 1995; Wagner et al., 1996). The majority of transplants have been in children, although a small number of adults have been transplanted as well. The Working Group on Ethical Issues in Umbilical Cord Blood recently concluded that "until additional data are obtained regarding safety and efficacy, umbilical cord blood banking and use ought to be considered an investigational technology rather than a proven treatment" (Sugarman et al., 1997).

Under an NIH-sponsored program, cord blood is now being collected and stored at several large banks around the United States, including the New York Blood Center, Duke University, Indiana University, and the

University of Minnesota. The International Cord Blood Registry, maintained by the University of Minnesota, matches requests for allogeneic transplants with cord blood banks. In addition, the NHLBI is sponsoring a five-year, $30 million study to show whether cord blood transplantation is a safe and effective alternative to bone marrow transplantation. The collection and storage centers for this study are located at Children's Hospital of Orange County, Duke University, and the University of California-Los Angeles.

In the last few years, privately owned companies have also begun offering umbilical cord blood banking services to individuals and families. When dealing with private storage companies, users pay a one-time fee for the collection, testing, and freezing of the blood. Then an annual fee is charged for storing the blood in liquid nitrogen. The stored cord blood may be withdrawn if illness occurs later in life. In contrast, when parents choose to donate their baby's cord blood to a public bank, they generally pay no fees, but they give up all rights to the sample in order to help build the public supply of cord blood for use in transplantation and research.

Public Donor Umbilical Cord Blood Banks

American Cord Blood Program. The American Cord Blood Program, located at the University of Massachusetts Medical Center, is the first nonprofit umbilical cord blood bank in New England. The American Cord Blood Program, which is partially funded through a grant from the National Children's Cancer Society, is only the eighth public donor cord blood bank in the world. To date, the American Cord Blood Program is the only academic health center in the country with a comprehensive program of cord blood collection, banking, transplantation, and research.

The first donation of cord blood was made on January 2, 1997. Since then, the American Cord Blood Program has collected more than 1,000 cord bloods and hopes to get 10,000 cord blood donations by the year 2007. Expectant mothers are asked to contact the program between 28 and 30 weeks of pregnancy to become donors. The mother is given a kit to bring with her to the hospital on the day of delivery; however hospitals also keep spare kits on hand. Blood collected from the umbilical cord vein is sent to the University of Massachusetts to be typed, frozen, and stored at the American Cord Blood Bank until a match is found.

The research component of this program is conducted at the University of Massachusetts. Research is ongoing in several areas, including investigating the ways cord blood cells divide, studying engraftment of transplanted cord blood cells in mice, and developing other applications of cord blood transplantation, such as for gene therapy.

Chicago Community Cord Blood Bank. The goal of the Chicago Community Cord Blood Bank (CCCBB) is to collect units of cord blood, test them for infectious diseases, identify the protein markers (HLA molecules) required for matching the cord blood to patients, and store them for transplantation into patients with cancer or other life-threatening diseases. The CCCBB, located at the University of Chicago Children's Hospital, is a community resource dedicated to providing units of cord blood for stem cell transplantation and medical research. The CCCBB is currently supported by grants and private donations that cover the cost of collection, testing, and storage (approximately $1,000 per cord blood unit).

The CCCBB has been in operation for about two years and has collected approximately 300 cord blood units. The majority of cord blood is donated for use in unrelated allogeneic transplants. However, less than ten percent of cord bloods stored at CCCBB are family donations for use in related transplants for family members at risk or in need of stem cell transplants. There is no charge to donors for the processing and storage of cord blood units.

Expectant mothers who choose to donate their babies' cord blood are asked to consent to providing medical, ethnic, and related information, donating the cord blood to the cord blood bank for transplantation and/or research, allowing blood to be drawn from the mother for tests including HIV testing, and granting permission

to track the newborn's medical history for up to one year. No blood is drawn from the baby for the cord blood bank. A minimum of 50 cc of cord blood is necessary for use in transplantation. However, approximately ten percent of cord blood collections yield less than 50 cc and are used for research or quality control purposes.

International Cord Blood Foundation. The International Cord Blood Foundation, established in 1995, is a nonprofit, public bank that stores umbilical cord blood for use in unrelated, anonymous transplants. The foundation holds the policy that before prospective donors decide to donate, they must be fully educated about the importance of cord blood, its potential uses, and the options available (family banking versus donation to a public bank versus disposal). Donors are required to supply a variety of personal information to ensure the safety of the cord blood supplied. The foundation keeps all of this information confidential and will not provide it in a form allowing personal identification unless compelled to by legal order or other lawful authority.

The International Cord Blood Foundation does supply cord blood for research purposes to universities and other institutions. Cord blood is usually used for research when it is not suitable for transplantation, such as when there is not enough blood collected from the placenta or there are not enough nucleated cells in the specimen. The possibility that the donated cord blood may be used for research is mentioned in the informed consent that donors sign.

New York Blood Center. The New York Blood Center's (NYBC's) placental blood program, established in 1993, was the nation's first program for storing umbilical cord blood for allogeneic transplantation. The NYBC placental blood program currently has an inventory of approximately 7,000 units of frozen umbilical cord blood (Torloni, 1997). The NYBC placental blood program is a nonprofit storage program funded by the NHLBI.

St. Louis Cord Blood Bank. The St. Louis Cord Blood Bank at Cardinal Glennon Children's Hospital/Saint Louis University is a public donor bank, not a private storage bank. In cooperation with other cord blood banks, the St. Louis Cord Blood Bank serves as a worldwide resource for children in need of stem cell transplants. The banking program includes community and donor education, cord blood collection, processing in the Cord Blood laboratory, release of the cord blood product, and evaluation of transplant outcomes. As of April 1997, there were more than 1,800 banked and fully characterized cord blood units available at the St. Louis Cord Blood Bank.

Private Umbilical Cord Blood Banks

Cord Blood Registry. The Cord Blood Registry, in partnership with the University of Arizona School of Medicine, provides state-of-the-art facilities for the collection, processing, and long-term cryogenic storage of umbilical cord blood for parents who wish to store their newborns' cord blood. The Cord Blood Registry also established the Designated Transplant Program to allow qualified families in imminent need of stem cell transplants to store their newborns' cord blood free of charge. Umbilical cord blood stem cells banked at the Cord Blood Registry have been used for both related and unrelated transplants.

Families not in imminent need of stem cell transplants store umbilical cord blood with the Cord Blood Registry on the remote chance that the child it came from or another family member may need a stem cell transplant in the future. The Cord Blood Registry requires that mothers sign an informed consent at least 30 days prior to collection of the cord blood. Clients who privately store cord blood receive a certificate of legal ownership for their deposits. When samples are not suitable for transplantation due to small sample size or not enough nucleated cells in the sample, the family is given a refund and recontacted as to the disposition of the sample. Families are given the choice to donate the cord blood for use in research or can request that the sample be disposed of.

The Cord Blood Registry also has programs in education and research. In 1996, more than a million pieces of educational material were distributed to the public and medical communities through the Cord Blood

Registry's national network of Medical Education Specialists and Cord Blood Educators outreach programs. The Cord Blood Registry also sponsors CME programs led by cord blood experts in major institutions across the country. As a founding member of the International Cord Blood Foundation (see *Public Donor Umbilical Cord Blood Banks*), the Cord Blood Registry provides substantial support to help fund the foundation's educational and public health initiatives and assists with the National Marrow Donor Program to educate the transplant and research communities. In addition, the Cord Blood Registry makes a $200 donation from each privately banked cord blood sample to the foundation to help in the collection and processing of cord blood. Combined, the Cord Blood Registry and the International Cord Blood Foundation have collected more than 8,000 umbilical cord blood units.

New England Cord Blood Bank. The New England Cord Blood Bank, Inc., is part of the New England Cryogenic Center, Inc., a private cryogenic laboratory. Since it was established in June 1997, the New England Cord Blood Bank has stored more than 200 units of umbilical cord blood for use in autologous transplants or for related transplants in family members. The New England Cord Blood Bank does not store cord blood for unrelated allogeneic transplants. If a family decides to terminate its storage agreement at the New England Cord Blood Bank, the sample can be donated to a public bank to possibly help others in need of stem cell transplants.

United States Center for Cord Blood. The United States Center for Cord Blood operates in the same facility as the United State Cryobanks of Florida, storing human umbilical cord blood.

Viacord. Viacord, Inc., is a medical service company that provides clients with private family cord blood banking. Physicians refer expectant families to Viacord to have their newborns' cord blood processed and banked for another immediate family member who is in need or at risk of needing a stem cell transplant due to a known malignancy, genetic blood disorder, or other relevant disease. In addition, families with no apparent need or risk also bank cord blood at Viacord, even though the chances of ever needing it within the family are relatively small.

Viacord's comprehensive cord blood banking services include everything from training of the obstetrician and labor and delivery staff on proper collection procedures, to testing and typing, cryopreservation, and storage of umbilical cord blood. Expectant mothers and their physicians complete an extensive health questionnaire and appropriate informed consents. The expectant mother is tested for infectious diseases once during the third trimester and again at delivery. The cord blood is tested for the number of stem cells (CD34 positive cells) and bacterial and fungal contamination and typed for blood type (ABO and Rh) and histocompatibility (HLA-A and HLA-B). The testing and typing results are provided to the referring physician.

A number of insurance companies have begun to pay for Viacord's services when the newborn's sibling or parent is in need or has significant risk of needing a stem cell transplant. Blue Cross Blue Shield, Aetna Health Plan, PruCare, and even some state Medicaid providers have paid in full for the collection, processing, and storage of cord blood for these families.

11. Organ Banks

Organ and tissue banks recover, process, store, and distribute human organs, bone, and tissue for transplantation. Donations are made from people who agree to donate upon their death. A single organ and tissue donor can save or improve the lives of 40–50 people by donating up to seven vital organs, both eyes for corneal transplants, and bone and soft tissue to benefit 30–40 others. Some organ and tissue banks may also have tissue available for use for educational and research purposes. However, the demand for organs, bone, and tissue usually exceeds the current supply. Therefore, usually only organs and tissues not suitable for transplantation are available for research. A few organ and tissue banks are described below, and Appendix 1 contains a partial list of organ and tissue banks in the United States.

Northwest Tissue Center

A division of the Puget Sound Blood Center, the Northwest Tissue Center provides musculoskeletal and cardiovascular tissue for transplantation in Washington, Alaska, Montana, and Idaho. Established in 1988, the center is the region's only full-service, nonprofit tissue bank. Each year, tissue is provided for more than 4,000 allografts. The donor's medical history and circumstances surrounding the donor's death are gathered from the healthcare provider. The donors are screened for infectious, neurological, and automimmune diseases as well as cancer and drug abuse. Information provided by family members provides additional information. Laboratory testing for HIV, HTLV-I and-II, hepatitis B and C, and syphilis ensures the safety of the donated tissue. The process is confidential, and the recipients do not know from whom the tissue was received.

New England Organ Bank

The New England Organ Bank (NEOB), a collaborative enterprise of six Boston hospitals started in 1968, is the oldest independent organ bank in the United States. Currently, it is a federally designated organ procurement organization for all parts of the six New England states including 13 transplant centers that have the capability to perform all types of organ and tissue transplantation. Through the United Network for Organ Sharing, the NEOB provides organs for transplant outside of New England when a compatible recipient is not found in New England. NEOB Tissue Services began recovering bone and other musculoskeletal tissues for orthopedic surgeons in 1988. All tissues procured are collected, processed, tested for infectious diseases, stored, and distributed according to the Standards for Tissue Banking of the American Association of Tissue Banks.

Mid-America Transplant Services

The Mid-America Transplant Services (MTS) is a fully accredited private, not-for-profit corporation designated by Medicare to coordinate the procurement of vital organs, eyes, bone, and soft tissue in hospitals throughout Missouri, southern Illinois, and northeastern Arkansas. Vital organs that are donated include heart, kidney, lung, liver, intestine, and pancreas. Tissues that are donated include eyes, long bones from the legs, heart valves, and tendons.

In 1995, MTS procured 318 vital organs from 97 local area donors and imported another 147 vital organs. MTS also had 234 bone/soft tissue donors and 1,215 eye donors. All potential organ and tissue donors are carefully tested for cancer, infectious diseases, and AIDS before donation can proceed. Organ and tissue donation can proceed only after death has been declared and the next-of-kin has given consent. There is absolutely no cost to the donor family for organ or tissue donation.

The MTS Eye Banking Services recovers human eye tissue from recently deceased donors and then processes and preserves the tissue for distribution to ophthalmologists for corneal transplantation surgery. Donor eyes not suitable for transplantation may be given to researchers studying the causes and possible cures of blindness and to ophthalmology residency programs for education purposes and for practicing ophthalmic surgery procedures. MTS also acts as a coordinating center for sharing of tissue between eye banks through its tissue sharing services.

The eye tissue that MTS provides for research purposes includes whole eyes, posterior poles (whole eye with cornea removed), lens, conjunctiva, retina, and choroid. Tissues can be preserved to meet the needs of individual researchers. Eyes from individuals with known eye diseases are especially valuable for study. In addition, MTS is involved in research to explore the possibility of retinal cell transplantation as a therapy for diseases such as retinitis pigmentosa and age-related macular degeneration. Donor tissue used for research on eye disease is extremely valuable and important to medical progress in treating blindness.

American Red Cross Tissue Services

The American Red Cross Tissue Services, established in 1984, collects, processes, and distributes human allograft tissue for use in transplantation. The Red Cross is one of the largest tissue collection and distribution organizations in the United States, supplying approximately one-quarter of the nation's tissues for transplantation. There are 17 tissue centers throughout the country and a national office in Washington, D.C. The American Red Cross Tissue Services distributes more than 70,000 units of tissue procured from more than 2,000 donors per year. For example, the Greater Northeast Area Tissue Services, the smallest of six Red Cross Tissue Centers, stores thousands of bone, skin, connective tissue, and heart valve samples from cadavers for transplantation and some research and education.

Tissue is obtained from deceased or surgical donors. Donors range in age from newborn to more than 80 years old. Tissue donors can sign a donor card, but they must also make their wishes known to their families since the family's consent is required before tissues can be donated after death. All tissues are tested for diseases such as AIDS, hepatitis, and syphilis.

The Red Cross distributes heart valves, skin, ligaments, tendons, bone, major blood vessels, and fascia, which covers muscles. These tissues are used in orthopedic, neurologic, opthamologic, plastic, cardiovascular, and oral reconstructive surgery for a wide range of medical procedures such as salvaging limbs after tumor surgery, reconstructing hip and knee joints, replacing corneas, and correcting curvature of the spine. Tissue transplantation does not require that the donor and the recipient have similar blood types.

The Tissue Services Research program was established to provide research and development support to optimize human bone processing methods and to ensure the safety of American Red Cross allograft bone. It is a multidisciplinary effort with several departments including biochemistry, coagulation proteins, experimental pathology, immunology, molecular biology, plasma derivatives, platelet biology, product development, transmissible diseases, and virology. The Tissue Services Research program is conducting *in vivo* and *in vitro* studies with human demineralized bone matrix to determine the bioactivity of various lots of bone. They are also developing a new bone delivery system for handling demineralized bone matrix during patient surgery. The Tissue Services Research program is also studying growth factors and viral inactivation.

12. Blood Banks

American Red Cross

The American Red Cross collected approximately 5.8 million blood donations in 1996. However, the Red Cross represents about half of all United States blood donations, so annually, about 12 million units of blood are donated in the United States. The American Red Cross usually maintains about a three-day supply of fresh blood as well as approximately 20,000 units of frozen blood at any one time. The American Red Cross also maintains the world's largest registry of frozen rare blood. Approximately 1,000 units of rare blood a year are supplied to recipients around the globe.

The Food and Drug Administration (FDA) requires the tracking of blood from “arm to arm;” however, this information is confidential and coded. Donors who test positive for HIV are notified and counseled. The consent form signed by donors asks them if excess or expired blood may be used for research.

Fresh red blood cells have a shelf life of 21–42 days depending on the preservative used, and platelets have a shelf life of 5 days. Plasma can be stored frozen for one to five years, and frozen whole blood can be stored for at least ten years. Platelets and red cells that expire are sold for research purposes. Researchers are informed that the samples have been found negative for all FDA-required tests and only by special request may be provided with the donor's age and gender. Plasma that cannot be transfused is used for making blood derivatives such as Factor VIII for hemophiliacs or for making diagnostic reagents. Nothing goes to waste.

Navy Blood Program

The Navy Blood Programs collects more than 140,000 units of blood per year. These units are stored for 35 days (like all blood). There are also 17,000 frozen units kept on hand at all times. There is only a six percent expiration rate. A small amount of the blood that has gone past the expiration date for transfusion may be used for research, but there is no specific program for supplying blood for research purposes. Any blood that tests positive for a disease is destroyed and is not used for research purposes.

13. Conclusions

Tissue collections vary considerably, ranging from formal repositories to the informal storage of blood or tissue specimens in a researcher's freezer. Table 8 reviews the sources of stored tissue samples described in this report. Archives of human tissue range in size from less than 200 to more than 92 million specimens. Table 9 provides estimates for the number of cases and specimens of stored tissue for each category of tissue collection and an estimate of the overall number of stored tissue samples in the United States. A conservative estimate is that there is a total of more than 282 million specimens from more than 176.5 million cases of stored tissue in the United States, with cases accumulating at a rate of more than 20 million per year.

Table 8. Sources of Stored Tissue Samples in the United States

Type of Repository	Institution	Number of Cases	Number of Specimens	Cases/Year
Large Tissue Banks, Repositories, and Core Facilities	AFIP DNA Specimen Repository		>2,000,000	10,000
	AFIP National Pathology Repository	>2,500,000	>92,000,000	50,000
	Coriell Institute for Medical Research		35,000	
	Eastern Cooperative Oncology Group (ECOG)		18,000	3,000
	Gynecologic Oncology Group Tissue Bank (GOG)	3,176	3,176	
	Hereditary Disease Foundation	14,000	14,000	
	Kaiser Permanente Center for Health Research		>26,000	
	LifeSpan BioSciences, Inc.		250,000	
	National Psoriasis Tissue Bank		1,300	
	NCI AIDS Malignancy Bank	3,134	8,874	
	NCI Cooperative Breast Cancer Tissue Resource	8,200	8,200	
	NCI Cooperative Human Tissue Network (CHTN)		>100,000	
	NCI-NAPBC Breast Cancer Specimen System	>130,000	>240,000	>460
	NHLBI Blood Specimen Repository		1,500,000	300,000
	NIH AIDS Research and Reference Reagent Repository		17,000	
	NIST Human Monitoring Program	12,000	12,000	
	NIST National Biomonitoring Specimen Bank	632	632	25
	PathServe Human Tissue Bank	300	30,000	300
	Radiation Therapy Oncology Group (RTOG)	4,470	4,760	1,500
	Rocky Mountain Multiple Sclerosis Center Tissue Bank		170	
	UCSF AIDS Specimen Bank		76,000	

Table 8. Sources of Stored Tissue Samples in the United States *continued*

Type of Repository	Institution	Number of Cases	Number of Specimens	Cases/Year
Large Tissue Banks, Repositories, and Core Facilities	Bogalusa Heart Study	14,000	14,000	
Longitudinal Studies	National Health and Nutrition Examination Surveys	85,000	85,000	
	NIH Women's Health Initiative	164,500	>329,000	
Pathology Specimens	Graduate Medical Education Teaching Institutions	>160,000,000	>160,000,000	>8,000,000
Newborn Screening Laboratories	50 states, District of Columbia, Puerto Rico, and Virgin Islands	>>13,500,000	>>13,500,000	<10,000 to >500,000
Forensic DNA Banks	32 states with Forensic DNA Banks	380,000	380,000	
Sperm, Ovum and Embryo Banks	California Cryobank Genetics & IVF Institute	>200	>7600 2,300	2,300 embryos
Umbilical Cord Blood Banks	American Cord Blood Program	>1,000	>1,000	
	Chicago Community Cord Blood Bank	>300	>300	
	Cord Blood Registry (CBR) & International Cord Blood Foundation (ICBF)	>8,000	>8,000	
	New England Cord Blood Bank, Inc.	>200	>200	
	New York Blood Center Placental Blood Program	7,000	7,000	
	St. Louis Cord Blood Bank	>1,800	>1,800	
Organ Banks	American Red Cross Tissue Services		>70,000	>70,000
	Mid-America Transplant Services		>1,500	>1,500
	Northwest Tissue Center		4,000	4,000
Blood Banks	American Red Cross		~5,800,000	~5,800,000
	Navy Blood Program		140,000	140,000
	All Other Blood Banks		~6,000,000	~6,000,000

Table 9. Summary of Stored Tissue Samples in the United States

Type of Repository	Number of Cases	Number of Specimens	Cases/Year
Large Tissue Banks, Repositories, and Core Facilities	>2,600,000	>96,000,000	364,825
Longitudinal Studies	>263,500	>263,500	
Pathology Specimens	>160,000,000	>160,000,000	>8,000,000
Newborn Screening Laboratories	>13,500,000	>13,500,000	<10,000 to >50,000
Forensic DNA Banks	380,000	380,000	
Sperm, Ovum, and Embryo Banks	>>200	>9,900	>2,300
Umbilical Cord Blood Banks	>18,300	>18,300	
Organ Banks		>75,500	>75,500
Blood Banks		~12,000,000	~12,000,000
Grand Total	>>176,500,000	>>282,000,000	>20,000,000

The two largest tissue repositories in the world, the National Pathology Repository and the DNA Specimen Repository for Remains Identification, are both housed within a single institution, the AFIP. These two repositories alone store more than 94 million specimens (Table 8). The tissue repositories supported by the NIH may not be as large as those at AFIP, however, the NIH is probably the largest funder of extramural tissue repositories, supplying more than $53 million in FY 1996. Finally, the pathology departments at GME teaching institutions collectively constitute the largest and oldest stores of tissue samples in the United States with some specimens more than 100 years old. The tissue bank with the oldest samples in the world is the Egyptian Mummy Tissue Bank[7] in Manchester, England, which contains mummy tissue dating back to the year 2686 BC.

The vast majority of tissues were originally collected for diagnostic or therapeutic reasons. Three sources, the AFIP National Pathology Repository, GME Teaching Institution pathology departments, and Newborn Screening Laboratories, represent more than 265.5 million diagnostic and therapeutic specimens from more than 176 million cases. At the AFIP National Pathology Repository alone, more than 92 million pathologic specimens from more than 2.5 million cases are stored (Table 8). Of the 1,687 GME Teaching Institutions with residency programs in cytopathology (68 institutions), hematology (54 institutions), and clinical and anatomic pathology (180 institutions), well over 8 million cases are accessioned cumulatively per year. Pathology departments at GME Teaching Institutions without pathology residency programs also accession pathology specimens, but most likely not at the same rate as institutions with pathology residency programs. Most GME Teaching Institutions retain pathology specimens indefinitely, with the oldest tissues archived anywhere from 20 years old to more than 100 years old. Therefore, at a rate of 8 million cases a year for 20 years, a conservative estimate is that there are more than 160 million cases stored at GME Teaching Institutions with pathology residency programs, with several million more stored at those without pathology residency programs. By 1994, the majority of Newborn Screening Laboratories had accumulated less than 500,000 Guthrie cards over the years, seven have amassed more than 500,000 (greater than 3.5 million), four reported collections of between 1–5 million cards (greater than 4 million), and one reported a collection of 6 million for a conservative estimate of more than 13.5 million Guthrie cards stored in the United States, Puerto Rico, and the Virgin Islands. Tissues collected for diagnostic or therapeutic reasons may sometimes be used for research, educational, and quality control purposes; however, the vast majority of them are not.

Several repositories have been established specifically for use in research (see Large Banks, Repositories, and Core Facilities in Table 8). In addition, several very large longitudinal studies collect and bank samples from their study participants. Likewise, a fair amount of research simultaneously creates tissue collections or contributes to tissue banks. Collectively, these tissue collections contain more than 2.3 million specimens. Because these tissues are collected specifically for research purposes, it is not surprising that the use of these tissues has resulted in numerous research publications: More than 8,000 publications have resulted from the use of cells from the Coriell Institute; more than 2,000 publications have resulted from studies using tissues from the CHTN; and more than 632 publications, 3 textbooks, and numerous monographs have been produced using samples and data from the Bogalusa Heart Study.

Other than for diagnostic and therapeutic purposes or for use in research, tissues are collected and stored for a variety of other reasons. Blood banks collect approximately 12 million units of blood a year, but only about 20,000 to 40,000 units are stored at any one time. Also, most of the blood collected is used for transfusions; very little is used for other purposes, such as research and quality control. Organ banks do not collect the volume of tissue that blood banks do, but are very similar in the respect that most of the organs and tissues collected are used for transplants, and very little is available for research purposes. Forensic DNA banks collect and store tissues for use in criminal investigations. The DoD DNA Specimen Repository and some commercial DNA banks store DNA samples for remains identification. Sperm, ovum, and embryo banks store specimens for anonymous donation or for later use by the individual storing the material. Umbilical cord blood banks also store blood for anonymous donation and later use by families banking their newborns' cord blood.

Many valuable specimens and data resources exist from a variety of sources, but no centralized database allows researchers to obtain access to and information about them. The NCI is developing a national information database of breast cancer resources to centralize information on biological specimens available to the research and clinical community, to promote access to the specimens, and to facilitate collaboration among basic, clinical, and epidemiologic researchers. This database will fulfill one of the priorities of NAPBC. However, this database is not an exhaustive national listing of all facilities holding breast cancer tissue; it is limited to resources that have a breast tissue bank and have the capability and desire to provide tissues or to participate in collaborations.

This RAND report brings together information about several sources of stored tissue samples in the United States. It represents the first time that this information has been assembled in a single document and the first time the magnitude of the archives of stored tissues has been assessed. This document may serve as a reference for researchers to identify potential tissue resources. It also may serve as a basis for developing a national database.

APPENDIX 1: Organ and Tissue Banks

The following list of organ and tissue banks was originally compiled by the New England Organ Bank. This is a partial list of the organ and tissue banks in the United States. The original list can be found at www.ultranet.com/~neob/opo.html.

Alabama

Alabama Organ Center
301 S. 20th Street, Suite 1001
Birmingham, AL 35233-2033
(205) 731-9200
www.uab.edu/aoc/index.html

Arizona

Donor Network of Arizona
3877 N. 7th Street, Suite 200
Phoenix, AZ 85014
(602) 222-2200
www.donor-network.org

Arkansas

Arkansas Regional Organ Recovery Agency
1100 N. University, Suite 200
Little Rock, AR 77207-6344
(501) 224-2623

California

CA Transplant Donor Network
55 Francisco Street, Suite 510
San Francisco, CA 94133
(415) 837-5888

Golden State Donor Services
1760 Creekside Oaks Drive, Suite 160
Sacramento, CA 95833-3632
(916) 567-1600

OTAC of Southern California
3665 Ruffin Road, Suite 120
San Diego, CA 92123-1871
(619) 292-8750

Regional OPA of Southern California
10920 Wilshire Blvd, Suite 910
Los Angeles, CA 90024
(310) 206-0222

Southern CA Organ Procurement Center
2200 West Third Street, 2nd Floor
Los Angeles, CA 90057
(213) 413-6219

Colorado

Donor Alliance, Inc.
3773 Cherry Creek N. Dr., Suite 601
Denver, CO 80209
(800) 448-4644

Connecticut

North East OPO and Tissue Bank
P.O. Box 5037
Hartford, CT 06102
(800) 874-5215

Florida

Lifelink of Southwest Florida
12573 New Brittany Blvd, #10
Fort Meyers, FL 33907
(813) 936-2772

Lifelink of Florida
2111 Swann Avenue
Tampa, FL 33606-2423
(813) 253-2640

Translife
2501 North Orange Avenue, Suite 40
Orlando, FL 32804
(407) 897-5560

University of Miami OPO
1150 Northwest 14th Street, Suite 208
Miami, FL 33136
(305) 548-7622

Georgia

Lifelink of Georgia
3715 Northside Parkway
100 Northcreek, Suite 300
Atlanta, GA 30327
(404) 266-8884

Hawaii

Organ Donor Center of Hawaii
1000 Bishop Street, Suite 302
Honolulu, HI 96813
(808) 599-7630

Illinois

Regional Organ Bank of Illinois
800 South Wells, Suite 190
Chicago, IL 60607-4529
(312) 431-3600
www.robi.org

Indiana

Indiana OPO
719 Indiana Avenue, Suite 100
Indianapolis, IN 46202
(317) 685-0389

Iowa

Iowa Statewide OPO
2732 Northgate Drive
Iowa City, IA 52245
(800) 831-4131

Kansas

Midwest Organ Bank
1900 West 47th Place, Suite 400
Westwood, KS 66205
(913) 262-1666

Kentucky

Kentucky Organ Donor Affiliates
305 W. Broadway, Suite 316
Louisville, KY 40202
(502) 581-9511

Louisiana

Louisiana OPA
3501 North Causeway Blvd, Suite 940
Metairie, LA 70002
(504) 837-3355

Maryland

Transplant Resource Center of Maryland
1540 Caton Center Drive, Suite R
Baltimore, MD 21227
(410) 242-7000

Massachusetts

New England Organ Bank
One Gateway Center
Newton, MA 02158
(800) 446-6362
www.ultranet.com/~neob/

Michigan

Transplantation Society of Michigan
2203 Platt Road
Ann Arbor, MI 48104
(313) 973-1577

Minnesota

Lifesource, Upper Midwest OPO
2550 University Avenue West,
Suite 315 South
St. Paul, MN 55114-1904
(612) 603-7800

Mississippi

Mississippi Organ Recovery Agency
12 River Bend Place, Suite B
Jackson, MS 39208
(601) 933-1000

Missouri

Mid-America Transplant Association
1139 Olivette Executive Parkway
St. Louis, MO 63132-3205
(314) 991-1661

Nebraska

Nebraska Organ Retrieval System
4060 Vinton Street, Suite 200
Omaha, NE 68105
(402) 553-7952

Nevada

Nevada Donor Network
4580 S. Eastern Avenue, Suite 33
Las Vegas, NV 89119
(702) 796-9600

New Jersey

New Jersey Organ and Tissue Sharing Network
150 Morris Avenue
Springfield, NJ 07081
(201) 379-4535
www.sharenj.org

New Mexico

New Mexico Donor Program
2715 Broadbent Parkway, Suite J
Albuquerque, NM 87107
(505) 843-7672

New York

New York Organ Donor Network
475 Riverside Drive, Suite 1244
New York, NY 10115
(212) 870-2240

Center for Donation and Transplant
218 Great Oaks Blvd
Albany, NY 12208
(518) 262-5606

University of Rochester Organ
Procurement Program
Corporate Woods of Brighton, Bldg 120
Rochester, NY 14623
(716) 272-4930

Upstate New York Transplant Services
165 Genesee Street, Suite 102
Buffalo, NY 14203
(716) 853-6667

North Carolina

Carolina LifeCare
Medical Center Blvd
Winston Salem, NC 27157
(910) 777-3130

Carolina OPA
702 Johns Hopkins Drive
Greenville, NC 27834
(919) 957-0090

LifeShare of Carolinas
P.O. Box 32861
Charlotte, NC 28232
(704) 355-7614

Ohio

Life Connection of Ohio
1545 Holland Road, Suite C
Maumee, OH 43537
(419) 893-4891

LifeBanc
20600 Chagrin Blvd, Suite 350
Cleveland, OH 44122-5343
(216) 752-5433

Lifeline of Ohio Organ Procurement
770 Kinnear Road, Suite 200
Columbus, OH 43212
(614) 291-5667

Ohio Valley LifeCenter
2939 Vernon Place
Cincinnati, OH 45219
(513) 558-5555

Oklahoma

Oklahoma Organ Sharing Network
5801 North Broadway, Suite 100
Oklahoma City, OK 73112
(405) 840-5551

Oregon

Pacific NW Transplant Bank
2611 S.W. Third Avenue, Suite 320
Portland, OR 97201-4952
(503) 494-5560

Pennsylvania

Delaware Valley Transplant Program
2000 Hamilton Street, Suite 201
Philadelphia, PA 19130
(610) 543-6391
clever.net/wwwmall/dvtp/index.html

The Center for Organ Recovery and Education
204 Sigma Drive
Pittsburgh, PA 15238
(412) 963-3550

Puerto Rico

Lifelink of Puerto Rico
Ponce de Leon Avenue, Stop 36 1/2
Hato Rey, PR 00919
(809) 758-2000

South Carolina

South Carolina OPA
1064 Gardner Road, #105
Charleston, SC 29407
(803) 763-7755
www.midnet.sc.edu/scopa/scopa.htm

Tennessee

Life Resources Regional Donor Center
2812 McKiney Road
Johnson City, TN 37604
(423) 929-1638

Mid-South Transplant Foundation
956 Court Avenue, Suite G-228
Memphis, TN 38163
(901) 448-5910

Tennessee Donor Services
5908-D Toole Drive
Knoxville, TN 37919
(423) 588-5903
www.korrnet.org/donors

Texas

LifeGift Organ Donation Center
5615 Kirby Drive, Suite 900
Houston, TX 77005
(713) 523-4438

South Texas Organ Bank
8122 Datapoint Drive, Suite 1150
San Antonio, TX 78229
(210) 614-7030

Southwest Organ Bank
3500 Maple Avenue, Suite 800
Dallas, TX 75219
(214) 821-1910
wg.dzn.com/swob/top.htm

Utah

Intermountain Organ Recovery System
230 South 500 East, Suite 290
Salt Lake City, UT 84102
(801) 521-1755

Virginia

Southeast Organ Procurement Foundation
5004 Monument Avenue, Suite 101
Richmond, VA 23230
(804) 342-1414

LifeNet Transplant Services
5809 Ward Court
Virginia Beach, VA 23455
(800) 847-7831
www.life-net.org

Virginia's OPA
1527 Huguenot Road
Midlothian, VA 23113
(804) 794-4122

Washington Regional Transplant Consortium
8110 Gatehouse Road, Suite 101W
Falls Church, VA 22042
(703) 641-0100
www.wrtc.org

Washington

LifeCenter Northwest
2553 76th Ave, SE
Mercer Island, WA 98040-2758
(888)543-3287
www.lifecenternw.org/

Wisconsin

University of Wisconsin OPO
600 Highland Avenue
Madison, WI 53792
(608) 263-1341

Wisconsin Donor Network
9200 West Wisconsin Avenue
Milwaukee, WI 53226
(414) 259-2024

APPENDIX 2: Stored Tissue Sample Websites

Appendix 2 lists all sources of stored tissue samples with websites referenced in this report.

Alabama Organ Center
www.uab.edu/aoc/index.html

American Cord Blood Program
www.ummed.edu/main/resource/cordrel.htm

American Red Cross
www.redcross.blood

American Type Culture Collection (ATCC)
www.atcc.org/

Armed Forces DNA Identification Laboratory
www.afip.mil/oafme/dna/afdil.html

Armed Forces Institute of Pathology (AFIP)
www.afip.mil/default.html

Bogalusa Heart Study
www.mcl.tulane.edu/cardiohealth/bog.htm

Cancer and Leukemia Group B (CALGB)
www-calgb.uchicago.edu/Default.nckl

Centers for Disease Control and Prevention (CDC)
www.cdc.gov/

Chicago Community Cord Blood Bank (CCCBB)
rmoldwin.bsd.uchicago.edu/cordblood/CCCBB_Donor__information.html

Cord Blood Registry
www.cordblood.com/home.html

Coriell Institute for Medical Research
arginine.umdnj.edu/info.html

Delaware Valley Transplant Program
clever.net/wwwmall/dvtp/index.html

Donor Network of Arizona
www.donor-network.org

Eastern Cooperative Oncology Group (ECOG)
ecog.dfci.harvard.edu/

Federal Bureau of Investigations (FBI)
www.fbi.gov/

Forensic Science Research and Training Center
www.fbi.gov/lab/report/research.htm

Genetics & IVF Institute
www.givf.com/

Gynecologic Oncology Group Tissue Bank
www.ncbi.nim.nih.gov/ncicgap/reagents.htm

Harvard Brain Tissue Resource Center
www.brainbank.mclean.org:8080/into.html

HELIX
healthlinks.washington.edu/helix

International Cord Blood Foundation
infinityweb.com/cordblood
www.icbf.org/

Kaiser Permanente Center for Health Research (CHR)
www.kbnw.org/

LifeCenter Northwest
www.lifecenternw.org/

LifeNet Transplant Services
www.life-net.org

LifeSpan BioSciences, Inc.
www.lsbio.com

Longitudinal Studies Branch of the National Institute on Aging (NIA)
www.grc.nia.nih.gov/Branches/lsb/lsb.htm

Mid-America Transplant Services (MTS)
www.midtrans.com:80/

National Cancer Institute (NCI)
www.nci.nih.gov

National Center for Environmental Health (NCEH)
www.cdc.gov/nceh/ncehhome.htm

National Center for Infectious Diseases (NCID)
www.cdc.gov/ncidod/ncid.htm

National Health and Nutrition Examination Survey (NHANES)
www.cdc.gov/nchswww/about/major/nhanes/nhanes.htm

National Heart, Lung, and Blood Institute (NHLBI)
www.nhlbi.nih.gov/nhlbi/nhlbi.htm

National Institute of Allergy and Infectious Diseases (NIAID)
www.niaid.nih.gov/

National Institutes of Health (NIH)
www.nih.gov/index.html

National Institute of Mental Health (NIMH)
www.nimh.nih.gov/

National Institute on Aging
www.nia.nih.gov

National Pathology Repository
www.afip.mil/repository/welcome.html

National Psoriasis Tissue Bank
www.psoriasis.org/tissuebank.html

NCI AIDS Malignancy Bank
cancernet.nci.nih.gov/amb/amb.html

NCI Cooperative Breast Cancer Tissue Resource (CBCTR)
www.cbctr.ims.nci.nih.gov

NCI Cooperative Family Registry for Breast Cancer Studies (CFRBCS)
www.dceg.ims.nci.nih.gov/cfrbcs

NCI Cooperative Human Tissue Network (CHTN)
wwwicic.nci.nih.gov:80/chtn/chtnmain.html

NCI-NAPBC Breast Cancer Specimen and Data Information System
cancernet.nci.nih.gov/breastdata/contents.htm

New England Cord Blood Bank, Inc.
www.cordbloodbank.com/overview.htm

New England Organ Bank (NEOB)
www.ultranet.com/~neob/tissbank.html

New Jersey Organ and Tissue Sharing Network
www.sharenj.org

New York Blood Center Placental Blood Program
stem.nybc.org/

NIH Women's Health Initiative (WHI)
odp.ld.nih.gov/whi/

Northwest Tissue Center
www.psbc.org/htm/services/tisuctr.htm

OncorMed
www.oncormed.com

PathServe
www.tissuebank.com/

Radiation Therapy Group (RTOG)
www.rtog.org/

Regional Organ Bank of Illinois
www.robi.org

Rocky Mountain Multiple Sclerosis Center Tissue Bank
www.swedmc.com:80/msc/tissue.htm

South Carolina OPA
www.midnet.sc.edu/scopa/scopa.htm

Southwest Oncology Group (SWOG)
www.oo.saci.org/

Southwest Organ Bank
wg.dzn.com/swob/top.htm

Specialized Program of Research Excellence (SPORE) in Gastrointestinal Cancer at Johns Hopkins
www.med.jhu.edu/gispore/gastro_can.html

St. Louis Cord Blood Bank
www.slu.edu/colleges/med/departments/pediatrics/cordbank/transplant/transpla.html

Tennessee Donor Services
www.korrnet.org/donors

United States Center for Cord Blood
www.uscryo.com:80/bio.html

United States Cryobanks of Florida
www.uscryo.com:80/index.html

Viacord, Inc.
www.viacord.com/welcome.htm

Virginia Division of Forensic Science
www.state.va.us/~dcjs/forensic/

Washington Regional Transplant Consortium
www.wrtc.org

Notes

1 The five regional divisions are the Eastern Division, the Midwestern Division, the Southern Division, the Western Division, and the Pediatric Division, which provides childhood tumors nationwide through the Children's Cancer Study Group.

2 The six CFRBCS collaborating sites are the Australian Breast Cancer Family Registry, the Metropolitan New York Registry of Breast Cancer Families, the Northern California Cooperative Family Registry, the Ontario Registry for Studies of Familial Breast Cancer, the Philadelphia Familial Breast Cancer Registry, and the Utah Cooperative Breast Cancer Registry.

3 It is estimated that approximately one-third of the women enrolled in the hormone replacement therapy trial will have had a hysterectomy and therefore will not undergo the endometrial biopsy.

4 Medical schools represented at the UAREP meeting included those at the University of Pittsburgh, the Johns Hopkins University, the University of Minnesota, the Robert Wood Johnson Medical School, the University of Kansas, Case Western Reserve University, the University of Pennsylvania, the University of Iowa, Northwestern University, Thomas Jefferson University, and Memorial Sloan-Kettering.

5 A single autopsy case may generate several slides and paraffin blocks.

6 The College of American Pathologists *Minimum Guidelines for the Retention of Laboratory Records and Materials* recommends a retention time of 10 years for bone marrow specimens, but only 24 hours for serum, cerebral spinal fluid, and other body fluids, and 7 days for peripheral blood and body fluid smears. Therefore, specimens recorded here represent the number of bone marrow aspirations and biopsies and resections of lymph nodes and related tissue accessioned at each institution listed.

7 The Egyptian Mummy Tissue Bank, www.museum.man.ac.uk/collections/egyptology/egyptology.html.

References

American Medical Association. 1997. *Graduate Medical Education Directory 1997–1998.* American Medical Association, Chicago.

Andrews LB. 1995. State laws and regulations governing newborn screening. American Bar Foundation, Chicago.

Bailar III JC. 1995. Monitoring human tissues for toxic substances: A follow-up to the National Academy of Sciences (NAS) report. *Environmental Health Perspectives* 103 (suppl 3):81–84.

Clinical Laboratory Improvement Amendments. 1996. Clinical Laboratory Improvement Amendments of 1988 (CLIA). 42 CFR 493 (10-1-96 Edition):796–921.

Department of Health and Human Services. 1991. Clinical Laboratory Improvement Amendments (CLIA). November 29, 1992. Press Release 1991.11.29.

Finn P. 1997. Revolution Underway in Use of DNA Profiles: Bid to Link U.S. Databanks is Crime-Solving Edge. *The Washington Post.* Sunday, November 16, 1997: B4.

Gluckman E, Broxmeyer HE, Auerbach AD, et al. 1989. Hematopoietic reconstitution in a patient with Fancon's anemia by means of umbilical-cord blood from an HLA-identical sibling. *New England Journal of Medicine* 321:1174–1178.

Graduate Medical Education. 1997. *Journal of the American Medical Association* 278(9):775–784.

Holmes M. 1997. Man Cleared of Rape To Be Pardoned. *Associated Press.* Wednesday, October 8, 1997; 12:39 p.m.

McEwen JE and Reilly PR. 1994. Stored Guthrie cards as DNA "banks." *American Journal of Human Genetics* 55:196–200.

McEwen JE and Reilly PR. 1995. A survey of DNA diagnostic laboratories regarding DNA banking. *American Journal of Human Genetics* 56(6):1477–1486.

McEwen JE. 1997. DNA Data Banks. In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*, MA Rothstein, ed., Chapter 11.

Mertz JF, Sanker P, Taube SE, and Livoisi V. 1997. Use of human tissues in research: Clarifying clinician and researcher roles and information flows. *Journal of Investigative Medicine* 45(5):252–257.

National Heart, Lung, and Blood Institute. 1996. Blood Specimen Repository: 1996 Catalog.

Perdahl-Wallace EB. 1997. Placental cord blood transplantation. *Transplant Forum* 4(2):4–5.

Reilly P. 1992. ASHG statement on genetics and privacy: Testimony to United States Congress. *American Journal of Human Genetics* 50:640–642.

Sugarman J, Kaalund V, Kodish E, Marshall MF, Reisner EG, Wilfond BS, and Wolpe PR. 1997. Ethical issues in umbilical cord blood banking. *Journal of the American Medical Association* 278(11):938–943.

Technical Working Group on DNA Analysis Methods (TWGDAM). 1989. The Combined DNA Index System (CODIS): A theoretical model. In *DNA Fingerprinting: An Introduction*, LT Kirby, ed., New York: Stockton Press, 279–317.

Torloni AS. 1997. Umbilical cord cells: A viable alternative for BMT. *Transplant Forum* 4(2):6.

Wagner JE, Kernan NA, Steinbuch M, Broxmeyer HE, and Gluckman E. 1995. Allogeneic sibling umbilical cord blood transplantation in children with malignant and non-malignant disease. *Lancet* 346:214–219.

Wagner JE, Rosenthal J, Sweetman R, et al. 1996. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: Analysis of engraftment and acute graft-versus host disease. *Blood* 88:795–802.

Wise SA and Koster BJ. 1995. Considerations in the design of an environmental specimen bank: Experiences of the National Biomonitoring Specimen Bank Program. *Environmental Health Perspectives* 103(suppl 3):61–67.

CONTRIBUTION OF THE HUMAN TISSUE ARCHIVE TO THE ADVANCEMENT OF MEDICAL KNOWLEDGE AND THE PUBLIC HEALTH

Commissioned Paper
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Stanford University School of Medicine

I. Introduction

The history of medical progress has been created over countless centuries from the careful observation and study of normal and diseased individuals. Medical historians place the birth of the discipline of pathology in Renaissance Italy, when physicians first began systematically to perform autopsies on patients they had treated and to incorporate the results into their final summary of the individual case record. From the 14th century until near the middle of the 19th century, autopsies were performed primarily by clinicians convinced of the importance of gaining a better understanding of the basis of their patients' symptoms and signs, as well as the causes of their deaths. The origin of the *science* of pathology—that is, the scientific study of the causes, mechanisms, and natural history of diseases, is generally traced to the middle of the 19th century in Germany, when a true visionary and giant of the field, Professor Rudolph Virchow, came to center stage. Virchow began the systematic application of light microscopy to the study of diseased human tissues, and from those studies he postulated one of the fundamental tenets of medicine, the cell theory of disease.

From that origin to the present time, the discipline of pathology has contributed essentially all of the vocabulary and much of the intellectual foundation of contemporary medicine. The development of this knowledge base has come largely from the systematic clinico-pathologic study of human tissue samples removed during the course of medical care, combined synergistically with experimentation in suitable animal models, employing over time the latest in contemporary scientific technologies. Put differently, the science of pathology, while never losing its focus on the systemic manifestations of disease, has probed the mechanisms of disease causation with ever-greater scientific sophistication, while proceeding progressively from whole organs and tissues to cells, and then from the subcellular to the supramolecular and molecular manifestations of disease expression.

In looking back over the history of pathology during the 20th century, two features stand out: First, as the science and knowledge of human disease have progressed, students of disease have developed or co-opted in steady succession the newest in scientific tools and methodologies. Second, as the new experimental approaches led to new insights and expanded knowledge of agents and mechanisms of disease causation, new biomedical scientific disciplines split off from pathology and subsequently flourished independently. Among the most prominent of these were microbiology, virology, and immunology. What tended historically to remain in pathology was the central focus on tissues as a primary research resource and morphology as the dominant experimental approach. But even here, the tools of investigation continuously changed. Thus, light microscopy, initially the exclusive optical tool, became in the late 1950s complemented by the then-new technology of electron microscopy; the use of a few standard dyes to enhance the optical interpretation of tissue specimens became complemented by ever more sophisticated histochemical approaches that represented an early attempt to probe the chemical composition and understand the chemical reactions of tissues in morphologically intact samples. These approaches have culminated in recent years in the development of monoclonal antibodies and gene probes, developments that have revolutionized diagnostic and experimental pathology as well as biomedical research more generally. With appropriately tagged monoclonal antibodies, it is possible by microscopic examination of tissue sections to identify with great precision the presence, location, or absence of specific protein molecules and thereby begin to understand specific, and ultimately differential, gene expression at the level of individual cells in normal tissues and pathological lesions.

It is only recently, within the past 30 years, that we can be said to have entered the remarkable new era of molecular and genetic medicine. But even now, with increasing emphasis on understanding the chemistry and genetics of normal biological functions and their pathological derangements, the discipline and methodologies of pathology continue to play an essential—and often irreplaceable—role as the base of medical knowledge expands at an ever quickening pace. The reason for this is rather straightforward: We define disease entities and their patterns of expression within individuals (whether they be patients or experimental animals for that matter) on the basis of pathologic criteria, and we understand their natural histories and their responses to

therapy on the basis of systematic clinico-pathological studies. All new methods for the study of disease, whether they be monoclonal antibodies, new molecular genetic technologies, or others yet to come, ultimately must be interpreted and validated with reference to known disease entities and appropriate controls, and that process requires, without exception, that the methods be developed and evaluated with authenticated pathologic materials.

From the practice of pathology in American academic medical centers for well over 100 years, the centers collectively have amassed a vast archive of human tissue specimens that constitutes a historical record of the manifestations and natural history of diseases over time. Although in recent years, because of increasing recognition of the applicability of new research technologies to pathologic tissue specimens, there has been increasing effort, largely stimulated by the National Institutes of Health (NIH), to create banks of human tissue samples to be made available exclusively for research purposes, the fact remains that the vast bulk of the human tissue collection continues to be represented in the pathology archives of academic medical centers. And from the very advent of pathology as a scientific discipline, human tissue samples obtained in the provision of medical care (or at autopsy) have been considered and managed (de facto, if not de jure) as a unique *public* research resource, the accessibility and use of which has immeasurably advanced medical knowledge for the enormous benefit of all humankind.

This report is built upon a number of specific examples, or perhaps better, vignettes, which illustrate how studies of both autopsy and surgical materials have contributed, often uniquely, frequently unexpectedly, but always in important ways, to the advancement of medicine, and in many instances, to the benefit of the public health as well. At the end of the report, which in many respects should be considered an anthology, I acknowledge my indebtedness to the many pathology colleagues who contributed ideas and examples, in many instances representing their own work.

II. "Low-Tech" Studies with Major Medical and Public Health Consequences

A. The DES Story and Related Genito-Urinary Pathology

During the late 1960s, a pathologist at the Massachusetts General Hospital (MGH), Dr. Robert E. Scully, who is an authority on the pathology of the female genital tract, observed over a relatively short time interval several cases of an unusual tumor removed from the vagina of young women. The lesion, dubbed clear-cell adenocarcinoma of the vagina, was indeed rare; none had previously been seen at MGH, and very few had been reported in the literature. An initial collaborative study of seven cases, involving pathologists and gynecological oncologists, came up with the first evidence of a common feature among the cases: all of the mothers reported that they had been treated with the nonsteroidal estrogenic hormone diethylstilbestrol (DES) during their pregnancies with the afflicted young women. DES and related drugs had come into common use in obstetrics after World War II to treat women with a history of previous spontaneous abortions or abnormal bleeding during pregnancy. As a result of this study, a national registry was established to collect additional cases of this lesion, and by 1981 the registry contained more than 400 cases, more than two-thirds of which were associated with maternal exposure to DES or related hormonal agents during pregnancy. Two of the most important consequences of this study were a dramatic reduction in the use of DES and related drugs during pregnancy and recognition of the need for methodical screening of young women (later it was recognized that boys also could be affected) whose mothers had been exposed to DES during pregnancy in order to detect these tumors as early in their development as possible. Data from the registry indicated that with early detection and appropriate surgical therapy, the survival rate for the afflicted young women could be greater than 90 percent; detection at later stages of tumor development resulted in a substantial frequency of tumor recurrence, metastasis, and death.

In discussing the history of this entity with Dr. Scully (a former mentor of mine), he offered two other examples from his own personal history that are pertinent to the subject of this report. First, while Dr. Scully was in pathology training during the early 1950s at Harvard, Dr. Arthur Hertig, then chairman of the department, oversaw the first study to examine the biological significance of dysplastic changes in the uterine cervix. Such changes had been observed and recorded by pathologists for more than 50 years, but prior to this study, which reviewed the pathology files from a major gynecological teaching hospital and was able to obtain examples of cases that dated back to the beginning of the 20th century, no systematic, long-term follow-up studies of these cases had been undertaken, and the biological significance of these changes and the natural history of the underlying disease process were unknown. The results indicated that the dysplastic changes were very frequently precursors to the development of carcinoma of the uterine cervix. The study was an early landmark, which led to profound changes both in understanding of the pathogenesis of cervical carcinoma and in the management of women with early dysplastic changes. The study also provided major impetus to the development and general application of the now routinely used Pap (Papanicolaou) smear.

The second example, which is not infrequent and is of contemporary relevance in an era of enhanced sensitivity to environmental integrity, involves the issue of whether the appearance of unusual forms of neoplasms represents new entities, or whether the tumors are simply very rare. The case in question was a very unusual tumor of the testis removed at MGH. The tumor was at first believed to be a new entity but later proved not to be, as a few examples of the neoplasm in tissue archives from the last quarter of the 19th century were found. Currently, there is considerable international debate about an alleged progressive diminution in the male sperm count over the past decades. It has been argued that the decrement directly results from exposure to one or more putative environmental toxins, presumably chemicals that can act like hormonal mimics. Similar concerns have been raised about a putative causative effect of pesticides on the apparent increase in prevalence of carcinoma of the female breast. The observation of a seemingly new form of neoplasm in, for example, the testis or the female breast, could be put forth as "evidence" of the presence in the environment of new hormonally active carcinogenic agents. The ability of pathologists to comb tissue archives that may go back more than 100 years can serve to put such observations into proper perspective and avoid premature, and often perfervid, interpretations that can have substantial public health and economic consequences.

Finally, it is important to keep in mind that there are numerous diseases that were previously treated primarily surgically but are no longer so treated (e.g., peptic ulcer), or have become rare, for which the only extant materials for study are those available in pathology archives, occasionally saved as frozen samples, but most typically as fixed specimens embedded in small paraffin blocks (from which the usual sections are prepared for microscopic examination). As science and technology continue to advance, occasions will inevitably arise in which investigators will wish to test new hypotheses to further understanding of these diseases, which, although now rare, may be neither irreversibly extinguished nor permanently reduced in prevalence. In such instances, the paraffin-embedded "relics" of formerly prevalent diseases may be the only research material that is any longer available (recall the recent debate about whether to destroy all remaining samples of smallpox virus).

B. Some Occupational and Environmental Carcinogens

1. Hepatic Neoplasia

The recognition of the carcinogenic potential of occupational and environmental agents has often begun with the suspicions of an occupational medicine physician or a pathologist, who observes even very small clusters of unusual neoplasms and begins to wonder about the possibility of shared histories of actual or potential exposure. One example of this phenomenon is an unusual malignant tumor of the liver known as hepatic angiosarcoma (HAS). Three occupational or environmental agents have been identified as causative for HAS:

vinyl chloride monomer, the starting material in the production of the widely used plastic, polyvinyl chloride (PVC); Thorotrast, a particulate agent that emits alpha-particle radiation and was widely used as an angiographic contrast agent from about 1930 to 1955; and inorganic arsenic, an agent that has been used in the past both as an agricultural pesticide and medically, e.g., as a component of a therapeutic cocktail called Fowler's Solution. The recognition of the hepatic carcinogenicity of vinyl chloride monomer began with the suspicions of a plant physician in a factory that was a major producer of PVC. Establishment of the association was critically dependent of the availability of pathologic archival materials from which collections of cases of HAS could be retrieved for study.

Similarly, the recognition of the hepatic accumulation, and thence, carcinogenicity of Thorotrast was first detected in the late 1940s from autopsy studies and led to the abandonment of the agent as a radiographic contrast material. The initial correlation of HAS with exposure to inorganic arsenic derived from clinicopathological studies in the 1940s and 1950s of German vintners exposed to inorganic arsenical pesticides. With respect to each of these agents, the recognition and establishment of carcinogenic potential led either to its abandonment or to the implementation of altered practices of usage of the agent, plant hygiene and worker exposure.

2. Bronchopulmonary Neoplasia

Cigarette Smoking. When the Surgeon General's first report on the hazards of smoking was issued in 1964, the vast majority of the cited evidence was derived from classical epidemiological studies. Among the few bits of hard evidence that rested in biological observations were the systematic observations of a pulmonary pathologist, Dr. Oscar Auerbach, who spent most of his career, and conducted his seminal studies, in the VA hospital in East Orange, New Jersey. Dr. Auerbach devoted the bulk of his investigative career to a massive, meticulous, and extraordinarily detailed study of the histopathological changes that occurred in the lungs of autopsied smokers and compared them with those observed in patients with lung cancer. These studies, carried out on thousands of autopsy samples over decades, described a pattern of progressive changes in bronchial lining cells, the increasing atypicality of which correlated with the magnitude and duration of smoking exposure and which were very similar to the atypical changes occurring in uninvolved portions of the bronchial tree in patients with lung cancer. When Dr. Auerbach died recently at age 92, his obituary in the *New York Times* appropriately described him as "a pathologist who found the first evidence in human lung tissue of a link between cancer and smoking.…"

Although most of Dr. Auerbach's research was observational, he also performed some of the earliest experimental studies to explore further the linkage between cigarette smoking and cancer. For example, he was able to train dogs to smoke chronically and demonstrated that about 15 percent of the animals developed cancer of the lung. This was the first direct demonstration that exposure to cigarette smoke could produce lung cancers in animals and probably the first that refuted the contentions of cigarette interests that there had been no direct and convincing experimental demonstration of the pulmonary carcinogenicity of cigarette smoking. Dr. Auerbach also showed that when individuals cease smoking, over a period of years their precancerous bronchial epithelial changes diminished in frequency and ultimately disappeared. These findings were the first indication of the potential reversibility of the precancerous changes and provided important rationale for the current commonplace public health strategy of trying to induce smokers to quit the habit.

Uranium Mining. If a VA hospital in East Orange, New Jersey, might be considered an unlikely site for what proved to be an extraordinarily fecund human tissue archive, so also might be Grand Junction, Colorado, where pathologist Dr. Geno Saccomanno has been amassing since the early 1950s a unique archive of pulmonary pathological and cytological specimens from underground uranium workers. The development and use of this archive have been supported continuously since its inception by funding from either the U.S. Public Health Service or the Department of Energy, and the archive has supported the largest continuous study on

underground uranium miners in the United States. Dr. Saccomanno and his associates have developed novel techniques for the collection, processing, and evaluation of pulmonary and other cytology specimens that have since become standard usage in the field. The studies of this group have contributed greatly to an understanding of the cytological changes involved in the morphologic progression of bronchial epithelium through its various metaplastic and dysplastic changes to overt carcinoma. The Saccomanno archive and research results complement those of Dr. Auerbach, with the important advantage that while the Auerbach studies were all conducted on postmortem tissues, the Saccomanno studies of specimens from living patients derived information that informed early lung cancer detection strategies and led to modification of occupational standards. For example, these studies confirmed early reports indicating a malevolent synergy between smoking and radiation exposure in uranium miners and stimulated major smoking cessation programs by the mining industry. The studies also played an important role in establishing maximum allowable environmental radiation exposures in this worker population.

To provide some sense of the size of this unique tissue archive, it contains serial sections of the entire tracheobronchial trees from 63 uranium miners and 71 matched nonminer controls, which demonstrate the full spectrum of pathologic changes leading up to and culminating in bronchogenic carcinoma; more than 250,000 sputum cytology specimens from nearly 18,000 uranium workers; both surgical and autopsy specimens from about 530 uranium miners who had been diagnosed with primary bronchogenic carcinoma; and frozen serum samples from nearly 700 uranium miners and control patients. Abundant epidemiologic data are also available for each of the patients whose pathologic samples are in the archive. This is an important point, because this unique trove of pathologic specimens now can serve as a fertile resource for contemporary studies developing and applying new molecular genetic technologies to determine the pattern of genetic changes that occur during the various stages of atypia through which normal bronchial epithelium progresses on its path to invasive carcinoma. Such studies are now under way.

The epidemic of lung cancer remains uncontrolled by current prevention and treatment strategies. More men and women die each year from lung cancer than from AIDS, breast cancer, and prostate cancer combined. Although therapy research has shown some success in improving short-term lung cancer survival, more than 85 percent who develop the disease will be dead within five years. Substantial effort and resources have been expended on attempts to detect early, developing lung cancers under the orthodox assumption that detection and diagnosis at an earlier stage of the disease would be more amenable to curative surgery. The most important of these early detection efforts have involved periodic chest radiographs (early shown to be ineffective) and examination of bronchopulmonary cytology specimens. Yet, three large National Cancer Institute (NCI)-sponsored clinical trials that were carried out in the 1970s and early 1980s at the Johns Hopkins University, Memorial Sloan-Kettering Hospital, and the Mayo Clinic demonstrated that while the then-available diagnostic procedures could detect some presymptomatic earlier stage cancers, they were not sufficiently sensitive to lower overall lung cancer mortality.

As will be further elaborated later in this report, recent advances in cancer biology have led to important discoveries of specific changes in gene structure and patterns of gene expression during the progression of different populations of normal cells to neoplasia. Clearly, it becomes of pressing societal interest to determine whether the further identification and detection of such newly recognized precursory milestones of carcinogenesis might prove to be sensitive and useful markers of very early stages in the evolutionary pathway of bronchopulmonary neoplasia. To attempt to answer these questions by launching *prospective* studies for each newly proposed marker would not only involve considerable expense but would carry enormous opportunity costs in terms of the time required essentially to repeat the earlier NCI-sponsored multicenter clinical trials. On the other hand, the availability of large archives of carefully documented and clinically correlated sputum cytology specimens permits the direct, much more rapid, and less expensive approach of applying new detection technologies for candidate genotypic and phenotypic markers directly to existing specimens.

This work has already proved valuable. Certain of the genetic changes that are beginning to be recognized in the evolution of bronchopulmonary carcinoma can be detected in sputum cytology specimens, and the earliest detection of a clonal population of cancer cells in sputum appears now to be possible more than one year prior to clinical diagnosis. In addition to genetic changes, which are still the object of intensive research, altered patterns of gene expression are becoming increasingly recognized in neoplastic cell populations by use of novel monoclonal antibodies. Such a presumptive "cancer neoantigen" has been recognized in human lung cancer and is expressed in sputum cytology samples by at least two years prior to clinical diagnosis with acceptably high sensitivity and specificity. On the basis of these results with archival sputum cytology materials, important new clinical trials are underway prospectively to determine the utility of these new markers as early signals leading to much earlier diagnosis of bronchopulmonary carcinomas, greatly enhanced opportunities for curative interventions, and measurable surrogates by which to monitor the efficacy of new chemoprevention strategies.

This last vignette demonstrates a particularly important, and often overlooked, point about the value of well-characterized and readily accessible archived human tissue samples in accelerating the evaluation and application of novel new scientific insights and technologies to improve the understanding, treatment, and even prevention of major human diseases. To try to initiate prospective studies de novo for each new promising candidate marker for each of the many varieties of human neoplasia would not only be extraordinarily costly in dollars and human effort, but would require study periods of many years, or even decades, before definitive endpoints could be reached. In contrast, being able to apply such new technologies to archival materials, where clinical course, therapeutic response, and outcome are already known, represents an incredible collapse of the time and money, to say nothing of the human suffering, required to evaluate the technologies, launch the necessary corroborative community trials, and possibly bring entirely new lung cancer screening strategies into general application.

C. Atherosclerotic Cardiovascular Disease

The leading cause of death in the United States continues to be atherosclerotic cardiovascular disease (ASCVD). It has been known for many decades that the major, medically devastating consequences of ASCVD tend to become manifest in middle and advanced age, and as late as the middle of the 20th century, it was generally believed that the underlying atherosclerotic disease processes were themselves processes of middle and old age. That belief, naturally, shaped the entire medical strategy for dealing with ASCVD. But during the past 40 or more years, there has been a remarkable shift in the approach to these diseases, based on new information that led to the recognition that a very large fraction of the morbidity, and probably the mortality, of ASCVD is preventable. There has been a remarkable change in the nation's dietary and recreational habits such that although heart disease continues as this country's number one cause of death, people live longer and healthier lives because of new knowledge about the relationship of diet, smoking, and exercise to cardiovascular health. In addition, of course, powerful new surgical and medical therapies have enabled many of those in whom ASCVD has become manifest to continue to lead active, productive lives.

The cornerstone of the science that led to this profound change in conception of ASCVD and the formulation of new preventive strategies for mitigating its impact on the population was laid in 1953. Three military pathologists who were performing autopsies on Korean war casualties were charged with documenting chest wounds from artillery. In the process they noticed and systematically recorded information on the types and extent of atherosclerotic changes in the coronary arteries of these young, otherwise healthy and largely male adults, a population not at that time considered to be at risk from ASCVD. The reports based on those observations revolutionized thinking about the onset and progression of coronary heart disease and subsequently other manifestations of ASCVD as well.

The reports were based on 300 autopsies of individuals averaging 22.1 years of age. The casualties were primarily U.S. soldiers, but some Korean prisoners of war and Japanese civilians were also studied for comparative

purposes. Evidence of coronary arteriosclerosis was found in 77.3 percent of the hearts from the U.S. soldiers, while in the Korean soldiers and Japanese civilians, although some early atherosclerotic changes were observed, the extent of the changes was strikingly less than in the U.S. casualties. Moreover, in the eight soldiers whose coronary arteries demonstrated occlusion ranging from 95 percent to total, only one was older than 22 years of age. An editorial published in *JAMA* some 35 years later reflected on how these carefully documented and totally unexpected autopsy findings had changed our thinking and behavior concerning atherosclerosis:

- Atherosclerosis is not a disease of middle to old age, but develops early in life and progressively increases in extent and severity.
- Atherosclerosis is not limited to any recognizable subset of the several hundred cases studied, but rather appears to be common in this American population.
- Atherosclerosis may be severe enough to occlude an artery, but apparently still be asymptomatic—a very surprising observation.
- A wide range of asymptomatic lesions can be found in healthy, vigorous young adults.
- American males have much more evidence of atherosclerosis than Japanese or Korean males of the same age group.

At the time these studies were published, open heart surgery was still in the developmental stages, and it would not be until the late 1960s that heart transplants and the first coronary bypass surgery would be performed. Thus, the only tools for research on the development of heart disease were the autopsy and related demographic information or very long-term prospective studies of large defined populations over many years to attempt to identify risk factors among those who eventually developed disease (e.g., the Framingham Study). In the 1950s and later, many systematic autopsy studies in defined geographical areas extended these initial observations to all age groups, to men and women, to ethnic groups, and to various countries. One such study, the Community Pathology Study in New Orleans, amassed retrospective and prospective information over a 20- to 30-year period on the relationship of atherosclerotic lesions, mainly in the coronary arteries and the aorta, to blood pressure, cholesterol and HDL, diet, and cigarette smoking.

This study also observed changes in the extent and severity of the lesions during the life of the study, an early observation that ultimately led to concepts of reversibility and its association with changes in population lifestyles. Such discoveries from autopsies led to new hypotheses and helped focus questions for atherosclerosis and hypertension research in many areas, including the development of animal models (none truly reflects the natural history found in humans without intense manipulation and intervention, but these models do provide the opportunity to test hypotheses conveniently), basic research on the biology of the diseases, the design of increasingly sophisticated epidemiologic studies (e.g., the Framingham Study and the Honolulu Heart Program), and the design of prospective clinical trials (Multiple Risk Factor Intervention Trial and the ongoing Physicians' Health Study). The research results have led to advances in medical and surgical therapies, as well as to new methods to detect risk factors long before the onset of clinical disease expression. This body of knowledge has also led to significant changes in the nation's smoking, dietary, and exercise habits and has provided the population with the hope that heart attacks need not be fatal and, more recently, that strokes can be prevented and the extent of residual disability from strokes minimized.

Despite this enormous accumulation of observational and experimental information about risk factors for ASCVD, heart disease, and stroke, there remains considerable interest in continuing to explore the possibility of other, more deeply underlying or related etiological factors, several of which will be mentioned here. In the early 1970s, pathologist Earl Benditt and his colleagues at the University of Washington used the relatively

simple techniques then available to demonstrate that the principal proliferating cell population in developing atherosclerotic lesions appeared to be of clonal origin. When these observations were first reported in 1973, they stimulated a good deal of speculation about underlying etiological factors that might plausibly be responsible for the clonality. Although evidence for a specific, pathogenetic transforming event involving the precursor cells (myoblasts) within the arterial wall has not yet been found, there continues to be considerable interest in the possible role of viral or bacterial infectious agents in initiating an inflammatory process that could result in the selective expansion of cell populations in the development of atherosclerotic lesions. One such agent newly of interest is *Chlamydia pneumoniae*; the research, in part pathological and in part serological, is still in a relatively early stage, and an etiologic role remains speculative.

An entirely different kind of etiologic agent of atherosclerosis, which is currently receiving great attention, is the amino acid homocysteine. The story behind homocysteine is a sobering one, which was featured in the August 10, 1997, *New York Time Sunday Magazine*. The so called "father of homocysteine" is a medical school and pathology residency classmate of mine, Kilmer McCully, who as a junior staff member at MGH had occasion to review the autopsy findings from two cases of children with homocystinuria, a rare genetic disease in which the levels of homocysteine in the blood are excessively elevated. In both of these children, the cause of death was astonishingly severe atherosclerosis. On the basis of the two autopsies, McCully speculated that homocysteine may directly damage arterial cells and tissues, and, more important, that such damage would be expected to occur not just in these rare genetic cases but (less dramatically and precipitously) in the population at large among any individuals with elevated serum homocysteine levels. Based on some experimental observations in animals, McCully went on to propose a probable cause for elevated levels of homocysteine, a deficiency of vitamins B6, B12, and folic acid, a theory entirely consistent with the known biochemical pathways by which homocysteine is synthesized and degraded. Moreover, dietary conditions that would lead to precisely such metabolic consequences were precisely those of the typical American diet of that time. Although subsequent research by McCully and others developed information in support of the hypothesis, the homocysteine theory began to lose favor in the mid-1970s as support for cholesterol was in the ascendency; McCully lost his research funding and ultimately his faculty appointments at Harvard Medical School and MGH. It was not until 1990 that fresh epidemiological evidence, especially from the Physicians' Health Study and the Framingham Study, reawakened interest in the predictive etiologic relationship of serum homocysteine levels in the development of ASCVD. Publication of these epidemiological studies occurred in 1993 and 1995, and both appropriately acknowledged McCully's role in developing the initial hypothesis.

Both of these vignettes make important points, and both demonstrate the profound medical and public health consequences that can result from the unplanned encounter of a curious and "properly prepared" mind with routine autopsy materials encountered in the day-to-day practice of medicine. The homocysteine story illustrates the dangers that can to this day befall a scientist whose ideas are too far ahead of his or her time or are otherwise not concordant with prevailing scientific dogma.

III. Central Nervous System and Neuromuscular Diseases

Perhaps nowhere in human disease is the importance of and dependence on human tissue specimens for research more strikingly illustrated than with respect to the central nervous system (CNS) and neuromuscular disorders. First, even in this era of remarkable advancement in the biomedical sciences, there are no accurate animal or tissue culture models for many common diseases of the human brain, including brain tumors and most of the primary neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or multiple sclerosis [MS]). Indeed, models are not uncommonly proposed that prove not to reflect accurately the expression of the corresponding human disease, and inferences drawn from such models

are often misleading or wrong. Second, it is clear that attempting to elucidate the etiology and pathogenesis of the major brain disorders continues to this day to be based largely on the meticulous investigation of human tissue samples in correlation with equally meticulous clinical evaluation of patients over relatively long periods of time.

Third, as is true in other human organ systems, the application of each new scientific or technological advancement to the study of human CNS and neuromuscular diseases is absolutely dependent on the availability of the human tissue archive for appropriate experimental and control materials. Fourth, new brain and muscle diseases continue to be identified through the routine investigation of appropriate human tissues by up-to-date research approaches. For example, new neurological diseases have emerged as the result of accepted medical procedures: These include central pontine myelinolysis caused by aggressive correction of serum electrolytes and subependymal germinal matrix hemorrhages in premature infants caused by aggressive pH and plasma volume correction by neonatologists. Both of these disorders result either in death or severe residual neurological abnormalities. Other diseases that have been either identified recently or found to occur more frequently than previously suspected include the new variant of Creutzfeldt-Jakob disease (CJD) epidemiologically linked to the bovine spongiform encephalopathy epidemic in Great Britain; Lewy body dementia and Lewy body variants of Alzheimer's disease, recently recognized to account for 15 to 20 percent of dementia cases over the age of 60 (Lewy bodies are classical histopathological structures characteristic of idiopathic Parkinson's disease); and HIV encephalopathy leading to severe dementia, which occurs in about one-third of HIV-infected patients with AIDS.

A. Brain Tumors

While current chemo- and radiation-therapy protocols have improved the quality of life for patients with glioblastoma and anaplastic astrocytic neoplasms, they have done little in the last 30 to 40 years to increase life expectancy, which remains dismal. Until relatively recently, most brain tumor research was conducted with animal models in which brain tumors were induced by exposure to carcinogens or viruses, with nude (immunologically impaired) mice into which tumor cells from glioma or meningeal cells lines were transplanted, or with cultured immortalized glioma cell lines.

Over the last five years, major advances have been made by several laboratories in the United States and Europe that correlate genetic alterations in human brain tumors with the degree of malignancy and prognosis. All of these studies relied on frozen samples and specially fixed samples of human brain neoplasms to assess gene amplification, gene deletions, gene mutations, and cell cycle parameters. Many insights into the pathobiology of brain tumors are emerging from these studies. For example, p53 mutations are characteristic of glioblastomas arising in childhood whereas Epidermal Growth Factor Receptor amplification is characteristic of glioblastomas arising in adults. Each type of brain and meningeal neoplasm has been found to have different patterns or degrees of gene defects. Ten to fifteen different genetic defects have been identified, of which many are concerned with control of the cell cycle and cell death pathways. To discover these defects has required study of the neoplasms removed directly from the patient. It appears that some, but not all, of the genetic abnormalities predict a different clinical behavior and may be the target of future immunological, pharmacological or gene therapies. Remarkably, based on the preliminary correlations of genetic abnormalities with the neurohistological characteristics of brain tumors, it also appears that it will eventually be possible to predict from the neuropathology what gene deletion, mutation, or overexpression is present in a neoplasm. However, it should be noted that the molecular approach to the investigation of brain tumors is still in its infancy. Neither cause and effect relationships nor therapeutic strategies have yet been established.

B. Cognitive Decline, Dementia, and Aging

Perhaps the most financially ruinous and emotionally debilitating disease for families, and one of the greatest stresses to the funding and working of our medical care system, is senile dementia. The cost of caring for individuals over the age of 60 who develop dementia is increasing, and the means to generate the funds required for that care are decreasing because of demographic shifts in the age of the population. A major family and social problem with Alzheimer's disease and related disorders is that many afflicted subjects require extended care for 5 to 20 years. Today there are 4 million new cases of Alzheimer's disease diagnosed each year in the United States, which accounts for less than half of the total number of patients with senile dementia.

Understanding of Alzheimer's disease and aging of the brain as recently as 10 to 15 years ago has proved to be naive and inaccurate because it was based on autopsy studies of patient populations that had been so poorly characterized clinically. Recent incremental improvements in understanding, which have come about largely because of a gradual tightening of clinical diagnostic criteria, have continued to be based on studies of human brain tissue because there are no animal models that mimic human brain aging, Alzheimer's disease, or other forms of senile dementia. To this day, a precise pathologic understanding of the dementing disease labeled as "Alzheimer's disease" remains elusive. Present-day arguments are waged over the importance/necessity of specific neuropathological findings, such as neuritic plaques in cerebral cortex, density of neurofibrillary tangles, or a combination of these two lesions; and more recently, infarcts in the basal ganglia, thalamus, or deep white matter, or the Lewy bodies. This continuing controversy regarding the defining neuropathological features of Alzheimer's and related dementing disorders in large part reflects the continuing imprecision of the clinical definition of these difficult, chronic dementing diseases. It is likely that a mixed bag of etiologic and pathogenetic factors contribute to these disorders, and the need for ever more precise clinical definition for correlation with neuropathological examination remains urgent.

At the same time, new kinds of information about these diseases have been obtained from the application of new scientific methods and technologies to archival tissue materials. Thus, for example, substantial information is now available about the detailed chemical composition of senile plaques and neurofibrillary tangles, and most recently, specific genetic changes (mutations in the beta-APP (*a*myloid *p*recursor *p*rotein) presenilin #1 and presenilin #2 genes) have been described. Yet, specific genetic changes still have not been identified in association with more than 50 percent of familial Alzheimer's disease cases. Sporadic Alzheimer's disease, which accounts for 80 percent of total cases, is multigenic and may well involve environmental factors. The dependence of research into these diseases of major societal import on well-characterized human tissue specimens would appear to remain near-absolute for the foreseeable future.

C. Prion Diseases

Currently, epidemiologists and neuropathologists around the world are asking whether CJD is an emerging infectious disorder. More specifically, neuropathologists are being asked whether they have identified an increase in the number of deaths due to CJD because of the possibility that some of the nation's meat supplies are contaminated with bovine spongiform encephalopathy and some pharmaceuticals that contain extracts from humans are contaminated with CJD. The only answers to these questions is by examination of autopsied or biopsied brain. It is clear that the new variant CJD in Great Britain has a unique neuropathological phenotype that is easily recognizable. Whether blood products have been contaminated is currently being tested by detailed examination of brains of hemophiliacs who die in dementia. Twenty-four hemophiliacs have been examined to date. All died with AIDS-related dementia, hepatic encephalopathy, or cerebral hemorrhage. The more general question being asked is whether or not there is a recent increase in the incidence of CJD in the United States and other countries. These questions can and will only be answered by examination of human tissues.

D. A Few Other Examples

There are many other examples that demonstrate the critical dependence of understanding the etiology and pathogenesis of brain and muscle diseases on research with human CNS and skeletal muscle samples from pathology archives.

1. Multiple Sclerosis (MS). For many years, investigators focussed on the favored model of experimental allergic encephalomyelitis in rodents; however, some of the conclusions derived from this model have been misleading and have not been verified by examination of human MS cases. An accurate and detailed sequence of immunological and molecular events involving lymphocytes, astrocytes, microglial cells, myelin, and oligodendrocytes in the genesis of an MS plaque has only recently emerged from studies of acute and chronic lesions in human brain samples.
2. Inclusion Body Myositis (IBM). The most common myopathy over the age of 55 is IBM, which is estimated to affect 1 in 3,000 to 5,000 individuals. Originally it was believed to be a viral disease because of the often intense endomysial lymphocytic inflammation and the presence of filamentous inclusions in skeletal muscle fibers. However, it is now believed to be a primary degenerative disease of skeletal muscle, perhaps initiated by an inflammatory event. Recent studies have detected in the inclusions evidence of portions of the beta-APP protein found in Alzheimer's disease and a prion-like protein, similar to that in CJD.
3. Muscular Dystrophy (MD). The histopathological features of skeletal muscle from a large variety of MD cases are similar. Through study of human tissues, it is now possible to separate these cases into those caused by mutations of the dystrophin gene and those caused by mutations of the sarcoglycan genes. Other genetic abnormalities have also been identified in an area of ongoing intense interest and active research.

Comment

An important lesson to be drawn from this section of the report is awareness of the critical—indeed, near-absolute—dependence on the human tissue archive as a unique and irreplaceable source of research materials for furthering understanding of diseases of the human CNS and neuromuscular systems. It is to be hoped that with better definition of clinical symptomatology and correlation of that symptomatology with precise neuropathological changes, including changes in genetic structure and expression, animal models (presumably recombinant) for at least some of these disorders may yet prove tractable. To this point, as indicated above, the animal models developed to date have failed to reproduce the essential neuropathologic features that, at present levels of understanding, continue to be the "gold-standard" for defining these complex and diagnostically challenging disease entities. At the same time, the recognition of new and more fundamental defining features of these diseases can only be done in concert with careful correlative neuropathologic studies on human tissue materials to validate and authenticate the new technological approaches. The disorders in question constitute an enormous burden to individuals, their families and the society, and facilitation of continuing research employing the most advanced scientific insights and technologies is an urgent national priority.

IV. "High-Tech" Studies Illuminate the Molecular Genetic Bases of Human Diseases

A. Oncogenes and Pathways of Neoplasia

Recent dramatic advances in biomedical science and technology, particularly the development of monoclonal antibody and genetic technologies that permit detailed studies of genetic structure and detection of mutations

in fixed, embedded, and sectioned tissue samples, have had a profound effect on investigative pathologists and other researchers studying human diseases in human tissue samples. The synergy between these new approaches and the availability of carefully studied archival human tissues, providing examples of sundry diseases, all with correlative clinical information and of widely varying ages, has been powerful. It has enabled the rapid application of novel techniques to define better the fundamental nature and behavior of particular diseases and has provided the investigators with adequate follow-up data to evaluate therapeutic responses and obtain outcomes. Thus, as noted earlier with respect to the use of human sputum cytology archives, important new information about the genetics of major human diseases and the effect of specific genetic changes on the natural history of those diseases, or their responses to therapy, has been gained in a fraction of the time that would have been required had the studies had to be done entirely prospectively.

It is important to re-emphasize this point: The problem with de novo prospective studies is not only the expense and effort required to assemble the desired populations and collect the experimental samples, but is also the considerable and irreducible time that must pass to allow appropriate clinical follow-up data to be collected, without which any observed molecular and genetic changes cannot be interpreted. For many of the major human neoplasms of interest, e.g., breast, prostate, and often, colon and ovary, the necessary follow-up times required for accurate interpretation of these kinds of experimental results may be 5, 10, or 15 years, or even longer.

1. The Genetics of Lymphoid Neoplasia

Although genetic pathology is still in its infancy, a number of important achievements have already taken place. Probably, the earliest application of molecular genetic methods to pathologic studies of human neoplasms involved lymphomas and a variety of "pseudo-lymphoid" proliferations, and were carried out roughly simultaneously and independently by Drs. Jeffrey Sklar at Stanford and Jeffrey Cossman at NIH in the early and mid-1970s. Lymphoid proliferations have always been difficult histopathological entities because of their general paucity of objective and reproducible distinguishing features accessible to conventional histopathological techniques. Accordingly, the pathological classification of these lesions has traditionally been in a state of constant flux, with successively favored systems of nomenclature generally promulgated by senior figures in the field on the basis of their long experience and personal prejudices. What Drs. Sklar and Cossman did in essence was to apply the then rapidly emerging knowledge of the normal genetic maturation of lymphocytes into immunocompetent cells to a variety of proliferative lymphoid lesions bearing different histopathologic diagnoses. (They were able to do this because, in addition to the enormous archives of fixed tissue samples of human lymphomas that had been collected for many years at Stanford and NIH, both institutions had amassed large collections of frozen tissue samples as well. The prescience for initiating the systematic accumulation of frozen samples was that of Drs. Ronald Dorfman and Roger Warnke in the Department of Pathology at Stanford, and Elaine Jaffe, Director of Hematopathology in the Laboratory of Pathology at NCI.)

Specifically, it was then becoming recognized that as lymphocytes mature from their earliest precursor stages, their immunoglobulin genes underwent a predictable sequential series of genetic rearrangements (homologous but different in B and T cells) that are associated with the generation of humoral and cellular immunological diversity. Drs. Sklar and Cossman were able to demonstrate initially that in accordance with physiological expectations, non-neoplastic lymphoid proliferations were always highly polyclonal, while neoplastic lymphoid populations proved to be nearly invariably monoclonal or oligoclonal. Moreover, in continuing work, these investigators were able to correlate the monoclonality of the neoplastic lymphocyte with developmental arrest at particular stages of the known pathway of physiological genetic rearrangements. This work truly qualified as a "breakthrough" and opened a new field of investigation. Continuing studies in many laboratories have now built a large genetic database on lymphoid malignancies that has provided for the first time a firm conceptual underpinning for the classification, therapy, and prognosis of these disorders. In some ways of

equal importance, these techniques have also been used to prove that certain lymphoid proliferations of ambiguous classification are clearly non-neoplastic, while others, although in fact neoplastic, proved to be quite indolent, with important consequences for the afflicted patients. An important feature of this new technology was its susceptibility to a series of adaptations that vastly increased its sensitivity, such that literally handfuls of neoplastic cells could be detected in vast populations of non-neoplastic but otherwise cytologically similar cells, thereby significantly enhancing the ability of the pathologist to detect, for example, residual lymphoid tumor cells in blood or bone marrow specimens from treated patients.

To provide the reader with a glimpse of the important advances in the field of hematolymphoid pathology that have come from the laboratory of a single investigator using modern genetic technologies with archival human tissue samples, I reproduce here portions of a memorandum [lightly edited for clarity] recently sent to me by Dr. Sklar that bears on this topic:

> ...I can say without exaggeration that almost everything my laboratory has published over the years regarding the molecular analysis of lymphoid malignancies has been based on study of archival tissue specimens....
>
> Among the highlights of [our] research have been the analysis of [B cell] immunoglobulin and T cell receptor gene rearrangements to diagnose non-Hodgkin's lymphomas; the demonstration of clonality and multifocality of lymphomas arising in immunosuppressed patients; the elucidation of the neoplastic origin of certain indolent lymphoid processes formerly thought to be reactive (e.g., lymphomatoid papillomatoses) and, therefore, the existence of benign neoplasms of the hematolymphoid system; the molecular cloning of the breakpoint in the (t14;19) chromosomal translocation and the isolation of the BCL2 gene; the development of a PCR-based method for detecting clonal antigen receptor gene rearrangements, most useful in diagnosing early mycosis fungoides, which really cannot be diagnosed accurately by any other means; the development of highly sensitive methods for monitoring residual lymphoid neoplasia, most useful in assessing residual acute lymphoblastic leukemia; the discovery of somatic hypermutation within rearranged immunoglobulin genes in follicular lymphomas; the detection of clonal immunoglobulin gene arrangements in cases of Hodgkin's disease; the discovery of Epstein-Barr virus (EBV) genomes in Reed-Sternberg cells of Hodgkin's disease and the demonstration of the clonality and essential neoplastic nature of these cells; the presence of EBV in certain cases of T cell lymphoma; and truncation of the *NOTCH1* gene by chromosomal translocations in certain T cell neoplasms.
>
> Many of these findings have had implications well beyond their immediate apparent significance. For instance, the detection of EBV DNA in Hodgkin's disease and T cell lymphoma led to the widespread search for and discovery of EBV in many other cancers; the demonstration of clonal immunoglobulin genes in Hodgkin's disease has helped revise thinking about the origin of the cancer, so that many now believe it to be a B cell malignancy; and the truncation of *NOTCH1* in T cell cancers has been critical to understanding how the cell surface receptor encoded by this gene, which is involved in many important aspects of development, is activated.
>
> More recently, we introduced the use of bacteriophage resolvases to detect point mutations in DNA—work that depended directly upon the availability of banked specimens from patients with cystic fibrosis and colon cancers. This method of mutation detection has gained considerable attention in the last few years, since there is currently great need for simple methods to

detect mutations in human tissues. We also have recently utilized archival tissues to identify a gene altered in MALT [*m*ucosa *a*ssociated *l*ymphoid *t*issue] lymphoma, and this effort almost exclusively utilized paraffin-embedded tissue rather than frozen material. The work is unpublished and too preliminary to discuss, but I expect it may have wide significance because of the unusual biology of MALT lymphomas (e.g., homing to mucosal sites, dependence for growth on the presence of *Helicobacter pylori* antigens in some cases, and the frequent origin in sites of autoimmune reactions, such as Sjogren's disease and Hashimoto's thyroiditis)….

All of our past studies and analyses recounted above have used frozen or paraffin-embedded tissues that had been stored for months to years prior to our work. Indeed, a major reason we have concentrated so much effort on lymphoid malignancies has been the fact that others [at Stanford and later, at Brigham and Women's Hospital] had preserved frozen lymph node specimens for their own purposes, mostly relating to immunophenotyping....It goes with saying that any attempt to limit the availability of archival tissue samples for research would severely cripple progress in understanding the molecular genetics of human disease....

2. The Genetics of Colon Cancer

A second organ system in which recent progress in elucidating the neoplastic pathway has been most dramatic and gratifying is that of colorectal cancer. In contrast to the limitations of conventional histopathologic analysis of lymphoid malignancies, growth disorders of the colorectal epithelium are typically exuberant and perhaps for that reason have long attracted the attention of pathologists. Thus, it has long been known that individuals tend to develop colorectal polyps, and there is a rich pathology literature dating back at least to the 1950s, which traces the debates among pathologists as to whether such polyps, with their variety of histopathologic expressions, were benign or premalignant, or whether they encompassed the full panoply of changes from benign to malignant. In addition, it has long been recognized that the colorectal mucosa adjacent to a typical polyp or carcinoma usually shows a gradient of histopathologic atypia that eventually blends indistinctly into what appears to be completely normal epithelium. During the past decade, the group led by Dr. Bert Vogelstein at the Johns Hopkins University has published a remarkable series of papers delineating five or more (and the number will surely continue to increase) specific genetic changes that seem to constitute an evolutionary pathway from normal mucosa to the benign, innocuous-appearing colorectal polyp, through various stages of histopathological atypia to frank carcinoma. Some of these revelations have been derived in subsets of patients with known hereditary forms of colorectal cancer, while others appear more generally to be present in those without known patterns of familial inheritance. At least one of these genetic changes, the inactivation of the p53 gene, is known to occur, at least at times, in the germline, while the others appear to be exclusively of somatic origin.

The work of the Hopkins group was enabled by the availability in that institution of a large human tissue repository containing various forms and stages of colorectal neoplasms, as well as blood specimens from the same patients. The tissue archive consisted largely of typically fixed and embedded specimens, but in addition (as with the lymphoma materials mentioned previously), the Hopkins group benefited immensely from a large collection of frozen samples that had been amassed at the instigation of Dr. Albert Owens, long-time Director of the Cancer Center at the Johns Hopkins University. To provide the reader with a sense of the astonishing speed with which the genetic pathway of colorectal cancer has been deciphered by the Hopkins group, I am inserting here excepts from a memorandum that was sent to me by Dr. Stanley Hamilton, the principal pathologist member of the Vogelstein team, who has been a collaborative participant from the inception of this research:

The availability of a human tissue repository, including colorectal cancer specimens, adenoma specimens, mucosal specimens, peripheral blood leukocytes, serum, and plasma has been critical to the advances in understanding the molecular genetics of colorectal cancer.…

Prospective accumulation of peripheral blood DNA specimens with informed consent of patients for investigations of the potential genetic alternations was begun for patients with familial syndromes. Transformation into lymphoblastoid cell lines was usually done to provide a renewable resource. In addition, prospective collection of frozen colorectal cancers, adenomas, and mucosa was begun in Surgical Pathology at The Johns Hopkins Hospital under the hospital's [general] consent for use of tissue for research….

These specimens were utilized in a variety of research efforts. The specimens were employed for determining the clonal origin of human tumors and identification of generalized hypomethylation of DNA in adenomas and carcinomas of the large bowel. The availability of formalin fixed, paraffin embedded tissue in the Surgical Pathology files led to the technical achievement of DNA extraction. As a basic science discovery led to the identification of the *ras* proto-oncogene, the availability of the tissue bank permitted us rapidly to evaluate the occurrence of these genes in human colorectal cancers, and they were found to be present at high frequency. As basic science knowledge led to the identification of tumor suppressor genes and their mechanisms of alteration, the availability of our specimen bank permitted us to evaluate a panel of allelic deletions, as well as *ras* gene mutations, in colorectal adenomas and carcinomas, resulting in the seminal publication in this area of investigation. The evaluation of allelotype of colorectal carcinomas followed, as well as recognition of the importance of inactivation of the p53 gene. The pace of basic discoveries increased with recognition of hypermethylation of specific genes in human colonic neoplasms, and the identification of allelic loss of chromosome 18q which subsequently was found to harbor the DCC [*d*eleted in *c*olorectal *c*ancer] and other genes. At that time, our attention turned to translational application of these alterations as we evaluated the clinical and pathological associations with allelic loss in colorectal carcinoma by linking the genetic findings in tumor DNA to clinical data available through Johns Hopkins Tumor Registry.

The availability of banked DNA specimens from patients with familial adenomatous polyposis [FAP], as well as frozen specimens of colorectal cancers, led to the identification of the APC [adenomatous polyposis coli] gene on the long arm of chromosome 5. Mutation of this gene or other genes regulated by it appears to be the initiating event for the vast majority of human colorectal neoplasms. In another clinical application of [these genetic findings], feces were collected from patients with colorectal tumors, and identification of the mutated *ras* gene in the feces corresponding to that in the tumor was demonstrated. This study proved the concept that genetic alterations could be used to screen for curable colorectal cancer. The availability of specimens of peripheral blood leukocyte DNA permitted development of the molecular genetic test for FAP. Recognition of abnormalities of DNA mismatch repair in patients with hereditary nonpolyposis colorectal cancer syndrome [HNPCC] resulted in investigations of tumor specimens from patients with the inherited predisposition and verified the pathogenesis of this form of cancer. The identification of the molecular basis of the two major inherited forms of predisposition to colorectal cancer, i.e., FAP and HNPCC, and the availability of specimens from our repository, permitted us to determine the molecular basis of the association of brain tumors with colorectal neoplasia (Turcot syndrome)….

The two major examples cited here, lymphoid neoplasia and colorectal cancer, are perhaps the best examples to date of how the application of contemporary genetic knowledge and technology can profoundly and rapidly help to illuminate the pathogenesis of a major disease entity and simultaneously spin off new approaches to diagnosis, prognosis, and therapy.

3. The Genetic Anatomy of Human Cancers

There are countless examples in the literature of studies in recent years in which investigators have used archival collections of human tissues to search for specific chromosomal and genetic abnormalities of pathogenetic interest. More recently, these kinds of efforts, stimulated by the development of some remarkable new technologies, have begun to be scaled up in truly remarkable ways. For example, a foundation started by Michael Millken in 1992 (the Association for the Cure of Cancer of the Prostate, or CaP CURE) has recently announced its intention to mount a major assault on deciphering the genetics of prostate cancers, the most common cancer in American men and a significant cause of cancer morbidity and mortality. The goal of this new multi-institutional project is to differentiate the various forms of prostate cancer, determine the most effective methods of treatment for each, and eventually find a cure. All of this work will be absolutely dependent on the availability of carefully characterized tissue samples of prostate cancers and close correlation with clinical data to establish both the natural history of the tumors and their responses to different therapeutic strategies.

But probably the most ambitious of these new scaled-up approaches must be the Cancer Genome Anatomy Project (CGAP), recently launched as a major initiative by NCI, with the goal of nothing less than producing a complete catalogue of all the genes expressed in human cancer cells! As recently described in a News & Comment article in the May 16, 1997, issue of *Science*, CGAP will begin with the five "big killers"—breast, colon, lung, prostate, and ovarian cancers—and will classify tumor genes by the type of cancer cell they came from and by the degree of the cell's malignancy. The NCI coordinator of the CGAP project is quoted in the article as stating "we want to achieve a comprehensive molecular characterization of cancer and precancerous cells.…" CGAP will also support the development of technologies for the rapid analysis of gene activity patterns in the thousands of tumors likely to be seen in a hospital pathology laboratory. The hope is that eventually, the tumor gene index and these new technologies will enable physicians to base a patient's diagnosis, prognosis, and treatment on the status of a particular tumor's genes and proteins rather than solely on its appearance under the microscope. Enabling the initiation of such an ambitious—indeed, breathtaking—project has been the recent development of several powerful new technologies.

Arguably one of the most important of these to date has been the development by a team of pathologists/investigators led by Dr. Lance Liotta, Chief of the Laboratory of Pathology at NCI, of an extraordinary new technology called "laser capture microdissection." By this ingenious, yet astonishingly simple technique, Dr. Liotta and his colleagues are able selectively to remove single cells and defined clusters of cells directly from a histopathological slide containing the typical admixture of malignant, premalignant, atypical, and normal cells. A colleague of Dr. Liotta, also at NCI, at around the same time developed a complementary technique that significantly increases the yield of cDNAs from tiny samples of tissues of precisely the kind collected by Dr. Liotta's new methodology. A third new technology, of enormous potential importance to these kinds of large-scale genetic analyses, is a novel chip methodology by which as many as 200,000 to 400,000 different DNA sequences can be deposited in linear arrays on a microchip, using approaches similar in many ways to those developed for use in the computer industry, and then screened with cDNA samples obtained from any cell or small cluster of cells of interest. By this technology, it becomes theoretically possible to obtain rapid insights into the total patterns of genetic expression in normal, atypical, premalignant, and malignant cells that might have been co-existing quite literally as neighbors in the same marginal zone of a human cancer specimen on a standard histopathological slide. To indicate that such extraordinarily ambitious, if not audacious, research objectives are not chauvinistically American, a consortium of European investigators has recently its intention of launching a similar effort, called the Cancer Gene Expression Program.

The importance of the laser capture microdissection technique and the new chip technology (and inevitably others, even more efficient, yet to be developed) cannot be overemphasized. Samples of cancers, whether human or animal, never constitute a homogeneous population of cells. Even samples taken entirely from the central portions of large cancers contain mixtures of healthy, dying, and dead cancer cells, fibrous and vascular elements, frequent hemorrhage, and often foci of inflammatory cell infiltrates. Accordingly, the performance of any kind of biochemical or genetic analysis on such materials is capable of detecting only the grossest kinds of changes because of the extreme heterogeneity of the starting materials. With the advent of such new technologies as described above, it now becomes feasible for the first time to develop the kinds of precise genetic and chemical data necessary to illuminate the complex pathways of human neoplasia.

Yet all of this promise is entirely dependent on the availability of human tissue archives containing known cancers accurately diagnosed by conventional methods of histopathology and the ability to correlate these samples with clinical responses and outcomes obtained from clinical records. As I have stated earlier, to begin these studies afresh with tissues yet to be collected would cost decades in terms of gathering the necessary materials and awaiting the necessary endpoints, absent which none of the experimental data, no matter how sophisticated or elegant, can be meaningfully interpreted or applied effectively to the diagnosis, treatment, and prevention of human neoplasia.

B. Viral Neoplasia

That viruses can cause cancers has been known for nearly a century from studies of natural and experimental animal models. However, it has been only in the last three decades or less that examples of viral carcinogenesis in humans have been unambiguously demonstrated. Probably the first human cancer for which a viral role in etiology was established was an unusual form of malignant lymphoma that is most prevalent in a certain geographical belt extending across central Africa, where it is the most common cancer in children. This entity was first identified by the English physician Denis Burkitt and subsequently named Burkitt's lymphoma. Early in the 1970s, Burkitt lymphoma cells were shown to harbor a virus by two British investigators named Epstein and Barr; the virus, of course, is the now common EBV that has become associated with a variety of malignant, "pseudo-malignant" and nonmalignant proliferations of lymphoid cells. For example, EBV has been established as the causative agent of infectious mononucleosis.

More recently, new molecular genetic technologies have permitted the identification of "viral footprints" in a number of human cancers, some commonplace, others less so. Two examples that I shall describe here are the human papillomavirus (HPV) and cancer of the uterine cervix and the more recent detection of a new, putatively causative herpes virus in Kaposi's sarcoma.

1. Human Papillomavirus (HPV) and Genital Tumors

There is a variety of human genital tumors, ranging from genital (venereal) warts (condylomata acuminata) to highly invasive and lethal malignancies like carcinoma of the penis, the female vulva, and the uterine cervix. Since ancient Greek and Roman times, the occurrence of genital warts, both in males and females, had been recognized as a sexually transmitted disease, and for over 100 years, epidemiological evidence had suggested that penile and cervical cancers might also be in some manner venereally transmissible. Early in the 20th century, the viral origin of warts was established, and transmissibility from human to human was demonstrated. During the 1930s, scientists became aware that certain animal papillomaviruses could not only initiate wart-like lesions, but that sometimes these warts could develop into frank tumors.

The introduction into widespread application of the Pap smear in the late 1940s dramatically expanded knowledge of the normal and abnormal patterns of morphological change exhibited by the epithelium of the uterine cervix. From study of the vast amounts of material made available from Pap smears, pathologists and cytologists came to recognize sequential patterns of progression from normal to dysplastic to neoplastic change

in cervical epithelial cells, and modifications of therapeutic strategies followed apace. This large "research resource" led pathologists to recognize unusual cell types as cancer precursors, to classify various cell types and their relationships according to the severity and invasiveness of disease, and concomitantly, to build up an enormous bank of well-characterized and clinically correlated cytological specimens. These materials, beginning around 1980, became the substrates for increasingly sophisticated research, starting with monoclonal antibodies and progressing to molecular genetic approaches, which eventually led to the identification of causative viral agents.

In 1956, Koss and Durfee described an unusual cell type frequently found in cervical smears. The features of these cells were consistent, morphologically with viral infection, and much attention was focused on herpes simplex as the likely virus in accord with preliminary serological evidence and prevalent cancer virus theories of the time, although no firm link could be established. In 1977, zur Hausen hypothesized that the relationship of these atypical cells to cervical cancer, as well as to genital warts, could mean that a papillomavirus of some sort might be an underlying cause of cervical cancer. This theory was consistent with epidemiological evidence of transmissibility and with the fact that both genital warts and cervical cancer had increased at exceptional rates over the prior 15 years.

HPVs are difficult to culture and tend to demonstrate very restrictive host and tissue specificity. A significant barrier to demonstrating the involvement of a papillomavirus in dysplastic or neoplastic tissues was the difficulty of establishing viral cultures from the human tissue specimens (or identifying permissive animal hosts). But with the advent of monoclonal antibody and molecular genetic technologies, an increasing body of experimental data was developed demonstrating the existence and strong association of a number of specific HPV types with both genital warts and cervical neoplasms. As of 1997, more than 77 HPV types (defined by nucleotide sequence homology) have been fully characterized, and data suggest that there may be at least an additional 30 HPV variants. These viral types and variants show distinctive tissue specificities and biological consequences. Thus, different papillomaviruses are associated with different stages of cervical epithelial atypia or neoplasia, or with penile cancer. One set affects only nongenital skin sites (for example, the tonsils), another set causes genital warts, and a number of variants lead to cancerous genital lesions, some more invasive than others.

The HPV life cycle is tightly linked to squamous cell differentiation. This virus infects the epithelial basal cells, where it can remain dormant—and undetectable by conventional morphological criteria—for long periods of time. With the onset of viral activation (i.e., productive infection), progressive morphological changes of increasing atypia can be observed, which are now designated pathologically and clinically as cervical intraepithelial neoplasia (CIN) of different grades of atypicality, i.e., CIN1, 2 or 3. Based on the association between specific HPV types and different grades of cellular atypicality, the HPVs have been grouped into categories—low risk, associated mainly with CIN1 but absent from invasive carcinoma (HPVs 6/11, 42-44); intermediate risk, detected mainly in CIN and a small fraction of cancers (HPVs 31,33,35,51, 52 and 58); and high risk, associated with CIN 2 and 3 and cancers (HPV 16) or mainly with invasive carcinomas and lymph node metastases (HPV 18, 45 and 46). The reason for these intriguing associations is not yet clear.

With continuing development of this rapidly expanding knowledge base, the routine pathological work-up of cervical dysplastic and neoplastic lesions will almost certainly come to include the definition of the causative viral type as a guide to therapy and prognosis.

The firm establishment of the diagnostic significance of sequential morphological patterns of atypical epithelial change leading to frank cervical neoplasia has radically changed the therapeutic approach to cancer of the uterine cervix. Staged treatment is now routinely triggered by early diagnosis based upon Pap smear abnormalities and biopsy confirmation, and under circumstances of early detection and appropriate therapy, cure rates for cervical carcinoma approach 90 percent. On the other hand, in many countries of the world where Pap smears are not widely accepted or used, for reasons ranging from religious to cultural to socioeconomic, cancer of the uterine cervix remains a highly lethal disease and a major cause of cancer mortality in women.

The remarkable unraveling of the puzzle of HPVs and cervical cancer as a sexually transmitted set of diseases is the result of widespread use of a relatively simple and inexpensive diagnostic technique, ready access for study of vast numbers of samples to permit recognition of patterns of neoplastic progression, the availability of correlative clinical information to determine responses to therapy and clinical outcomes, and the availability of large populations of these clinically-correlated tissue samples for testing of new hypotheses using increasingly sophisticated molecular tools developed in clinical and basic science laboratories.

2. Kaposi's Sarcoma and Kaposi's Sarcoma-Associated Herpesvirus (Human Herpesvirus 8 [HHV8])

Kaposi's sarcoma (KS) is a peculiar spindle cell and vascular tumor that has long been known to be endemic in parts of Africa, where it behaves as a generally indolent tumor in adults, but with a fulminant and often fatal course in children. The appearance of KS in African populations to this day has not been associated with any specific predisposition, including predisposing infectious diseases, including HIV. On the contrary, among patients with HIV infection and AIDS, the presence of an aggressive form of KS was identified as an early, defining feature at the very inception of recognition of this new devastating disease entity. During the last five years, relying heavily on the availability of archival tissue materials derived from HIV-positive individuals with and without AIDS, Dr. Yuan Chang and a host of co-workers and collaborators at Columbia University have discovered in KS cells a unique human herpes virus, designated HHV8. A plethora of studies since the early 1990s have provided very strong circumstantial evidence that HHV8 may be the causative agent of KS in HIV-positive patients; the very same immunological and molecular genetic approaches have more recently been used to demonstrate the likely causality of HHV8 in KS in HIV-negative African populations. The association of this new human herpesvirus with KS has unleashed a large number of studies that attempt to elucidate the molecular and cellular mechanisms by which HHV8 drives normal fibroblasts and vascular endothelial cells (the precursor cells of the KS lesions) into neoplastic proliferation. These mechanistic studies have also been heavily dependent upon the availability of archival human tissue samples and have already led to the identification of a number of novel HHV8 gene products, including chemokines and cell-cycle regulators, that are expressed in HHV8-infected neoplastic tissues. The studies proceed at a rapid pace, and the results to date fit nicely into an emerging paradigm of cell-cycle deregulation instigated and driven by perfidious tumor virus products.

Although the data supporting the causal association of HHV8 with KS are strong, they cannot yet be deemed conclusive, and within the field there remains substantial debate as to the precise role played by HHV8 and other potential contributory agents and factors. As one writer recently put it: "It is too early to conclude whether [HHV8] is the elusive (KS co-factor) or if all forms of KS share a common etiology, but it appears to be the single most plausible agent to be identified to date." It is also of interest that the same viral footprints have been detected in two unusual forms of abnormal lymphoid proliferation seen in patients with AIDS—a rare AIDS-related body cavity-based lymphoma and AIDS-related Castleman's disease, an entity originally described as a generalized mediastinal lymphoid hyperplasia of unknown etiology. These findings, together with the detection of HHV8 footprints in non-neoplastic tissues from KS patients, suggest that in the presence of immune suppression and likely other stimulatory and promoting factors, HHV8 may have tumorigenic potentialities beyond those now abundantly documented in KS.

The HHV8-KS story again demonstrates the remarkable utility of large human tissue archives, well characterized pathologically and clinically, in supporting novel kinds of research, not predictable at the time the tissue samples were originally collected, but of significant public benefit.

C. Viruses Old and New (or Newly Recognized)

1. Viruses Old

We have learned a great deal in the last 80 years about the influenza virus, its modes of replication and recombination, its natural hosts, and some of the biological factors that lead to the periodic outbreak of serious "flu" epidemics. Yet, the influenza pandemic of 1918, which claimed more than 20 million lives, an unusually high fraction of which were young and previously healthy adults, remains as an enigmatic 20th century landmark in the annals of human infectious disease.

Interest in the 1918 influenza virus is more than historical or academic, because obtaining a detailed understanding of that virus could provide major insights into influenza virus infectivity in general, as well as help scientists to prepare for the next influenza pandemic, which many believe is sure to come (witness the current scare involving an apparently new form of virulent avian flu virus in Hong Kong). The idea of attempting to gain such genetic insight into the 1918 virus would only a few years ago have been considered a fanciful musing of science fiction, but in fact approaches to this challenge are now feasible.

Recently, a team of investigators based at the Armed Forces Institute of Pathology (AFIP) in Washington, D.C., probably the largest repository in the world of archived, clinically correlated human tissue specimens, was able to obtain samples of autopsied lung tissue from 198 soldiers who had died of the so called "Spanish Flu" nearly 80 years ago. After two years of effort, the research team was able to sequence a portion of the influenza virus genome amounting to less than ten percent of the virus's genetic complement. This work is still in progress, but it has already yielded results that effectively rule out two of the hypotheses proffered to explain the Spanish Flu's lethality.

A complementary approach to this problem involves an expedition that is being planned to exhume the bodies of a number of Norwegian miners who succumbed to the 1918 flu epidemic and were buried in permanently frozen tundra well above the Arctic Circle. Arguing that the burial site augurs unusually good preservation of the remains, the goal of the research team is to attempt to obtain tissue specimens akin to those in the AFIP archive, but not fixed or otherwise processed for pathological study. The importance of this "archeological expedition" to the public health was underscored by Nobel Laureate Joshua Lederberg who, in a *New York Times* article dated March 21, 1997, was quoted as calling influenza "the most urgent, patently visible, acute threat in the world of emerging infections.…the sooner we can learn what to anticipate, the more likely we will be able to blunt the next appearance of a deadly flu virus."

2. Virus New (or Newly Recognized)

In 1993, healthy young people began dying in the Four Corners area of the American Southwest from a fulminant pneumonia characterized by massive bilateral pulmonary hemorrhage. A massive scientific assault was launched to decipher the cause of this mysterious and presumptively new lethal disease, and within months the hantavirus had been identified as the culprit. This remarkably rapid solution of a public health mystery owed its success to many sources including a suspicious clinician, an astute epidemiologist, observant Navajo elders, and two invaluable archives: the first, from the Centers for Disease Control and Prevention (CDC), containing vast libraries of viruses, viral proteins and serum specimens from around the world; the second, pulmonary tissues from the autopsied victims of this strange new disease. The CDC archive permitted initial serological screening tests, from which arose the first suggestion that a hantavirus might be involved. The initial screens were followed by tests of autopsy tissue samples with specific hantavirus monoclonal antibodies, and ultimately, the tissue samples were exposed to hantavirus genetic probes that revealed the presence and tissue distribution of viral genetic material. These novel molecular tools permitted identification of the local deer mouse as the host of the pathogenic hantavirus, and studies of older human autopsy tissue established that the virus was in fact not a new variant but a fairly old virus with a well-established symbiotic relationship with the mice in the region.

About six months after the epidemic was first recognized, scientists had isolated and begun to culture the hantavirus strain, and this ultimately led to the development of a new and specific diagnostic test for a disease that had already spread from the west to the east and, if undiagnosed, demonstrated a mortality rate of more than 50 percent. This vignette again demonstrates the great public health benefit that can be obtained from the felicitous application of novel molecular technologies to well-characterized human tissue samples.

V. Commentary

As I have stated earlier in this report, the history of medical progress is deeply rooted in the careful study of archival patient materials, that is, medical records and tissue samples. Our nation's hospitals, and especially the academic medical centers, collectively contain an enormous archive of human tissue samples, comprising a unique resource that records the prevalence and protean expressions of human diseases over time. The samples were removed for medical reasons, under sparing consent language that usually included a proviso for research and educational uses, and were submitted to the pathology laboratory for routine diagnostic evaluation, after which portions of the specimens were permanently stored as part of the patient's medical record, in accordance with sound medical practice and legal and accreditation requirements. Although not specifically collected for research purposes, these specimens have served as a rich and irreplaceable source of materials for clinico-pathological investigations that have provided over the past more than 100 years most of the vocabulary and much of the intellectual foundation of modern medicine.

The enduring record of these studies fills contemporary textbooks of pathology. In preparing this document, I have exercised my own taste in selecting a relative handful of examples that illustrate some of the medical advances and public health benefits that have resulted during the past five decades from typically unforeseen and unplanned studies of accessible, carefully documented, and clinically correlated human tissue samples, obtained and archived during the routine delivery of medical care. Quite literally, hundreds or even thousands of additional studies could be presented to make the case, but that is hardly feasible or desirable. The examples demonstrate that carefully studied and well-documented pathological specimens, with readily accessible correlative clinical information, provide a research resource that is rich, unique, irreplaceable, and virtually indestructible. The permanence and relatively nonselected (except, of course, by incidence and prevalence of disease) characteristics of the archive, as well as its size and ready accessibility to whatever new scientific insights and technological modalities may arise, all serve to define its unique epidemiological and biomedical research value. There is quite literally no comparable research resource to substitute for it. To attempt to gain the kinds of new insights obtainable from archival human tissue research studies largely or exclusively from prospective studies would impose on society time, money, and opportunity costs of unfathomable and unacceptable magnitude.

In the public debate over access to human tissue samples for research, abundant input has been obtained from the bioethical, legal, and theological communities, but too little, and only recently, from the scientific community. Inadequate attention has been given to scientific opportunity, the individual, family, and societal burdens of major, chronic diseases, and the rich prospects of public benefit that are now in sight as a result of 50 years of generous public investment in biomedical research. As a consequence, the debate has distorted the delicate equipoise that must always be respected in research involving human subjects by an excessive focus on private interest at the expense of public benefit. Now more than ever before, the dramatic growth of the biomedical knowledge base and the applicability of powerful new technologies to tiny samples of diseased human tissues offer promise of major breakthroughs in understanding—and effectively managing—some of the most intractable diseases of humankind. *To achieve that promise, public policy must continue to encourage the accumulation of the human tissue archive and facilitate its accessibility for medical research.*

The preservation and reaffirmation of the defining characteristic of the human tissue archive, that it is a public treasure readily accessible for medical research for the benefit of all humankind, should constitute a priority

of the highest order. The historic record of medical advancement and public benefit that has flowed from this research is overwhelming; the evidence that any harm has occurred to any individual or group of individuals from the accessibility of the human tissue archive is, to my knowledge, nonexistent. New fears arising from the power of new genetic technologies can best be handled by strengthening the protection and ensuring the confidentiality of all research records and data derived from studies on human subjects or archival patient materials (medical records and tissue specimens), not by the promulgation of complex new schemes to regulate (and restrict) access to the research materials. Such strengthening of the security of human research data and assurance of its confidentiality can readily be accomplished, largely, in my view, by the skillful adaptation of existing mechanisms in federal law and regulations.

As this important debate continues over the always difficult issue of identifying the appropriate balance between important conflicting goods, the individual's expectation of the right to privacy versus the public benefit that accrues from biomedical research and improvement of the public health, it would be well to bear in mind the extraordinary record of past research accomplishment that has been built on the human tissue archive and the plethora of research opportunities that are now within reach. It would also be wise in dealing with such complex and often emotional issues to heed the ancient admonition that the oft-repeated assertion of anecdotes generates neither data nor sound public policies.

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References

I.

Rosai J. Pathology: A historical opportunity. *Am J Path* 1997; 151:3–6.

II. A.

Herbst AL, Scully, RE. Adenocarcinoma of the vagina in adolescence. *Cancer* 1970; 25:745–757.

Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. *NEJM* 1971; 284:878–881.

Herbst AL, Robboy SJ, Scully RE, Poskanzer DC. Clear-cell adenocarcinoma of the vagina and cervix in girls: Analysis of 170 registry cases. *Am J Obstet Gynecol* 1974; 119:713–724.

Herbst AL. Clear-cell adenocarcinoma and the current status of DES-exposed females. *Cancer* 1981, July 15; 48(2 Suppl.):484–488.

Younge PA, Hertig AT, Armstrong D. A study of 135 cases of carcinoma in situ of the cervix at the Free Hospital for Women. *Am J Obstet Gynecol* 1949; 58:867–892.

II. B. 1.

Creech JS, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 1974; 16:150–151.

Falk H, Herbert J, Crawley S, et al. Epidemiology of hepatic angiosarcoma in the United States: 1964-1974. *Environ Health Perspectives* 1981; 41:107–113.

Dannaher CL, Tamburro CH, Yam LT. Occupational carcinogenesis: The Louisville experience with vinyl chloride-associated hepatic angiosarcoma. *Am J Med* 1981; 70:279–287.

Popper H, Thomas LB, Telles NC, et al. Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic-comparison with cases of unknown etiology. *Am J Pathol* 1978; 92:349–376.

Roth F. The sequelae of chronic arsenic poisoning in Moselle vintners. *German Med Monthly* 1957; 2:172–175.

Regelson W, Kin U, Ospimam J, et al. Hemangioendothelial sarcoma of liver from chronic arsenic intoxication by Fowler's Solution. *Cancer* 1968; 21:514–522.

II. B. 2

Burkhart F. Oscar Auerbach, 92, Dies; Linked Smoking to Cancer (Obituary). *NY Times*, Jan 16, 1997, p19.

Auerbach O, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking, 1955–1960 vs 1970–1977. *NEJM* 1979; 300:381–386.

Auerbach O, Stout AP, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to sex, age, residence, smoking and pneumonia. *NEJM* 1962; 267:111–119.

Saccomanno G. Personal communication.

Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996. *CA Cancer J Clin* 1996; 65:5–27.

Berlin NI, Buncher CR, Fontana RS, et al. The National Cancer Institute cooperative early lung cancer detection program: Results of the initial screen (prevalence). Early lung cancer detection: Introduction. *Am Rev Respir Dis* 1984; 130:545–549.

Frost JK, Ball WC Jr, Levin ML, et al. Early lung cancer detection: Results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. *Am Rev Respir Dis* 1984; 130:549–554.

Flehinger BJ, Melamed MD, Zaman MB, et al. Early lung cancer detection: Results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. *Am Rev Resp Dis* 1984; 130:555–560.

Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection: Results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Resp Dis* 1984; 130:56–565.

Tockman MS, Gupta PK, Myers JD, et al. Sensitive and specific monoclonal antibody recognition of human lung cancer antigen on preserved sputum cells: A new approach to early lung cancer detection. *J Clin Oncol* 1988; 6:1685–1693.

Mao L, Hruban RH, Boyle JO, et al. Detection of oncogene mutations in sputum precedes diagnosis of lung cancer. *Cancer Research* 1994; 54:1634–1637.

Mao L, Lee DJ, Tockman, MS, et al. Microsatellite alterations as clonal markers in the detection of human cancer. *Proc Natl Acad Sci USA* 1994; 91:9871–9875.

Zhou J, Mulshine JL, Unsworth EJ, et al. Identification of a heterogeneous nuclear ribonucleoprotein (hnRNP) as an early lung cancer detection marker. *J Biol Chem* 1996; 271:10760–10766.

Qiao YL, Taylor PR, Yao SX, et al. Risk factors and early detection of lung cancer in a cohort of Chinese tin miners. *Ann Epidemiol* 1997; 7:533–541.

II. B. 3.

Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea. *JAMA* 1953; 152:1090–1093.

Enos WF, Beyer JC, Holmes RH. Pathogenesis of coronary disease in American soldiers killed in Korea. *JAMA* 1955; 152:912–914.

Strong JP. Coronary atherosclerosis in soldiers. A clue to the natural history of atherosclerosis in the young. *JAMA* 1986; 256:2863–2866.

Solberg LA, Strong JP. Risk factors and atherosclerotic lesions. A review of autopsy studies. *Arteriosclerosis* 1983; 3:187–198.

Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis. An assessment of the evidence and need for future research. *Circulation* 1997; 96:4095–4103.

Grayston J, Kuo C, Coulson A, et al. Chlamydia pneumoniae (TWAR) in atherosclerosis of the carotid artery. *Circulation* 1995; 92:3397–3400.

Kuo C, Grayston J, Campbell L, et al. Chlamydia pneumoniae (TWAR) in coronary arteries of young adults (15–34 years old). *Proc Natl Acad Sci USA* 1995; 92:6911–6914.

Benditt EP, Benditt JM. Evidence for a monoclonal origin of human atherosclerotic plaques. *Proc Natl Acad Sci USA* 1973; 70:1753–1756.

Pearson TA, Dillman JM, Solez K, et al. Clonal markers in the study of the origin and growth of human atherosclerotic lesions. *Circ Res* 1978; 43:10–18.

Murry CE, Gipaya CT, Bartosek T, et al. Monoclonality of smooth muscle cells in human atherosclerosis. *Am J Path* 1997; 151:697–705.

Stacey M. The Fall and Rise of Kilmer McCully. *NY Times Sunday Magazine*, August 10, 1997.

III.

Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and the senile change in the cerebral gray matter of elderly subjects. *Br J Psychiatry* 1968; 114:797–811.

Mirra SS, Hart MN, Terry RD. Making the diagnosis of Alzheimer's disease. *Arch Pathol Lab Med* 1993; 117:132–144.

Masliah E, Terry RD, Alford M, et al. Cortical and subcortical patterns of synaptophysin-like immunoreactivity in Alzheimer's disease. *Am J Path* 1991; 138:235–246.

Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer's disease: The nun study. *JAMA* 1987; 277:813–817.

Hanson L, Salmon D, Galasko D, et al. The Lewy body variant of Alzheimer's disease. *Neurology* 1990; 40:1–8.

Masters CL, Beyreuthen K. Amyloid A4 protein in the plaques and tangles of Alzheimer's disease and Down syndrome. *Alzheimer Disease and Associated Disorders* 1989; 3(Suppl. 1):37.

Wischik CM, Edwards PC, Lai RY, et al. Quantitative analysis of tau protein in paired helical filament preparations: Implications for the role of tau protein phosphorylation in PHF assembly in Alzheimer's disease. *Neurobiol Aging* 1995; 16:409–417; discussion, 418–431.

Brown P. The risk of bovine spongiform encephalopathy ("Mad Cow Disease") to human health. *JAMA* 1997; 278:1008–1011.

Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996; 347:921–925.

Raine CS. The Norton Lecture: A review of the oligodendrocyte in the multiple sclerosis lesion. J *Neuroimmunol* 1997; 77:135–152.

Arkansas B, Bilak M, Engel, WK, et al. Prion protein is abnormally accumulated in inclusion-body myositis. *Neuro Report* 1993; 5:25–28.

Duggan DJ, Gorospe JR, Fanin M, et al. Mutations of the sarcoglycan genes in patients with myopathy. *NEJM* 1997; 336:618–624.

Worton R. Muscular dystrophies: Disease of the dystrophin-glycoprotein complex. *Science* 1995; 270:755–756.

Sharer LR. Pathology of HIV-1 infection of the central nervous system. A review. *J Neuropathol Exp Neurol* 1992; 51:3–11.

von Deimbling A, Louis DN, Wiestler OD. Molecular pathways in the formation of gliomas. *Glia* 1995; 15:328–338.

IV. A. 1.

Davi F, Gocke C, Smith S, Sklar J. Lymphocytic progenitor cell origin and clonal evolution of human B-lineage acute lymphoblastic leukemia. *Blood* 1996 July 15; 88(2):609–621.

Pear WS, Aster JC, Scott ML, et al. Exclusive development of T cell neoplasms in mice transplanted with bone marrow expressing activated Notch alleles. *J Exp Med* 1996 May 1; 183(5):2283–291.

Veelken H, Wood GS, Sklar J. Molecular staging of cutaneous T-cell lymphoma: Evidence for systemic involvement in early disease. *J Invest Dermatol* 1995 June; 104(6):889–894.

Marshal RD, Koontz J, Sklar J. Detection of mutations by cleavage of DNA heteroduplexes with bacteriophage resolvases. *Nat Genet* 1995 Feb; 9(2):177–183.

Rowley JD, Aster JC, Sklar J. The impact of new DNA diagnostic technology on the management of cancer patients. Survey of diagnostic techniques. *Arch Pathol Lab Med* 1993 Nov; 117(11):1104–1109.

Seiden MV, Sklar J. Molecular genetic analysis of post-transplant lymphoproliferative disorders. *Hematol Oncol Clin North Am* 1993 Apr; 7(2):447–465.

Sklar J, Longtine J. The clinical significance of antigen receptor gene rearrangements in lymphoid neoplasia. *Cancer* 1992 Sep 15; 70(Suppl. 6):1710–1718.

Sklar J. Polymerase chain reaction: the molecular microscope of residual disease. *J Clin Oncol* 1991 Sep; 9(9):1521–1524.

Ellisen LW, Bird J, West DC, et al. TAN-1, the human homolog of the Drosophila NOTCH gene, is broken by chromosomal tranlocations in T lymphoblastic neoplasms. *Cell* 1991 Aug 23; 66(4):649–661.

Tycko B, Sklar J. Chromosomal translocations in lymphoid neoplasia: A reappraisal of the recombinase model. *Cancer Cells* 1990 Jan; 2(1):1–8.

Sklar J. What can DNA rearrangements tell about solid hematolymphoid neoplasms? *Am J Surg Pathol* 1990; 14(1):16–25.

Weiss JM, Movahed LA, Warnke RA, Sklar J. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. *N Engl J Med* 1989 Feb 23; 320(8):502–506.

Sklar J, Weiss LM. Applications of antigen receptor gene rearrangements to the diagnosis and characterization of lymphoid neoplasms. *Annu Rev Med* 1988; 39:315–334.

Weiss LM, Strickler JG, Hu E, et al. Immunoglobulin gene rearrangements in Hodgkin's disease. *Hum Pathol* 1986 Oct; 17(10):1009–1014.

Hu E, Horning S, Flynn S, et al. Diagnosis of B cell lymphoma by analysis of immunoglobulin gene rearrangements in biopsy specimens obtained by fine needle aspiration. *J Clin Oncol* 1986 Mar; 4(3):278–283.

Bagg A, Cossman, J. Molecular genetic biomarkers in hematological malignancies. *J Cell Cytochem* 1996 (Suppl.); 25:165–171.

Cossman J, Zehnbauer B, Garrett CT, et al. Gene rearrangements in the diagnosis of lymphoma/leukemia. Guidelines for use based on a multi-institutional study. *Am J Clin Pathol* 1991 Mar; 95(3):347–354.

Abbondanzo SL, Medeiros LJ, Cossman J. Molecular genetics and its application to the diagnosis and classification of hematopoietic neoplasms. *Am J Pediatr Hematol Oncol* 1990; 12(4):480–489.

Cossman J, Uppenkamp M, Andrade R, Medeiros LJ. T-cell receptor gene rearrangements and the diagnosis of human T-cell neoplasms. *Crit Rev Oncol Hematol* 1990; 10(3):267–281.

Cossman J, Uppenkamp M, Sundeen J, et al. Molecular genetics and the diagnosis of lymphoma. *Arch Pathol Lab Med* 1988 Feb; 112(2):117–127.

IV. A. 2.

Lengauer C, Kinzler KW, Vogelstein B. Genetic instability in colorectal cancers. *Nature* 1997 Apr 10; 386(6625):623–627.

Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet* 1997 Jan; 6(1):105–110.

Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996 Oct 18; 87(2):159–170.

Polyak K, Hamilton SR, Vogelstein B, Kinzler KW. Early alteration of cell-cycle-regulated gene expression in colorectal neoplasia. *Am J Path*ol 1996 Aug; 149(2):381–387.

Thiagalingam S, Lengauer D, Leach FS, et al. Evaluation of candidate tumor suppressor genes on chromosome 18 in colorectal cancers. *Nat Genet* 1996 July; 13(3):343–346.

Liu B, Parsons R, Papadopoulos N, et al. Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients. *Nat Med* 1996 Feb; 2(2):169–174.

Liu B, Nicolaides NC, Markowitz S, et al. Mismatch repair gene defects in sporadic colorectal cancers with microsatellite instability. *Nat Genet* 1995 Jan; 9(1):48–55.

Parsons R, Li GM, Longley M, et al. Mismatch repair deficiency in phenotypically normal human cells. *Science* 1995 May 5; 268(5211):738–740.

Jen J, Kim H, Piantadosi S, et al. Allelic loss of chromosome 18q and prognosis in colorectal cancer. *N Engl J Med* 1994 July 28; 331(4):213–221.

Kin H, Jen J, Vogelstein B, Hamilton SR. Clinical and pathological characteristics of sporadic colorectal carcinomas with DNA replication errors in microsatellite sequences. *Am J Path*ol 1994 July; 145(1):148–156.

Powell SM, Petersen GM, Krush AJ, et al. Molecular diagnosis of Familial Adenomatous Polyposis. *N Engl J Med* 1993 Dec 30; 329(27):1982–1987.

Kinzler KW, Nilbert MC, Su LK, et al. Identification of FAP locus genes from chromosome 5q21. *Science* 1991 Aug 9; 253(5020):661–665.

Kinzler HW, Nilbert MC, Vogelstein B, et al. Identification of a gene located at chromosome 5q21 that is mutated in colorectal cancers. *Science* 1991 Mar 15; 251(4999):1366–1370.

Baker SJ, Preisinger AC, Jessup JM, et al. p53 gene mutations occur in combination with 17p allelic deletions as late events in colorectal tumorigenesis. *Cancer Res* 1990 Dec 1; 50(23):7717–7722.

Baker SJ, Markowitz S, Fearon ER, et al. Suppression of human colorectal carcinoma cell growth by wild-type p53. *Science* 1990 Aug 24; 249(4971):912–915.

Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990 Jun 1; 61(5):759–767.

Kern SE, Fearon ER, Tersmette KW, et al. Clinical and pathological associations with allelic loss in colorectal carcinoma. *JAMA* 1989 June 2; 261(21):3099–3103.

Vogelstein B, Fearon ER, Kern SE, et al. Allelotype of colorectal carcinomas. *Science* 1989 Apr 14; 244(4901):207–211.

Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988 Sep 1; 319(9):525–532.

Fearon ER, Hamilton SR, Vogelstein B. Clonal analysis of human colorectal tumors. *Science* 1987 Oct 9; 238(4824):193–197.

Bos JL, Fearon ER, Hamilton SR, Verlaan-de Vries M, et al. Prevalence of ras gene mutations in human colorectal cancers. *Nature* 1987 May 3; 327(6120):293–297.

Goelz SE, Hamilton SR, Vogelstein B. Purification of DNA from formaldehyde fixed and paraffin embedded human tissue. *Biochem Biophys Res Commun* 1985 Jul 16; 130(1):118–126.

Goelz SE, Vogelstein B, Hamilton SR, Feinberg AP. Hypomethlation of DNA from benign and malignant human colon neoplasms. *Science* 1985 Apr 12; 228(4696):187–190.

Vogelstein B, Fearon ER, Hamilton SR, Feinberg AP. Use of restriction fragment length polymorphisms to determine the clonal origin of human tumors. *Science* 1985 Feb 8; 227(4687):642–645.

IV. A. 3.

Smith JR, Freije D, Carpten JD, et al. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science* 1996; 274:1371–1374.

Pennisi E. A catalogue of cancer genes at the click of a mouse. (News and Comment). *Science* 1997; 276:1023–1024.

Emmert-Buck MR, Bonner RF, Smith PD, et al. Laser capture microdissection. *Science* 1996; 274:998–1001.

Woodhouse E, Emmert-Buck MR, Zhuang Z, et al. The revolution in cancer molecular diagnostics. *The Cancer Journal* 1996; 2:197–198.

Pappalardo PA, Emmert-Buck MR, Liotta LA. Microdissection, micro-chip arrays, and molecular analysis of tumor cells (primary and metastases). *Semin Radiat Oncol* 1998; 8(3):217–223.

IV. B.

Burkitt D. A lymphoma syndrome in tropical Africa. *Int Rev Exptl Pathol* 1963; 2:67.

Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1964; II:702.

IV. B. 1.

Gross G, Jablonska S, Pfister H, Stegner HE (editor). Genital Papillomavirus Infections: Modern Diagnosis and Treatment 1990. New York: Springer Verlag.

Crum CP, Cibas ES, Lee KR. Pathology of Early Cervical Neoplasia (Contemporary Issues in Surgical Pathology, Vol. 22). 1997. New York: Churchill Livingstone.

Koss LG, Durfee GR. Unusual patterns of squamous epithelium of the uterine cervix: Cytologic and pathologic study of koilocytotic atypia. *Ann NY Acad Sci* 1956; 63:1245–61.

zur Hausen H. Human papillomaviruses and their possible role in squamous cell carcinomas. *Curr Top Micrbiol Immunol* 1977; 78:1–30.

Gissman L, Wolnik L, Ikenberg H, et al. Human papillomavirus types 6 and 11 DNA sequences in genital and laryngeal papillomas and in some cervical cancers. *Proc Natl Acad Sci USA* 1983; 80:560–563.

Durst M, Gissman L, Ikenberg H, zur Hausen H. A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proc Natl Acad Sci USA* 1983; 80:3812–3815.

Kurman RJ, Norris HJ, Wilkinson E. Human papillomavirus and cancer of the lower female genital tract. In *Tumors of the Cervix, Vagina, and Vulva*. 1992. American Registry of Pathology, 19–28

IV. B. 2.

Chang Y. Kaposi's sarcoma and Kaposi's sarcoma-associated herpesvirus: Where are we now? (Editorial) *J Natl Cancer Inst* 1997; 89:1829–1831.

Strathdee SA, Veugelers PJ, Moore PS. The epidemiology of HIV-associated Kaposi's sarcoma: The unraveling mystery. *AIDS* 1996; 10(Suppl. A):S51–S57.

Moore PS, Chang Y. Detection of herpesvirus like DNA sequences in Kaposi's sarcoma in patients with and those without HIV infection. *NEJM* 1995; 332:1181–1185.

Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. *Science* 1996; 274:1739–1744.

Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; 266:1865–1869.

IV. C. 1.

Kolata G. Genetic material of virus from 1918 flu is found. *NY Times*, March 21, 1997, A1.

Gladwell M. The Dead Zone. *The New Yorker*, September 29, 1997, 52–65.

Taubenberger JK, Reid AH, Kraft AE, et al. Initial genetic characterization of the 1918 "Spanish" influenza virus. *Science* 1997 Mar 21; 275(5307):1793–1796.

Pannisi E. First genes isolated from the deadly 1918 flu virus. *Science* 1997 Mar 21; 275:1739.

IV. C. 2.

Wrobel S. Serendipity, science and a new Hantavirus. *FASEB J* 1995; 9:1247–1254.

V.

Korn D. Dangerous Intersections. *Issues in Science and Technology* 1996; 13(1):55–62.

Korn D. Genetic privacy and the use of archival patient materials and data in research. In *Genetic Testing and the Use of Information*, Long C, ed. 1999. American Enterprise Institute Press.

The Ongoing Debate About Stored Tissue Samples, Research, and Informed Consent

Commissioned Paper
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Introduction

The debate over the appropriate use of stored tissue samples has been simmering for a number of years in the United States.[1] National publicity at various times has focused on parental disputes over cryopreserved pre-embryos in assisted reproduction programs, the use of stored neonatal blood spots for anonymous epidemiological studies of HIV prevalency, and the federal government's requirement that military personnel provide blood samples and cheek swabs for military identification purposes to the Department of Defense's DNA databank.

Specifically in terms of biomedical research, considerable controversy has developed in recent years over the collection, storage, and use of fluids and tissues removed from individuals in research and clinical settings. With the continually expanding abilities of genetics investigators in the era of molecular biology, body fluids (e.g., blood, urine, amniotic fluid) and tissues (e.g., cheek swabs and skin biopsies) that have traditionally been collected by physicians and biomedical researchers for diagnostic and investigative purposes (in both basic and clinical research) can now be used for the multiple purposes of genetic analysis.

As a consequence, three sets of issues have come to the fore in the ongoing debate about the multiple types of research that can be done with stored tissue samples. How specific do the consent documents used in *research settings* need to be about the intended purpose(s) of a research study with stored tissue samples in order for research participants to give *informed* consent? How much information about the possibility of post-diagnostic research on stored tissue samples needs to be given to patients in *clinical settings* in order for them to give *informed* consent? How much can the ethical and legal requirement of informed consent for research be expanded and strengthened before the socially *beneficial research* done by geneticists, pathologists, and other biomedical researchers is seriously impeded?

This national debate over the appropriate research uses of blood and other human tissues that can be stored for long periods of time raises important questions about some of the traditional *research practices* of pathologists and other biomedical investigators who often work with archival biological materials (e.g., paraffin-embedded tissue blocks, histological slides, frozen tissue) for which no informed consent was ever given by the individual sources of the materials other than, one assumes, a consent for surgery. The debate also raises questions about some previously routine *clinical practices*. For example, some persons are convinced that, given the personal and familial information hidden in a DNA sample, there may no longer be "a simple blood draw" in contemporary clinical medicine. In addition, the debate raises questions about currently acceptable practices that cut across any neat *clinical care/research* distinction, such as the cryopreservation of human pre-embryos, the storage of blood samples received in the context of genetic counseling, the collection of neonatal blood spots, and the study of blood and other tissue samples in a cytogenetics laboratory.

This debate has enormous implications for biomedical investigators in many fields, for physicians who sometimes depend on diagnostic tests using stored tissue samples, and, potentially, for every person who in the future will be asked by a physician or biomedical investigator to supply blood or some other tissue sample for diagnostic or investigative purposes. My purposes in this paper are to describe the origins of this debate; to raise questions about how and when the concept of informed consent may apply to research on stored specimens; to interpret the more important positions in the debate; to provide some specific examples that demonstrate why the debate is complex and important; to describe and assess alternative policy changes; and to make some concluding recommendations.

Origins of the Debate

For biomedical scientists, physicians, and members of Institutional Review Boards (IRBs), the important implications of the debate over stored tissue samples were first seen most clearly in an otherwise uncontroversial

series of studies carried out by the Centers for Disease Control and Prevention (CDC). Since 1966, more than 70,000 persons have participated in the National Health and Nutrition Examination Surveys (NHANES). The third National Health and Nutrition Examination Survey (NHANES III) is different from the previous two surveys in that it is the only national survey in which physician examinations are performed to measure individuals' health. Beginning in the 1980s, NHANES III had multiple purposes: to provide a natural history of diseases in the population; to give an accurate description of the distribution of diseases in the country; to monitor changes in the health of the population; to study the etiology of diseases; and to establish empirical data for recommended changes in health policy.

The NHANES III methodology consisted of identifying 40,000 sample persons in 26 states; selecting high sample rates for certain groups (e.g., children, older adults, racial minority groups); interviewing 30,000 of these persons regarding nutrition practices, reproductive health, physical activity, mental health, and health habits; giving them an extensive physical examination with multiple laboratory tests of blood and urine; doing a home study examination regarding socioeconomic status, demographic information, and environmental influences; and promising a long-term follow-up. (The NHANES III consent document stated the following: "After several years, we will check back with you to note any changes in your health."[2]) All of the medical and health data were linked to other personal information to facilitate the multiple purposes of the study and to make long-term follow-up more valuable. By the mid-1990s, the CDC scientists also had produced an archive of approximately 19,500 blood samples stored in liquid nitrogen and immortalized cell lines from approximately 8,500 persons.

To meet the ethical and legal requirements for informed consent, the NHANES III administrators, working with the IRB at the CDC, initially prepared a very detailed and technical statement on consent to be given to prospective participants in the study. That document was later judged to be too technically difficult, and it was replaced by a simple six-page booklet with descriptive text and pictures about NHANES III. The only language in the booklet that pertains to informed consent for banked samples is a one-sentence, descriptive statement: "A small sample of your blood will be kept in long-term storage for future testing."[3]

In early 1994, some officials at the CDC faced a major problem. On the one hand, they possessed an invaluable "national treasure chest" of health information on a cross-section of the U.S. population and an unmatched archive of nationally representative DNA samples for biomedical research. On the other hand, they had several concerns in the light of recent professional literature on molecular genetics and ethics: whether the CDC scientists had adequately informed the sample population regarding the planned storage and scientific uses of their blood samples; whether the persons in the study population had understood themselves to be consenting to long-term research on their banked blood samples; and whether the CDC would need to get additional, more specific consent (at an estimated cost of $2 million) from these persons before carrying out the planned research with the stored samples.

Because of this concern at the CDC, a meeting was held at the National Institutes of Health (NIH) in 1994 to address questions related to "Informed Consent for Genetic Studies Using Stored Tissue Samples." The meeting was jointly planned by representatives from the CDC and the National Center for Human Genome Research (NCHGR; renamed the National Human Genome Research Institute, or NHGRI, in 1997) at the NIH. Several persons invited to participate in the meeting had previously received funding from the ELSI (ethical, legal, and social implications) Branch of the NCHGR. The planned purpose of the meeting was to produce a consensus statement regarding informed consent and the use of stored tissue samples in genetics, whether at CDC or elsewhere. An initial version of the statement was drafted by a small group under the leadership of Ellen Wright Clayton, M.D., J.D., who chaired the meeting. However, the desired "consensus" proved difficult to accomplish, with the group expressing important differences over traditional research uses of stored specimens, the ownership and control of stored samples, the impracticability of recontacting persons for consent to

anonymize stored samples, and the limits to be placed on the use of anonymized samples. As it turned out, this group discussion at the CDC/NIH meeting foreshadowed much more specific positions in the debate that appeared in the following years.

Questions in the Debate

In multiple settings—clinical medicine, biomedical research, and numerous combinations of diagnostic, therapeutic, educational, and investigative endeavors—serious questions are now being raised about the process of informed consent and its applicability to the collection and use of tissue samples that can be stored in a number of ways for long periods of time. Some of the questions are new, some of the questions are threatening to biomedical investigators in some fields, and all of the questions indicate that some traditional practices in biomedicine and some traditional assumptions on the part of patients and research participants are going to have to be reexamined as medicine and the biomedical sciences become increasingly geneticized.

A number of questions pertain to the role of informed consent in *prospective* scientific studies. For example, should patients and potential research participants be told about the possibilities of long-term storage of their tissue sample(s) and subsequent biomedical research on the sample(s)? What information, if any, should they be given about the *likely nature of the planned storage* of their tissue samples, including, perhaps, the cryopreservation of the tissue samples, or the biological transformation of the tissue samples into immortalized cell lines, or the computerized storage of their personal genetic information in a DNA database? Should they be informed about the ways in which the confidentiality and privacy of their personal genetic information (derived from a DNA sample) will be protected, or about the possibilities of future secondary use of the stored tissue sample for different scientific purposes than the purposes for which it was obtained? Should they be given information about the *planned identity status of their stored sample* in terms of whether it will be 1) identified as their sample, 2) linkable (by breaking an identifying code) to them as the source of the sample, 3) completely anonymous as to individual origination, or 4) anonymized after collection? If identified or linkable genetic information about them is likely to be entered into a DNA database, should individuals be given written assurances that this information will not be disclosed to governmental officials who might request it for forensic purposes? And what information, if any, should they be given by biomedical investigators about planned scientific uses of the tissue sample(s) so that they can *communicate personal choices* about the control and ownership of the biological materials, future personal access to the information derived from the banked materials, the access of third parties (including employers and health insurance companies) to the same information, the remote possibility that a particular DNA sample might become commercially valuable, and the possibility that they might subsequently want to withdraw their tissue sample (and/or derivative DNA data) from scientific storage?

The questions related to *retrospective* studies on stored tissue samples are different, but equally important. Should archival tissue samples (e.g., paraffin blocks in pathology departments, neonatal blood spots in newborn screening laboratories) have a planned, limited "life-span" in terms of a specified number of years for storage, or should they be retained essentially forever for long-term clinical follow-up possibilities, long-term epidemiological studies, or long-term medico-legal purposes? As an alternative, should all stored tissue samples (whether banked for biopsy tests, autopsy studies, epidemiological studies, or genetic studies) be destroyed after the planned testing has been done? For that matter, how broadly or narrowly should "genetic studies" be defined in order to establish guidelines for the appropriate use of various molecular research methods with stored tissue samples? In terms of the *identity status* of the stored samples, should all such tissue samples be anonymized as a condition for long-term storage, or should some or all of the samples be retained as identified or, more likely, linkable samples in the event that potentially relevant clinical information is discovered and could be disclosed by appropriate clinicians to the individual sources of the samples? If some identified or linkable samples are stored, should the persons from whom those samples came be contacted again (assuming they

are still alive) for consent in the event that new diagnostic tests become possible, the tests are promising in terms of possible benefit, and the tests are wanted by physicians or scientific investigators? In the same kind of situation, should individuals (the sources of the samples) be contacted again for consent in the event that promising new research possibilities come into being that did not exist when the samples were originally collected and stored? If the residual stored samples are *anonymous*, does that status of the samples mean that investigators who have the samples can use them in whatever ways they regard as appropriate (e.g., as positive or negative controls, as biopsy specimens, as materials for virtually any kind of biomedical research) without ongoing IRB review? Does the status of anonymity mean that such samples, including cell lines, can be accessible to virtually any biomedical investigator (in any university, any commercial firm, any country) who gets them in collaboration with other scientists, and that the samples can then be used for any scientific purpose that he or she has, without regard to whether such a purpose might have been offensive or harmful in some other way to the (now unknown) individual from whom they came? Can any samples be made *truly anonymous* so that there is no way that even genetics investigators can trace a tissue sample to the person from whom it came, even if there were a potentially beneficial clinical reason for that person to be identified?

Additional questions pertain to *post-diagnostic research* done with stored tissue samples that were originally provided by patients in clinical settings. Do patients have any expectations as to what may be done with their blood samples, biopsy samples, or other tissue samples taken by nurses, phlebotomists, or physicians in a clinical setting after the diagnostic tests have been completed? Does it matter ethically if the post-diagnostic research is subsequently done by the same physician who made the clinical request for a diagnostic sample, by other biomedical researchers in the same academic or hospital department, by other researchers in other departments within the same university or hospital, or by yet other biomedical researchers who finally end up with the tissue sample (or a portion of the tissue sample) in a commercial lab of some sort? Does it matter in terms of informed consent if the post-diagnostic research is subsequently done two weeks after a patient provided the tissue sample, or two years later, or 20 years later under significantly different research circumstances (e.g., using investigative methods and technologies not available 20 years earlier)? Granted that the possibility of such post-diagnostic research is currently often undisclosed to patients or disclosed only in a vaguely worded sentence (e.g., as part of a hospital admissions form or a surgical consent document), should this traditional practice be changed in the era of molecular genetics? Is the current "consent" by patients to the *possibility* of post-diagnostic or post-surgical research most accurately interpreted as *implied consent* (as though the situation is an emergency), or as *general or generic consent* (by persons voluntarily going to a medical clinic, or by persons voluntarily seeking admission as patients to a hospital where nurses, phlebotomists, surgeons, and other physicians work), or possibly as a kind of *minimally informed consent*? Should physicians (including primary care physicians) and hospitals provide more information to patients about the possibility of post-diagnostic research, with the goal of actually having *adequately informed* consent to this research practice?

Positions in the Debate

In early 1995, George Annas, J.D., along with Leonard Glantz, J.D., and Patricia Roche, J.D., began distributing a model piece of legislation that had been drafted with ELSI funding through the Department of Energy. Called "The Genetic Privacy Act" (GPA), the model Act is intended as a proposal for federal legislation—although it could be, and has been proposed as well for state legislation.[4] The GPA is based on four premises: genetic information is different from other types of personal information; the genetic information contained in DNA is like a "coded probabilistic future diary;" this information can be accessible to many parties in the era of molecular biology; and, because of the highly personal nature of the information and its accessibility, individually identifiable DNA samples need to be protected by law. Consequently, the overarching premise of the GPA

> is that no stranger, should have or control *identifiable* DNA samples or genetic information about an individual unless that individual specifically authorizes the collection of DNA samples for the purpose of genetic analysis, authorizes the creation of that private information, and has access to and control over the dissemination of that information (emphasis added).[5]

The proposed GPA addresses several of the concerns mentioned earlier, with most of the proposed legislation depending on the identity status of stored DNA samples. The central claim in the GPA is that individually identifiable DNA samples are the property of the person from whom they come (identified as the "sample source"). Therefore, if tissue samples will be individually identifiable, the Act states that the sample source must grant advance authorization in writing to the collection, storage, and proposed use(s) of the samples, as well as to the possible disclosure of private genetic information gained from genetic analysis. In addition, the sample source (or that person's representative in the event of incompetency or death) has a number of rights: to revoke consent to genetic analysis at "any time prior to the completion of the analysis," to inspect records that contain information derived from a genetic analysis, to prohibit the use of the DNA sample for research or commercial purposes "even if the sample is not in an individually identifiable form," to consent (with 45 days advance notice) to the transfer of a DNA sample to other scientists for secondary research purposes, and to order the destruction of the DNA sample upon the research study's completion or the withdrawal of the sample source from the study.

By contrast, the GPA would permit *anonymous* tissue samples to be used for research purposes *if such use was not previously prohibited by the sample source*. The authors emphasize the following: "Nothing in this Act shall be construed as prohibiting or limiting research on a DNA sample that cannot be linked to any individual identifier."[6] Moreover, research by pathologists, geneticists, and other medical investigators can be done on *archival* tissue samples, even if the stored samples are individually identifiable, as long as the samples were stored "prior to the effective date of this Act." However, no individually identifiable genetic information may be disclosed without the authorization of the sample source's representative.

In late 1995, two published papers staked out additional positions in the developing debate. The first paper was a position statement of the American College of Medical Genetics (ACMG), written by John Phillips, M.D., and other members of the ACMG Storage of Genetics Materials Committee.[7] Emphasizing the importance of informed consent, the authors make several recommendations regarding the storage and use of genetic materials that are obtained for *clinical* tests. They recommend that *patients be informed* about the purpose and possible outcomes of the genetic test, the anticipated use of the blood or other tissue samples (including whether the sample will be stored for additional scientific purposes), and their options regarding future access to the genetic information and the possibility of subsequently requesting that the samples be destroyed. They also recommend that if samples are going to be stored, patients should be asked for permission to use the samples and the derivative genetic information in counseling and testing their relatives, and for permission to anonymize the samples for the purposes of additional scientific research.

In terms of tissue samples that are obtained for *investigational* purposes, the ACMG committee recommends that *potential participants in research be informed* about the purpose and possible outcomes of the current research study, the investigator(s)' policy regarding the length of storage time for samples and subsequent destruction of samples, and the possibility that the research may lead to the development of diagnostic tests having several related issues (e.g., the possible need to disclose personal genetic information in a family setting, and the remote chance that diagnostic tests will be commercially profitable). They also recommend that research participants be asked for permission to anonymize their tissue samples for other types of research, and to recontact them for additional consent for (currently unknown) future research efforts with their stored samples. As to research on *archival* samples, the committee simply points out the inherent conflict between the desirability (in terms of ethics and law) of recontacting individuals to secure their informed consent for

ongoing research studies and the impracticability (in many research settings) of recontacting persons from whom samples were previously collected, but makes no specific recommendations regarding how this conflict can or should be resolved.

The second paper, the report coming out of the 1994 CDC/NIH meeting, was controversial before and after its publication. Written by Ellen Wright Clayton and several other persons with diverse professional backgrounds, the paper "Informed Consent for Genetic Research on Stored Tissue Samples" was supported by most of the individuals who attended the 1994 meeting, including me.[8] However, portions of the paper were unacceptable to some geneticists at the meeting who work with archival tissue samples, and they refused to be signatories of the document.

The Clayton et al., document emphasizes the importance of conducting research with stored tissue samples within the ethical and legal framework provided by federal regulations for the protection of human subjects, and by local review by IRBs. The document addresses a range of situations and questions pertaining to genetic research on stored tissue samples: 1) whether anonymous samples for research are exempt from federal regulations regarding informed consent, 2) whether removing identifiers from existing samples can be done without the consent of the individual "source" of the sample, 3) whether limits (related to the preferences of sources, or the psychosocial risks of the research) need to be placed on the use of linkable or identified samples for research, 4) whether genetic research can be done on samples (in pathology or elsewhere) obtained from persons who subsequently died, 5) whether tissue samples from children can be used in genetic research, and 6) whether public health investigations involving genetic studies can be done without the consent of the tissue sources.

The "consensus" document makes several specific recommendations. In terms of tissue samples that have *already been collected*, the document emphasizes the distinction between anonymous samples and samples that are identifiable or linkable at the time a research project is proposed. Samples that are *already anonymous* (e.g., anonymous pathology samples that might be used for a genetics study) do not require informed consent for the obvious reason that it is impossible to identify the individual source directly or indirectly. For this reason, research on existing anonymous tissue samples usually qualifies for a waiver from federal regulations. Even genetic studies with anonymous samples, however, should be reviewed by IRBs, at least in part to determine if the desired scientific information could be obtained in a protocol that allows individuals to consent. By contrast, stored samples that are *currently identified or linkable* to the individual source (e.g., samples originally obtained for diagnostic purposes, numerous kinds of pathological samples) require informed consent by that person if investigators plan to do genetic studies on the samples without anonymizing them.

What about the fairly common practice whereby investigators take existing identified or linkable samples and make them anonymous for use in research by removing all identifiers or linking codes? Current federal regulations permit this practice of *anonymizing samples without the consent* of the individual source. For the writers of this document, this practice is problematic, sometimes disingenuous, and occasionally deceptive when, for example, clinician investigators obtain a tissue sample for diagnostic purposes, know that they plan later to anonymize the sample for research purposes, do not convey that information to the source of the sample, and subsequently remove the identifiers without consent. Consequently, the writers recommend that this practice be curtailed by changing the federal regulations and by having IRBs weigh the benefits of any such proposed research with to-be-anonymized tissues against the difficulty of requiring the investigators to recontact the individual sources for their consent for such anonymization.

In terms of *collecting samples in the future*, the document is quite clear: "People should have the opportunity to decide whether their samples will be used for research."[9] In research and in clinical settings, information about possible research studies with tissue samples should be provided to individuals when their tissue samples are collected. Whenever individuals agree to such research use of their tissues, the writers of this document

recommend that they be given the following options: 1) they are willing to have their samples used in identifiable or linked research (with appropriate information about confidentiality, psychosocial risks, and possible withdrawal from the study) and 2) they prefer or are willing to have their samples stripped of identifiers and linking codes for use in research (again, with appropriate information about the investigators' personal interests, possible commercial benefit, and so on). Additional recommendations involve giving research participants other choices about the research use of their tissue samples: whether they are willing to have their tissues shared with other scientists for secondary research purposes, whether they want to limit their tissue samples to certain kinds of research studies, and whether they want to restrict their tissue samples from being used in scientific studies they do not want to support.

Critical responses to the Clayton et al. consensus statement began even before the paper was published. Wayne Grody, M.D., Ph.D., wrote a sharply critical editorial in *Diagnostic Molecular Pathology* about the consensus statement when the paper was still in final draft form, arguing that the traditional practices ("as long as anyone can remember") of pathology were threatened by an undue ELSI emphasis on informed consent. Stating incorrectly that the paper had been written by members of the ELSI Working Group, a group "too heavily weighted toward the ethicists and lawyers at the expense of the views of working geneticists," he said that the recommendations of the consensus document "would severely restrict access to archival clinical specimens for molecular genetic research and other purposes." The recommended choices to be given patients about the uses of their tissue samples would require "a multitiered consent form with more options and permutations than an airline frequent-flyer program." Moreover, the same lengthy consent form would have to be administered to patients in all sorts of settings: "every phlebotomy, urinalysis, sputum collection, and even haircut." If actually put into practice, "these restrictive and burdensome policies...would seriously impede, or completely block, a major proportion of molecular research on human disease, especially impacting those research questions that can be addressed in no other way" than through retrospective study of large numbers of archival specimens.[10]

Soon thereafter, a "Rapid Action Task Force" (RATF) of the American Society of Human Genetics (ASHG) circulated a draft proposal regarding "Informed Consent for Genetic Research."[11] Chaired by Edward McCabe, M.D., and comprised of ten members (including John Phillips and Wayne Grody), the RATF draft criticizes the Clayton et al. document by affirming the "traditional research practices in human genetics" and calling for the development of consent forms that are "as clear and brief as possible." Accepting virtually all of the consensus statement's recommendations regarding *prospective* genetic research, the RATF agreed that investigators need to obtain informed consent for research on 1) anonymous samples and 2) anonymized samples, unless a particular research protocol qualifies for an waiver under the federal regulations (e.g., the research could be classified as involving no more than minimal risk to the participants). The RATF's important differences with the earlier document pertain to *archival samples*, such as those contained in pathology laboratories and newborn screening laboratories.

The RATF draft was subsequently revised by the Board of Directors of the ASHG and published as a policy statement in the *American Journal of Human Genetics*. The published version differs significantly from the Clayton et al. document and the RATF draft most notably by stating, in specific contrast to the RATF draft, that *informed consent is not necessary* in *prospective* genetic studies using 1) anonymous samples ("biological materials [that] were originally collected without identifiers and are impossible to link to their sources") or 2) anonymized samples ("biological materials that were initially identified, but have been irreversibly stripped of all identifiers and are impossible to link to their sources [but may be linkable] with clinical, pathological and demographic information [gained] before the subject identifiers are removed").[12] The ASHG policy statement also *affirms the practice of anonymizing samples without consent* in *retrospective* studies, because the practice has two important benefits for investigators: it reduces the "chance of introducing bias" in a study by means of an incomplete study sample (some persons may refuse to consent, and others may be impossible to contact for

additional consent); and "importantly, making samples anonymous will eliminate the need for [investigators to] recontact [sources] to obtain informed consent."[13]

In January 1996, additional concerns were expressed by some geneticists and pathologists attending a meeting convened by the NCHGR on "Genetics Research on Human Tissues: Conflicting Implications for Scientific Discovery, Informed Consent, and Privacy." As Richard Lynch, M.D., observed at the meeting, the role of pathologists as legal custodians of stored diagnostic tissue samples largely involves noncontroversial investigations of anonymous, anonymized, and identifiable tissue samples, with biomedical benefits arising from each kind of research. He commented: "99 percent of what pathologists do with stored tissues is just aimed at better characterizing a lesion that already exists and has been excised by the surgeon."[14] But as pointed out by privacy advocates at the meeting, problems arise when the tissue samples are subjected to genetic tests that may reveal personal genetic information that was neither known nor anticipated by the patient, the surgeon, or the pathologist, and that may now involve substantial psychosocial risks for the source of the tissue sample and relatives of that person.

Later that year, the College of American Pathologists (CAP) drafted a position paper entitled "Uses of Human Tissue" that was approved by 15 pathology societies. Stating that "the distinction between use of tissue for diagnosis and research is often unclear," the CAP paper points out that tissues used for research purposes can be collected in three different ways: 1) *prospective* collection for research requires informed consent as part of a research protocol where a patient's identify is clearly known to the researchers, 2) *concurrent* collection involves research done on preserved, "anonymized or linkable" portions of "therapeutic or diagnostic specimens left over after all the work necessary for the patient's care has been completed," and 3) *retrospective* collection involves the research use of "material already archived from specimens originally obtained for diagnostic and therapeutic purposes."[15] Since the "left over" tissues from concurrent collection and the "already archived" tissues from earlier collection "can be made free of patient direct identifiers," the CAP paper maintains that *general consent* for research (not "separate patient consent for each research study on archived or remnant tissues") is sufficient to protect the rights of patients. Written as a response to the papers on genetics research and informed consent by the ACMG, the CDC/NCHGR, and the ASHG, this unpublished paper calls for general consent forms that are "worded broadly and include statements that tissues may be used in research approved by IRBs and for educational purposes." The proposed choice that would appear in such general consent forms would be simple, and very general: "I __ CONSENT ___ DECLINE TO CONSENT to the use of my tissues for research."[16]

In January 1997, the Council of Regional Networks for Genetic Services (known as CORN) issued an unpublished position paper titled "Issues in the Use of Archived Specimens for Genetics Research." The CORN paper points out that *existing collections* of tissues come in several forms: 1) newborn screening blood spots, 2) research samples in various labs, and 3) archived clinical specimens. Regarding post-diagnostic research on these samples, the paper states: "tissue specimens obtained for diagnostic and therapeutic purposes may reasonably be used for the continuing further advance of medical science."[17] As to *new and future collections*, the CORN paper emphasizes that the increasing use of genetic studies in medicine means that "all newly gathered tissue samples may well be collected with the *dual intent* of providing immediate and/or future benefit for the source person *as well as* providing tissue for subsequent research in genetics or in other disciplines." Indeed, the paper states that "the most forthright approach to the possibility of *multiple uses of new collections* would be an acknowledgement of the *assumption* that such specimens will be used in genetics research."[18]

In terms of *anonymized* samples, the CORN paper rebuts the frequent claim by genetics investigators that "use of anonymous samples is ethically justifiable, regardless of the purpose for which the samples were collected." In response, the paper emphasizes the importance of 1) "the fiduciary relationship between medical professionals and their patients/subjects," 2) "the *right* of source persons to disclosure of possible future uses of

their tissues," and 3) informed consent to prospective genetic studies, including, depending on relevant regulations and IRB requirements, research studies done on newborn screening blood spots and research carried out with surgical and other clinical specimens. The paper then calls for the use of consent forms whenever a specimen is collected for "genetic study (either diagnostic or research)," and concludes with a proposed model consent document that would give the source of a tissue sample the options of 1) consenting to have an *identifiable* sample placed in storage (with ten yes/no choices as to the types of research that could be done), 2) consenting to have an *anonymized* tissue sample stored for research (with three yes/no choices), or 3) refusing to consent to have "any excess specimen" stored in any form after the initial "genetic study and/or research purpose" for which the tissue sample was taken has been completed.[19]

A very different type of position paper was subsequently circulated by the Association of American Medical Colleges (AAMC). Titled "Patient Privacy and the Use of Archival Patient Material and Information in Research," the AAMC paper acknowledges the intense concerns over "genetic privacy" and the various technologies that "enable precise genetic information to be extracted from any human tissue sample that contains DNA." The unpublished paper also points out that several legislative bills in Congress "threaten to burden, or even imperil, a large body of...research that is absolutely dependent on ready access to patient records and tissue samples, most often in coded, but linkable, form."[20] Again, the document emphasizes the importance of researchers having "ready accessibility of personally identifiable, i.e., linkable, archival patient materials, such as medical records and tissue specimens removed in the course of routine medical care." However, neither "the general public or legislators" recognizes the benefits that can be gained from "sophisticated genetic analyses on archival human tissue samples that may be decades old," or the clinical reasons why "all archival patient materials to be used in research cannot be made anonymous, that is, totally and irrevocably unidentifiable, or "the crushing financial, administrative and logistical burdens" that would accompany recent proposals for explicit informed consent for research on archival patient specimens."[21]

The AAMC document then puts forth a number of principles pertaining to research on stored samples, most of which are consistent with the earlier CAP position paper: the medical necessity of research on *archival* tissue samples, the medical benefits that can be gained from research on *linkable* samples, the importance of protecting the confidentiality and privacy of *identified* patient information, the need for institutional confidentiality policies with severe penalties for violators, and the adequacy of permitting research on archival patient materials ("whether linkable or not") under "a general informed consent mechanism." The paper emphasizes the distinction between 1) "the forms of stringent informed consent appropriate for research in the typical clinical setting" and 2) the general informed consent that is sufficient for research on archived materials. The paper concludes with a policy proposal for all clinical and research organizations: namely, "to give each patient at his/her first encounter with the health care system two unique identifiers, one for clinical use, the other for research." The proposal suggests that both numbers would be "permanently associated with the specific individual," and the linkage between the two numbers would be "securely maintained in a protected location [a databank of some sort] with controlled access," thereby protecting the confidentiality of the stored information.[22]

Why Is This Debate Important?

The stakes in this debate are high. In its simplest form, it is a debate between 1) professional groups and individuals who think that in the era of molecular genetics, increased emphasis needs to be placed on the distinctive importance of personal and familial genetic information, the right of personal choice about the use of one's body and the tissues 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 tissues; and 2) professional groups and individuals who think that in an era of ever-increasing professional and legal regulations, renewed emphasis needs to be placed on the invaluable

and often irreplaceable research resource represented by stored tissue samples, the inestimable societal and individual benefits that have been gained by means of biomedical research done with stored samples, and the serious threat posed to the continuation of these research efforts by unnecessarily restrictive policy proposals and legislative bills aimed at strengthening the ethical and legal requirements of informed consent. Beyond this overly simple contrast, the issues involved in the debate about informed consent and research with stored tissue samples are numerous and complex.

Some of the complexity of these issues has been indicated in previous sections of this paper, as we have discussed proposals pertaining to appropriate language (e.g., the identity status of stored samples), different categories of research, different kinds of research, and different kinds of concerns that people have about research with stored tissues. Now I want to try to illustrate both the complexity and the importance of this debate with two examples taken from papers developed for a nationally competitive, faculty research seminar at the University of Iowa in 1996 that addressed some of the ethical and legal implications of research on stored tissue samples.

The first example focuses on problems in informed consent brought about by research done with tissue samples originally gathered in a clinical setting: namely, the blood spots on anonymized newborn screening cards. As described by Therese Lysaught and her co-authors, approximately four million newborns are currently screened each year in the U.S. for a number of medical conditions (e.g., phenylketonuria, hypothyroidism, hemoglobinopathies, and galactosemia), with the specific conditions being screened varying from state to state. The blood samples are collected according to legal statutes in 48 states and the District of Columbia (Delaware and Vermont are the exceptions), retained for at least one year (indefinitely by a number of states) on filter-paper cards, and analyzed by means of microbiological, biochemical, and radio-immuno assays, with some genetics investigators now also using DNA-based techniques. Especially with the advent of DNA-based techniques, these stored blood spots increasingly represent an extremely valuable type of DNA databank on entire state populations, a databank that could be used for several purposes (e.g., diagnostic, research, commercial, forensic) that are secondary to and different from the original purpose of screening neonates for medical conditions.[23]

The role of informed consent in newborn screening varies significantly from state to state, at least in part because states differ in terms of legally mandating newborn screening (in Arkansas, Iowa, Michigan, Montana, and West Virginia), offering newborn screening as a voluntary option for parents (in D.C., Maryland, and North Carolina), or giving parents a legal “opt-out” option in the remaining states. In addition, the role of informed consent in newborn screening varies because states differ in terms of 1) whether parents are even informed that newborn screening tests are going to be done, 2) what information parents are actually given about newborn screening and the medical conditions being screened for, and 3) whether parents are told that they have a right to refuse the tests. It is even less clear how many, if any, hospitals and state-funded newborn screening labs provide parents with information about the planned storage of the blood spots from their baby, the planned retention of demographic information about their baby, any planned anonymization (or, perhaps, coding) of the blood spots for research purposes, any planned research that will be done with the blood spots, or the possibility of any other secondary research use of the stored blood spots.[24]

Should prospective parents be provided with this information so that they can make much more adequately informed choices about consenting or refusing to consent to have their baby screened for the medical conditions mandated by the state? The answer to this question, especially in terms of public policy, depends largely on whether policy makers believe that the important traditional goals of newborn screening programs—promotion of public health and therapeutic interventions for individual children at risk—can still be carried out if parents are informed about the planned or anticipated post-screening research uses of the stored blood spots.

The second example is intended to show that research done with stored tissue samples can sometimes pose psychosocial risks to the individuals who supply the tissue samples, that considerations of harm and risk need

to extend beyond these individuals to include the families and communities with which they identify, and that an expanded understanding of the harm that can sometimes be done through research is especially important in genetic research studies. As William Freeman demonstrates, individuals who belong to American Indian and Alaska Native (AI/AN) Tribes share a distinctive history, a set of values that differs from the values of the majority group(s) in the U.S., and a sense of distrust toward scientific investigators who want them to participate in research studies. Although members of AI/AN communities have clearly benefited from medical research (e.g., treatments for trachoma and tuberculosis), they have also been harmed by the external stigmatization and self-stigmatization that has sometimes followed their participation in scientific studies (e.g., in recent studies of alcoholism, syphilis, and the Hantavirus pulmonary syndrome).[25]

As a consequence, the Indian Health Service (IHS) (with the IHS's 12 IRBs) has developed a detailed set of guidelines for the collection and use of research specimens that applies to tissue samples gathered either as part of "clinical care that saves specimens" or as part of research protocols. In general, the guidelines emphasize that 1) research with blood or tissue specimens is both valuable and problematic for AI/AN communities; 2) researchers who save specimens must "inform each volunteer participant in the original consent process about the saved specimens, and the nature of future tests and uses" of the specimens; 3) each proposed future use of saved specimens must first be approved by the Tribal IRBs; 4) each proposed use "must be within the limits and conditions of the original consent" document, even if the specimen has been anonymized or the person from whom it was obtained has died; 5) the IHS has particular concerns about genetic research, storing or testing "tissues with special cultural meaning or value" (e.g., placenta, umbilical cord blood), and attempts to patent human specimens; and 6) specimens must be stored with security, and "handled and disposed of with respect."[26]

When the guidelines are analyzed in some detail, they reveal some of the specific concerns that AI/AN communities have about research with stored samples. Regarding the importance of informed consent, the guidelines specifically exclude "blanket consents" and state that if informed consent is going to be *truly informed* consent, research participants must be told about the plans to store specimens, the tests to be done under the protocol (e.g., "DNA tests, or other genetic tests"), the tests that may be done with tissues having "strong social meaning or value," whether perpetual cell lines are going to be developed, and the nature of future "secondary uses" of the stored samples. As to secondary use of stored specimens, the guidelines require that "researchers of the original protocol" neither give specimens to other investigators nor carry out "tests or other uses not explicitly mentioned" in the original protocol and consent form, at least in part because stored specimens "are a nonrenewable resource" that should not depleted with research projects that have not been reviewed and permitted by IRBs. Researchers working with *identifiable* specimens must agree in writing that "the specimens and their data" will not be used for any purpose not approved by an IRB, that they will not attempt to contact any individual or family without IRB approval, and that they will obtain specific informed consent from each person before releasing the results of any "tests with clinical relevance." Researchers working with *anonymous* specimens must agree in writing that they will not attempt in any way "to establish the identity of the subjects of the specimens or data."[27]

As to the informed consent process itself, the guidelines distinguish among three possible approaches to gaining informed consent for research on stored samples. One approach maximizes the importance of future research and grants considerable flexibility to researchers by means of "a broad consent that gives general permission" to save specimens and do research with them, with wording that simply says that research is going to be done, for example, with "leftover blood" for "future tests about diseases of importance to AI/AN people." This kind of blanket consent approach is unsatisfactory because it "does not recognize possible harms" to individuals or communities, it "covers too much, from alcoholism to otitis media, from non-stigmatizing conditions to highly stigmatizing conditions," and participants "could not know what the risks and benefits might be."

A second approach maximizes participant control by means of "a detailed consent" document. When this approach is used, each participant decides in advance and by himself or herself "whether to permit saving a specimen, what tests can and cannot be done, and whether to be contacted about results of future tests." In most instances this kind of detailed consent is impractical because "the control is exercised when participants lack relevant information," future tests are too varied to list, and the future risks and benefits of tests yet to be developed cannot be known.

A third approach, and the approach taken in the IHS guidelines, is a process of informed consent that emphasizes the connection between individuals and the community of which they are a part. The community through its IRB(s) reviews proposed research studies with stored tissues in an effort to "check against misuse of the specimens," assess possible risks and benefits, and consider the chances of long-term stigmatization to the community and the people in it. Once the IRB has approved the research protocol, each potential participant can then make a decision, in the context of "pre-test counseling," as to whether to participate, whether the known risks and benefits are appropriately balanced, and whether to be contacted with the result of future tests. In this way, participant decisions are made "when maximal information is available," and community values are protected.[28]

Alternative Solutions

What should be done to address the competing interests and values at stake with stored tissue samples? What recommended changes need to take place in current research practices to address the concerns about informed consent that have been raised about research with existing collections of specimens, research with not-yet-collected samples, and any kind of research with stored samples that involves the possibility of psychosocial harm to individuals, families, and identifiable groups? What possible solutions are available that can help us manage the complexities and conflicts over stored tissue samples in the era of molecular genetics?

As indicated by the chronological developments and positions described earlier, six possible solutions have been suggested and/or tried. One possible solution is to *retain as many traditional research practices as possible*, especially regarding retrospective research on archival samples. As illustrated by the CAP policy statement, the ASHG policy statement, and the AAMC policy statement, there are some pathologists, geneticists, and other biomedical investigators who want to downplay the importance of informed consent with stored tissue samples and thereby to continue traditional research practices, especially the practice of anonymizing samples without consent in pathology laboratories, newborn screening laboratories, and other locations for archived specimens. The ASHG policy statement, while emphasizing the importance of informed consent in prospective studies using *identifiable* or *identified* samples, clearly favors placing greater weight on traditional research practices than on considerations of informed consent when the stored samples in question are samples that have been and could continue to be anonymized without the consent of the sample sources or their relatives or surrogates. No mention is made of possible ways of anonymizing samples in an expanded context of informed consent, either by 1) recontacting the still-identifiable adult sources before anonymizing the samples (as had been discussed in the CDC/NIH meeting and Clayton et al. paper) or 2) initiating a request to an adult sample source (or the parent(s) of a neonatal sample source) for consent to anonymize samples for research purposes *before* the samples gain the status of "existing" or archival samples. The CAP and AAMC documents even raise questions about the importance of informed consent with identified or linkable samples, with the emphasis that both policy statements place on the adequacy of a general consent statement that, whenever granted by an individual, would give researchers blanket permission to carry out virtually any kind of studies they choose with the tissue samples they secure from that person, including secondary research studies having significantly different purposes than the purposes for which the sample was originally given.

A second possible solution is to *recommend new professional society guidelines* that can update and change professional practices in the light of new technological developments and new ethical and legal concerns about stored samples. The strongest feature of this possible solution is the importance placed on self-governance and change from within professional ranks, with the hope that choosing to adopt *peer-influenced change* will preclude imposed change from forces outside the profession (e.g., by law, federal regulations, or patient-advocacy groups).

Thus the Storage of Genetics Materials Committee produced a position statement for the American College of Medical Genetics that briefly interpreted the concept of informed consent in the context of stored tissue samples, and then gave a series of recommendations regarding the collection of tissue samples for prospective genetic tests in clinical and research settings, and the currently acceptable uses of stored DNA or genetic materials. Somewhat similarly, the RATF made a proposal to the American Society of Human Genetics regarding the application of informed-consent considerations to prospective and retrospective studies that could have been helpful in modest ways in changing the practices of genetics investigators. However, the ACMG document failed to make several needed recommendations pertaining to DNA banking and informed consent, and the RATF document, already primarily protective of the research interests of some of its authors, became even more protective of the research interests of investigators who use anonymized samples without consent in the revised form published by the ASHG.

A third possible solution is to *try to arrive at consensus about acceptable research practices through special meetings of interested parties* who have conflicting interests and concerns about stored DNA samples. This is the solution that has been favored by the NCHGR at NIH, as illustrated by the multidisciplinary meetings it planned and hosted in July 1994, and January 1996. In the first of these meetings, representatives from the CDC and NCHGR (now NHGRI) met with invited genetics investigators, ethicists, attorneys, and patient advocates in the hope of reaching agreement on whether the CDC could proceed to do research on its 19,500 tissue samples, or whether investigators at the CDC and elsewhere need to gain more specific consent of individual sources before carrying out research on identifiable and/or anonymized tissue samples. In the 1996 meeting, several leading pathologists were invited to meet with NCHGR representatives, ELSI representatives, advocates for physicians and biomedical investigators, and patient advocates in order to enable the pathologists to express professional concerns over the issue of informed consent and stored tissues. Neither meeting resulted in unanimous agreement of the participants, but both meetings seem to have been educationally and politically beneficial. Both meetings also ended with a renewed sense that compromise was possible on at least some of the issues in question, with several participants voicing hope for soon achieving a reasonable balance (e.g., in *improved* consent forms) between 1) the rights and preferences of individual research participants and patients and 2) the practices and interests of biomedical researchers and physicians. How much compromise is actually achieved remains to be seen, given the vested interests and high stakes involved in the debate.

A fourth possible solution is to *recommend changes in the federal regulations and IRB review practices* pertaining to genetic studies using human participants and stored tissue samples. The clearest example of this approach is the Clayton et al. paper published in *JAMA*. This document states that the authors place considerable weight on the federal regulations regarding the protection of human subjects (and related publications by the federal Office for Protection from Research Risks) because the regulations "are legally enforceable and because they are the embodiment of an attempt to strike a balance between the desire to increase knowledge and the protection of individual interests."[29] The document therefore quotes the federal regulations at numerous places in the text and sometimes goes to considerable lengths to show how the regulations can and should apply to some important research issues that have developed since the regulations were written, namely the emerging questions about the collection and use of stored tissue samples.

Nevertheless, this proposed solution depends not merely on professionals in multiple fields being able to know, interpret, and apply the federal regulations to state-of-the-art concerns about the collection and use of

stored DNA samples, but more importantly being able to bring about changes in the regulations (and their use by IRBs) so that they will continue to balance the competing interests of scientific investigators and individuals (and families) who participate in research studies. Therefore the Clayton et al. paper indicates several ways in which the regulations need to be updated, clarified, and changed to provide needed guidance for investigators and the IRB members who review their research proposals: the appropriate limits to be placed on genetics studies with anonymous samples, IRB review of studies using anonymous samples, the practice of anonymizing existing samples, the limits of impracticability in securing consent, and the degree of deference to be given to individuals' preferences not to have their tissue samples used for specific types of genetic research. William Freeman's paper is another example of this approach, with his emphasis being placed on changing IRB review practices concerning informed consent to protect the preferences, beliefs, and values of AI/AN Tribes and other minority communities participating in research studies. In fact, the new IHS guidelines for research with stored tissue samples may be the most effective example of this approach, since AI/AN Tribes have *legal* standing to enforce their new IRB review practices.

A fifth possible solution is to *produce updated consent forms* in clinical and research settings that more accurately describe current research practices with stored samples and more adequately enable individuals to make informed choices about how their DNA samples (and personal genetic information contained therein) are to be used. The ACMG committee, the Clayton et al. group, the RATF group, and the CORN position paper all seem to assume that many of the conflicts over stored samples can be addressed by means of 1) more appropriately worded consent documents and 2) improved IRB review of research protocols using identified, linkable, anonymous, or anonymized tissue samples. The catch, of course, is whether updated consent forms will be more protective of the rights of individual sources to make informed-consent choices about their banked tissues, or of the professional interests of the biomedical investigators who frequently write the documents. The challenge will be to see if multidisciplinary interests can be reflected in updated consent documents that contain workable compromises, such as including modest amounts of information to patients about pathological research practices in surgical consent forms before any biological samples are collected as part of the surgery.

The CORN position paper, in fact, proposes the use of a model consent form that goes well beyond the general consent limit that the CAP and AAMC position papers find sufficient. The CORN Committee on Ethical and Legal Issues proposes that patients and research participants be given a consent document that contains "a menu of options, each to be marked affirmatively or negatively by the patient" or research participant. If this individual chooses to permit research on *identifiable* samples, he or she can indicate specific preferences regarding secondary research, the requirement of additional consent in the future, the destruction of the specimen after this person dies, and the possibility of research having commercial implications. If this individual consents to research on *anonymized* samples, he or she can indicate preferences regarding secondary research, including whether that research is done by the same investigator(s) or by investigators in other facilities or institutions. If the individual does not consent to any research "after completion of the original testing for which the specimen was taken," that choice can also be expressed on the document.

The sixth possible solution is to *mandate by law* the changes in the era of genetic medicine that are necessary to protect individuals from unauthorized analysis of their DNA samples, unauthorized disclosure of personal genetic information resulting from genetic studies, and unauthorized transfer of their stored biological materials to other investigators. The clearest and most comprehensive attempt to work on this solution is the proposed GPA written by Annas, Glantz, and Roche. According to this model piece of legislation, an individual "sample source" has property rights to his or her sample and therefore can determine who may collect and analyze a blood or other tissue sample, limit the purposes for which a DNA sample can be analyzed, know what information her DNA samples can reasonably be expected from the genetic tests, order the destruction of stored DNA samples, delegate authority to a surrogate to order the destruction of stored DNA samples, prohibit even

the anonymous use of their samples in research, refuse to permit the use of the DNA sample(s) for research or commercial activities, and inspect (and obtain) copies of records containing information derived from genetic analysis of the DNA sample(s).[30]

This proposed solution is, of course, quite different from the other strategies. Rather than relying on peer-influenced change, consensus-driven change, updated changes in the federal regulations, and research-oriented consent forms, this approach would force change through the power of law and the threat of legal penalties. Thus the proposed GPA has a section on civil remedies according to which a person (e.g., a clinician, a biomedical investigator, a professional in a biomedical lab) who violates the provisions of the GPA through negligence would be liable for a $25,000 fine plus other monetary damages, and a person who willfully violates the GPA would be liable for a $50,000 fine plus other monetary damages.

As with the other proposed solutions, it remains to be seen whether this proposal will actually work. At the present time, the GPA remains a controversial proposal for a model law that has been frequently discussed and often praised, but also frequently rejected as unnecessary and counterproductive to biomedical progress.[31-33]

Concluding Recommendations

Given the complexity of the debate about research on stored tissue samples, the National Bioethics Advisory Commission (NBAC) can hardly be expected to provide the final answers or have the last word in its publication on the subject. What NBAC can do, however, is to produce a document that 1) correctly and fairly describes the various positions that have been taken on this issue, both in published and unpublished documents, 2) sorts out the competing interests and agendas that comprise the debate, and 3) advances the discussion in some important ways. I hope that this paper proves to be helpful to NBAC in achieving the first two of these tasks. Now I conclude with a series of recommendations that I hope will be helpful in advancing the discussion of this important issue.

1. The NBAC report should be realistic about the research that is actually being done with stored tissue samples, with some of the tissue samples originating in research settings under IRB-approved research protocols and some of the tissue samples originating in clinical settings that are not on the IRB "radar screen." This post-diagnostic research on tissue samples gathered from patients can be placed in two broad categories: a) some of it is done for "clinical assistance" in individual cases (e.g., to verify or strengthen the confidence in the diagnosis) or for patients as a group (e.g., for reasons of clinical quality control) and b) some of it is done, especially in teaching hospitals, for reasons that have little if anything to do with the clinical care of patients, except in the general sense that biomedical research usually has as one of its justifying reasons the hope and promise of long-term clinical benefit to future patients. At the very least, the NBAC report should reflect one of the most common themes that appears in most of the documents discussed in previous sections of this paper: tissues are collected for storage and research purposes in both research and clinical settings, and the recognition of this "dual intent" (to use the language from the CORN document) or "concurrent collection" (in the language of the CAP paper) that sometimes accompanies requests for consent to take tissue samples from individual patients is an important part of sorting out some of the variables in this complex subject.
2. The NBAC report should try to balance the competing interests in this national debate without placing too much emphasis on the interests and claims of either a) the advocates for a continuation of biomedical research on stored tissue samples that is unfettered by serious considerations of informed consent or b) the advocates for an expansive and legally enforced interpretation of informed consent that risks placing crippling restrictions on socially beneficial research. In addition, the NBAC report should emphasize the importance of introducing c) a new, and thus far largely silent participant in this national debate: *actual participants* in

research studies and *actual patients* in clinical settings. What kind of data, if any, is available regarding their knowledge about the research that is done with stored tissue samples? What kind of data, if any, is available regarding their concerns about research on identifiable or linkable samples, or their preferences about research on anonymous or anonymized samples? Are very many patients and participants in research protocols actually concerned about research on anonymized samples, or is this concern only theoretical in nature? Would very many patients be concerned if they found out that post-diagnostic research had been done on their tissue samples without their consent?

3. As suggested by the previous recommendation, the NBAC report should emphasize that thus far a lot of time, energy, thought, emotion, and position papers have gone into this national debate about research on stored tissue samples, but *very little data* have been produced to document or defend the positions that have been developed. For example, we may know that the Armed Forces Institute of Pathology has approximately 2.5 million samples in its DNA Registry, and we may have estimates that the pathology departments in medical schools receive from 10,000 to 25,000 tissue samples a year, but we do not have much data regarding the number of tissue samples currently in storage in the nation's blood banks, tissue (transplant) banks, genetics labs, reproductive endocrinology laboratories, state tumor registries, forensic science departments, and so on. If the NBAC report could provide some of these national numbers, the data would be helpful.

4. The NBAC report would also be helpful if, in the era of molecular genetics, it called for an updating of the *federal regulations* that govern research with human participants. In particular, it would be helpful to call for the federal regulations to be updated in four ways: a) a *broadening of the concept of harm* that underlies the "minimum harm" language, specifically to include consideration of the multiple psychosocial risks of harm that persons now take when they participate in genetic studies, b) an extension of considerations of harm beyond the individual to include families, identifiable groups, or communities that can also be harmed by unexpected new self-knowledge through genetics, unexpected knowledge through genetics about relatives or identifiable group members, stigmatization by others, self-stigmatization, drastically changed personal relationships, possible loss of hospitalization insurance, employment problems based on genetic tests, and so on, c) an extension of considerations of harm to include possible harms that can be done with research even on *anonymized samples*, such as group or community stigmatization, and d) an expanded perspective on what research studies with stored tissues commonly include, specifically addressing the widespread practice of *secondary research* done with stored tissue samples or immortalized cell lines that differs in purpose (and often personnel and place) from the purpose(s) of the original research study described in the original consent documents.

5. In terms of *retrospective* studies done with stored samples, the NBAC report should a) call for the development of more precise criteria regarding when and why some collections of samples count as "existing" samples, b) recommend the "grandfathering" of collections that clearly count as "existing" collections from any new federal regulations or laws, c) emphasize the importance of primarily retaining and protecting *linkable* samples (rather than identified or anonymized samples) in the existing collections, for reasons of long-term potential clinical benefit to individual patients and families, and d) call for a discontinuation of the practice of *anonymizing stored samples without the consent* of the person from whom the sample(s) came (or the parents of the baby, when the stored samples are dried neonatal blood spots).

6. In terms of *prospective* studies in *research settings*, the NBAC report should reaffirm the importance of using the *reasonable person standard* for informed consent for participants in research protocols, including research protocols that will use DNA banking or other long-term storage of tissue samples. The reasonable person standard is the correct standard to use for informed consent in research settings because it requires more

disclosure of information to potential participants than the professional practice standard requires (and, hence, more disclosure than is frequently done by researchers), and it requires less disclosure of information than the subjective standard would require (and thus is achievable in practice, even given the diversity of persons who choose to participate in research studies). For prospective studies that will use DNA banking or other long-term storage of tissue samples, the reasonable person standard of informed consent would seem to require that researchers disclose information to potential research participants regarding a) how the tissue samples and derivative genetic information will be kept confidential and private (e.g., by coding the samples and information), b) the control and ownership of the tissue samples, c) how participants will be able, should they later choose to do so, to withdraw their continued contribution to or personal identification with the research project (e.g., by requesting that their tissue samples be destroyed), d) how long the tissue samples will be stored for research purposes, e) any future access they may have to personally and clinically relevant information gained through the study, f) any future third-party access (e.g., by health insurance companies) to the personal genetic/medical information gained through the study, and g) any planned or possible secondary research use of the stored samples, transformed cell lines, or derivative genetic/medical information.[34]

7. In terms of the possibility of *post-diagnostic research with clinical samples*, the NBAC report should acknowledge that such research frequently occurs, especially in teaching hospitals, and that this research practice is largely unknown to patients. But in addition, the report could try to "raise the bar" regarding informed consent for research done with tissue samples gathered in clinical settings. In other words, the report could call for an extension of the *reasonable person standard* for informed consent to include the *possibility* of post-diagnostic and post-surgical research that may be done with clinical samples. Again, the reasonable person standard is the correct standard to use for informed consent to this possible research because it would require some disclosure (in contrast to the *presumed consent* that is acceptable in emergency situations), and it would require that this disclosure actually have some content (in contrast to the vague, single-sentence, *general consent* language commonly used in hospital admission forms and surgical consent documents). However, the reasonable person standard for informed consent would not seem to require the same degree of specificity for disclosure in general clinical settings as it does for participation in research protocols, because what is being disclosed is *only the possibility* that post-diagnostic research may occur with tissue samples originally collected for diagnostic tests.

8. As to the *practical* application of this expanded reasonable person standard for informed consent, the NBAC report could call for the "front loading" of this informed consent when patients enter clinical settings. The CORN report has already stated that "the most forthright approach" to collecting new tissue samples would be to acknowledge to patients the assumption that the samples will also be used for genetic research; they suggest using a detailed consent form that gives patients a chance to communicate their preferences about this possible research. The AAMC position paper also calls for an up-front acknowledgement that samples collected for diagnostic tests may also be used for research purposes; they suggest giving each patient two unique identifiers at the "first encounter with the health care system," one to be used for tracking each patient's clinical care and the other to be used for tracking the research done with that patient's tissue samples.

The NBAC report could helpfully do four things: a) emphasize the appropriateness of the reasonable person standard for the possibility of post-diagnostic research, b) suggest the substantive content that might be initially disclosed to all patients using the reasonable person standard (less specific content than the same standard seems to require in regular research settings), c) call for the development of institutional consent forms or institutional advance directives that would enable decisionally capable patients to communicate choices upon

admission about the possible research use of their tissue samples, and d) call for the development of alternative institutional documents (e.g., a delayed consent form for possible research on stored tissues) that would enable seriously ill patients to wait a set period of time (e.g., three days after admission, seven days after surgery) before communicating their preferences about any post-diagnostic or post-surgical research unconnected to their clinical care that might be done with their stored tissue samples.

Notes

1 Portions of this paper are revised versions of some of the material included in Robert F. Weir, "Advanced Directives for the Use of Stored Tissue Samples," in Robert Weir, ed., *Stored Tissue Samples: Ethical, Legal, and Public Policy Implications* (Iowa City: University of Iowa Press, 1998).

2 Centers for Disease Control and Prevention (CDC), Department of Health and Human Services, "National Health and Nutrition Examination Survey III," January 1994, 3.

3 CDC, "National Health and Nutrition Examination Survey III," 3.

4 George J. Annas, Leonard H. Glantz, and Patricia A. Roche, "The Genetic Privacy Act and Commentary," unpublished model law, February, 1995.

5 "Genetic Privacy Act," 6.

6 "Genetic Privacy Act," 24.

7 Storage of Genetics Materials Committee, American College of Medical Genetics. "Statement on Storage and Use of Genetic Materials," *American Journal of Human Genetics* 57 (1995):1499–1500.

8 Ellen Wright Clayton, et al., "Informed Consent for Genetic Research on Stored Tissue Samples," *Journal of the American Medical Association* 274 (1995):1786–1792.

9 Clayton, 1791.

10 Wayne W. Grody, "Molecular Pathology, Informed Consent, and the Paraffin Block," *Diagnostic Molecular Pathology* 4 (1995):156.

11 Edward R.B. McCabe, et al., American Society of Human Genetics Rapid Action Task Force, "Report on Informed Consent for Genetic Research," unpublished document, 1–10.

12 American Society of Human Genetics, "Statement on Informed Consent for Genetic Research," *American Journal of Human Genetics* 59 (1996):471–474.

13 American Society of Human Genetics, "Statement on Informed Consent," 474.

14 Joan Stephenson, "Pathologists Enter Debate on Consent for Genetic Research on Stored Tissue," *Journal of the American Medical Association* 275 (February 21, 1996):504.

15 College of American Pathologists, "Uses of Human Tissue," unpublished policy statement, August, 1996, 7–8.

16 College of American Pathologists, "Uses of Human Tissue," 8.

17 Committee on Ethical and Legal Issues, Council of Regional Networks (CORN) for Genetic Services, "Issues in the Use of Archived Specimens for Genetic Research," unpublished manuscript, January, 1997, 3.

18 CORN, "Issues in the Use of Archived Specimens," 4.

19 CORN, "Issues in the Use of Archived Specimens," 7–8.

20 Association of American Medical Colleges, "Patient Privacy and the Use of Archival Patient Material and Information in Research," unpublished paper, April, 1997, 1–2.

21 AAMC, "Patient Privacy and the Use of Archival Patient Material," 2.

22 AAMC, "Patient Privacy," 4.

23 M. Therese Lysaught, et al., "A Pilot Test of DNA-Based Analysis Using Anonymized Newborn Screening Cards in Iowa," in Robert Weir, ed., *Stored Tissue Samples*, 14–17.

24 Lysaught, “A Pilot Test,” 40–45.

25 William L. Freeman, “The Role of Community in Research with Stored Tissue Samples,” in Robert Weir, ed., *Stored Tissue Samples*, 267–301.

26 Freeman, “The Role of Community,” 294.

27 Freeman, “The Role of Community,” 294–299.

28 Freeman, “The Role of Community,” 300–301.

29 Clayton, 1787.

30 George J. Annas, Leonard H. Glantz, and Patricia A. Roche, “Drafting the Genetic Privacy Act: Science, Policy, and Practical Considerations,” *Journal of Law, Medicine, and Ethics* 23 (1995):361.

31 Ellen Wright Clayton, “Panel Comment: Why the Use of Anonymous Samples for Research Matters,” *Journal of Law, Medicine, and Ethics* 23 (1995):375–377.

32 Neil A. Holtzman, “Panel Comment: The Attempt to Pass the Genetic Privacy Act in Maryland,” *Journal of Law, Medicine, and Ethics* 23 (1995):367–370.

33 Philip R. Reilly, “Panel Comment: The Impact of the Genetic Privacy Act on Medicine,” *Journal of Law, Medicine, and Ethics* 23 (1995):378–381.

34 Robert F. Weir and Jay R. Horton, “DNA Banking and Informed Consent,” *IRB* 17 (1995):1–4.

MINI-HEARINGS ON ISSUES IN HUMAN TISSUE STORAGE

Commissioned Paper

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1. Introduction

1.1 Background

Human tissue samples have long been stored as a record of individual pathology and to assure laboratory quality. For human genetic research, these stored tissues provide a vast source of potential research material. The value of these materials increases to the degree that the tissue samples are well characterized, that is, the circumstances and procedures with which they were collected and the clinical and demographic characteristics of the patient are recorded. We lack consensus, however, on the circumstances under which it is appropriate to allow researchers access to stored tissues. Must consensus be obtained for each use? Clearly this recognizes the autonomy of the patient in deciding the disposition of his or her tissue, but imposes a large and costly burden on researchers. And there are many other questions as well regarding ownership of tissue samples, the provision of informed consent for research, privacy concerns, and the potential for stigmatization of individuals and groups. The National Bioethics Advisory Commission (NBAC) must weigh evidence and opinion concerning these issues and produce recommendations surrounding the use of stored human tissue for genetic research.

The Commission saw the value in ascertaining the opinions of nonexpert members of the American public—meaning those who are not medical researchers or ethical experts—regarding the use of stored human tissue. The opinion of nonexperts provides a counterpoint to the learned testimony that the Commission would otherwise hear. Therefore, NBAC contracted with the Center for Health Policy Studies (CHPS) to conduct a series of "mini-hearings" in selected locations to provide some insight into the opinions of nonexperts regarding the use of stored tissues samples for research purposes.

1.2 Purpose

The purpose of this project was to explore knowledge, beliefs, and attitudes of nonexperts about human tissue storage issues. Five distinct areas of inquiry were explored during mini-hearings:

- Consent and Ownership
- Privacy and Confidentiality
- Stigmatization of Ethnic Groups
- Third Party Concerns
- Sponsorship of Research
- Safeguards

CHPS conducted mini-hearings across the country to explore what nonexperts know and believe about the use of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Mini-hearings were held in Richmond, Virginia; Honolulu, Hawaii; Mililani, Hawaii; San Francisco, California; Cleveland, Ohio; Boston, Massachusetts; and Miami, Florida.

NBAC will use findings from this study as it develops its reports to the President and the nation regarding these issues.

1.3 Report Overview

This report is organized in four chapters. Chapter Two discusses the approach to organizing and conducting the mini-hearings, including recruitment of participants and limitations of the approach taken. Chapter Three presents findings from the mini-hearings. Chapter Four presents conclusions and possible directions for future research.

2. Methodology

2.1 Introduction

This chapter describes the methodology used to explore the opinions of nonexpert mini-hearing participants regarding tissue storage issues. The following section includes a description of the mini-hearing approach. Section 2.3 describes how participants were recruited. The chapter concludes with a discussion of the limitations of the approach used.

2.2 Approach

CHPS employed a qualitative approach to gathering nonexpert public opinion. Mini-hearings were conducted in selected cities across the country. Small groups of participants (7 to 14 individuals) from the local communities in which the mini-hearings were held were convened to actively share their knowledge and opinions. The mini-hearings were open to the public and were attended, in all but one instance, by a member of NBAC and NBAC staff.

NBAC Commissioners and staff provided CHPS with a list of preferred locations for the mini-hearings. At least one Commissioner resided in or near each of the chosen cities and participated in the planning process. In all but one instance, the local Commissioner also attended the mini-hearing. The first mini-hearing was held in Richmond, Virginia, and served as a pilot test of the approach. The remaining mini-hearings were held in Honolulu, Hawaii; Mililani, Hawaii; San Francisco, California; Cleveland, Ohio; Boston, Massachusetts; and Miami, Florida. Once locations were identified, Commissioners in each city were contacted by CHPS and NBAC staff to discuss preferences for date, location, and participants to target.

During the group discussion portion of the mini-hearing, a moderator led the discussion, a small number of participants were included to afford everyone an opportunity to express their ideas, and sessions were recorded and comparisons were made across groups to identify common themes. However, the purpose of these mini-hearings was to elicit the range of opinions of the participants, not to draw conclusions about the public in general or, necessarily, to prepare for a larger survey.

CHPS developed a moderator guide and mini-hearing protocol to aid the discussions. Four hypothetical scenarios were created to highlight different issues surrounding the use of human tissue in research. The scenarios and related questions were reviewed by NBAC Commissioners and staff. In addition, the scenarios were tested at the Richmond, Virginia, mini-hearing and a few minor changes were made based on feedback from that hearing. Modifications included:

- Allotting time for additional discussion and education about what is written in treatment and research consent forms,
- Adding questions about the linking of stored tissue to individuals' medical histories, the use of scrambled identifiers for research, and safeguards for such research, and
- Providing information to participants regarding who typically sits on an Institutional Review Board (IRB).

The moderator began each mini-hearing by asking participants questions regarding their knowledge about human tissue, tissue storage, and medical research in order to assess what participants knew prior to the mini-hearing and to address basic concepts about tissue storage prior to discussing specific issues. The moderator then presented the participants with the hypothetical scenarios, each of which was followed by a series of questions. Participants were asked to share their thoughts on issues regarding ownership of stored tissue, informed consent, research on specific groups, sponsorship of research, privacy and confidentiality, and safeguards for research. Additionally, each participant completed a self-assessment form prior to and following the discussion

to see if his or her thoughts and feelings about tissue storage, research, and protection of privacy rights changed as a result of the discussion. Self-assessments served to stimulate participants' contemplation of the issues; these forms were used for discussion purposes only and were not collected.

The moderator was assisted by two associates who observed the dynamics of the mini-hearing and took thorough notes. Each mini-hearing was also transcribed. CHPS used the same moderator and note-takers for each mini-hearing to ensure consistency among the reports of group discussions. CHPS staff reviewed the notes and transcripts to identify trends, similarities, and differences across and within groups. This approach consisted of three steps:

- Extraction of generalizations and divergent opinions from each mini-hearing,
- Compilation of quotes that support generalizations and identification of differing opinions, and
- Comparison of data across groups to determine similarities and differences.

Immediately following each mini-hearing, the moderator and associates met to discuss results and key findings. A summary report was then written to present generalizations, quotes, and other relevant findings from the group. Upon completion of all of the mini-hearings, comprehensive issue area tables were prepared to compare results across groups. These tables are presented in chapter three.

2.3 Participant Recruitment

To facilitate an effective discussion, an effort was made to recruit a relatively homogenous group of 7 to 14 participants for each mini-hearing. Different groups were targeted for participation in each location to ensure that diverse viewpoints were represented overall. Table 2-1 shows groups that were targeted in each location.

Table 2-1 Mini-Hearing Composition

Location	Group Participants
Richmond, Virginia (pilot site)	Educated baby boomers
Honolulu, Hawaii	Members of an urban neighborhood board
Mililani, Hawaii	Members of two suburban neighborhood boards
San Francisco, California	Students and young adults
Cleveland, Ohio	African-Americans
Boston, Massachusetts	Senior citizens
Miami, Florida	Jewish women

CHPS worked with the Commissioners in each city to identify the appropriate target groups. In most instances, Commissioners identified a point of contact to assist in obtaining participants. Tools for recruiting participants included letters of invitation printed on NBAC stationery, personal invitations (telephone or in-person) from points of contact in the cities, and reminder phone calls from CHPS staff on the day prior to the mini-hearings. For two of the mini-hearings, we compensated participants for attending. Compensation was set at $25. For the remaining mini-hearings, compensation was deemed to be unnecessary by either the Commissioner or the point of contact helping to recruit participants.

Each mini-hearing was open to the public, and time was allotted for public comment following the facilitated discussion. The mini-hearings were advertised through local newspapers, public radio stations, flyers, and/or word of mouth, as appropriate for each location. CHPS developed a flyer to be distributed to potential mini-hearing participants. The flyer "Would You Mind Donating Your Tissue to Science?" was reviewed and approved by NBAC staff. We also modified the flyer to create an advertisement that we ran in the University of San Francisco student newspaper.

2.4 Limitations of the Mini-Hearings Approach

Overall, the mini-hearing approach used in this study succeeded in providing the Commission with information about different thoughts, beliefs, feelings, and attitudes that participants held regarding the storage and use of human tissue. The approach proved effective for evaluating complex issues with a nonexpert population. The moderator was able to guide the discussion, answer specific technical questions, and respond to participant concerns. Some other approaches, survey questionnaires or group approaches such as focus groups, would not have allowed for the far-reaching discussions that occurred in the mini-hearings. It is important to note, however, that a questionnaire or focus group could have been designed for this purpose. NBAC Commissioners and staff determined that the mini-hearing approach best suited their need to quickly obtain a general feeling for the range of opinions that could be held by nonexperts. The data collected at the mini-hearings was not intended to be considered to be representative of the country as a whole. Rather, by holding mini-hearings in different areas of the country and with different types of groups, we collected a broad spectrum of information that, viewed together, could present a story of how many people might feel about these issues.

Groups were of an appropriate size so that participants shared their opinions comfortably and asked questions when necessary. Categorically, participants were not inhibited, and they actively shared their thoughts and opinions. Additionally, the hypothetical scenarios and the self-assessment forms enabled participants to better understand and contemplate the issues.

There are some limitations to the mini-hearing approach. A few of these are summarized below. Many of the limitations of focus groups could also apply to the mini-hearing approach.

- Location. First, NBAC Commissioner preferences weighed heavily in choosing mini-hearing locations and recruiting participants, due in part to the short timeframe of the project. As a result, all locations were relatively urban, and the viewpoints of people who live in more rural areas are not necessarily represented.
- Targeted Population Subgroups. Specific population subgroups were targeted in each city (e.g., African-Americans and the elderly) so that each mini-hearing would be relatively homogenous and differing viewpoints would be represented across the hearings. However, because only one mini-hearing was held for each subgroup, the ideas expressed may not be representative of the general opinion the entire subgroup population. While representation of each subgroup was not a goal in designing the approach, one or two additional mini-hearings for each subgroup would have helped ensure greater reliability and generalizability of results.
- Sample Size. Sample size was relatively small and nonrandom, meaning that the opinions of the mini-hearing participants may have been skewed by the opinions of the person who helped recruit participants. Study findings, therefore, are not generalizable across the entire American population or across any subgroup.
- Participant Focus. Participants sometimes wanted to focus on issues other than what was asked. Therefore, questions may not have been fully answered or addressed before the moderator had to refocus and move on to the next question or issue.

It is important to note that these limitations were recognized prior to the start of the project. NBAC was working under a very short timeframe and did not have the luxury, in terms of either time or funding, to develop a full-blown survey of the American population. Therefore, the mini-hearing approach was used to provide some useful input into the discussion from the perspective of nonexperts, but not to determine what the populace knows or feels about stored tissue research.

We still believe, however, that valuable information can be gleaned from the common threads that ran through all of the mini-hearings and from the unique comments that occasionally came out. We have shared many of these common themes with the Commissioners and NBAC staff in our posthearing reports. We discuss these findings in more detail in the next chapter and present a series of conclusions in Chapter Four.

3. Findings

3.1 Introduction

This chapter presents findings from the seven mini-hearings on tissue storage that were held in Virginia, Hawaii, California, Ohio, Massachusetts, and Florida. Findings regarding participants' knowledge about tissue storage are presented, followed by a discussion of their beliefs and attitudes toward tissue storage issues. These issues relate to ownership of tissue, consent for research, privacy and confidentiality, the potential stigmatization of certain groups, third party concerns regarding research on stored tissue, sponsorship of research, and safeguards for research and individuals' privacy. Findings are summarized in tabular form for each area studied to show comparisons of responses across locations and to present selected quotes from the mini-hearings that support general findings. These tables can be found at the end of this chapter.

3.2 Knowledge About Tissue Storage

At the beginning of each mini-hearing, participants were asked a number of questions to assess their knowledge of tissue storage prior to the discussion of specific issues. Groups were asked to identify what items may be classified as human tissue and ways that tissue can be collected. Participants' knowledge of the use of tissue for research was also assessed. These findings are presented in Exhibit 3-1.

Across groups, participants generally understood what constitutes human tissue and what tissue can reveal about people. Most participants had never considered what happens to tissue samples once they have been used for their initial purposes. Many believed that samples were destroyed or discarded. One exception was a participant in the Honolulu mini-hearing who knew that tissue could be stored for later retesting or for comparison purposes. Many participants stated that they had had tissue removed during a medical or surgical procedure, although not all of them recalled the issues covered in the consent forms or even if they had signed consent forms. Most were not sure whether the consent forms they had signed discussed the disposition of the tissue sample.

3.3 Beliefs and Attitudes About Tissue Storage

The following sections present findings from the mini-hearings regarding the participants' beliefs and attitudes about tissue storage issues. Their responses to hypothetical scenarios regarding issues pertaining to ownership and consent, privacy and confidentiality, stigmatization of ethnic groups, third party concerns, sponsorship of research, and safeguards for research are discussed.

3.3.1 Ownership and Consent

Exhibit 3-2 presents findings related to ownership of stored tissue and consent for research. Regarding ownership, many participants felt that if consent was provided for a procedure during which tissue was removed, then the hospital or provider owns the tissue. A few felt that the individuals from whom tissue is taken should own the tissue samples. Participants in one of the Hawaii mini-hearings made the distinction between the hospital or provider owning the sample and patients owning information that may be revealed by the sample.

Participants were also asked whether specific consent should be obtained from patients to use tissue samples for research and if they would want to consent to each potential study of their tissue. There were varying opinions across groups regarding this issue. Some felt that there was no need to specifically consent to research on their stored tissue, especially if samples are anonymous. Other participants, particularly in Cleveland and Miami, wanted to provide consent for each potential study of their tissue. Many felt that a general, one-time consent (i.e., blanket consent) for research was enough.

3.3.2 Privacy and Confidentiality

Participants were asked to share their feelings about their privacy rights and the importance of confidentiality. Issues concerning insurance companies' access to research results, linkages between names and research, and potential threats to confidentiality were discussed. Study findings on privacy and confidentiality issues are presented in Exhibit 3-3.

Overwhelmingly, mini-hearing participants felt strongly that insurance companies should not have access to results of genetic research on stored tissue samples. One exception was a participant in the Mililani, Hawaii, mini-hearing who wondered why insurance companies should not have access to such research results.

Across groups, participant views varied when considering how to balance the advantages of research into genetic diseases with possible abuses of privacy. In general, most felt positively about medical research. Participants in the two Hawaii mini-hearings and in San Francisco were vocal about the importance of medical research, and they were not concerned about potential abuses of their privacy. Participants in Cleveland and Miami were more concerned about the protection of their privacy rights. Many participants across mini-hearing locations stated that they wanted to be notified if researchers later discovered medically useful information about them from stored tissue, although some participants in Cleveland disagreed and felt that their privacy was more important. Some participants in Boston felt that it was important to define what comprises "medically useful information," since they did not consider findings that indicate propensity for disease, as opposed to the actual presence of disease, to meet their criteria for notification. San Francisco participants felt strongly that research results should be relayed by their physicians, not researchers, since they have an established relationship with their physicians.

Most participants agreed that use of anonymous tissue for research was acceptable and necessary for the public good. Moreover, most participants across groups were not concerned about the linkage of certain facts (e.g., age, sex, ethnic group) with their stored tissue, although participants in Miami wanted to ensure that their privacy was maintained. There was diversity of opinion regarding linking identifying information with stored tissue. Most participants in Hawaii, San Francisco, and Miami felt that linked research was acceptable and appropriate. Many participants in Cleveland and some in Boston did not want any links between their stored tissue and their identities.

Across locations, participants balked when asked to consider what would happen if confidentiality of research findings was not maintained. Instead, they believed that privacy and confidentiality could not be ensured due to the sophistication of computers and the commercial health care environment.

3.3.3 Stigmatization of Ethnic Groups

Mini-hearing participants were asked how they felt about researchers studying specific groups of people, such as ethnic or racial groups. These findings are summarized in Exhibit 3-4. Groups were specifically probed to consider whether such research could potentially stigmatize certain groups of people. Generally, participants did not express concern that research could stigmatize specific groups. Participants in most of the mini-hearings mentioned that there could be negative impacts from this research, such as issues with insurance coverage for the groups being studied and the potential to disseminate research findings prematurely that might later be disproved. Participants in each mini-hearing mentioned that the groups being studied generally tended to benefit from such research and gave examples such as the research on Tay Sachs disease and sickle cell disease.

3.3.4 Third Party Concerns

Mini-hearing participants responded to a number of questions regarding genetic research in which an individual's stored tissue could reveal information about family members. These findings are presented in Exhibit 3-5. Across mini-hearings, participants had mixed feelings about how and under what circumstances family members should be informed of such research. Many participants stated that they would want to be informed if

genetic research revealed information about them. Some recognized, however, that many family members might not want to know, and there were issues regarding who should inform family members of such research results (e.g., physicians, researchers, or the individuals from whom the tissue was taken). When asked if family members should be provided the opportunity to consent to a study of their relative's tissue, most felt that this would be inappropriate and difficult to achieve. Across mini-hearings, most participants did not feel that there were negative consequences from studying diseases that tend to run in families.

Participants were also asked (with the exception of Richmond, Honolulu, and Boston mini-hearings) who should make decisions about tissue storage for those who are unable to make such decisions. Categorically, participants felt that legal guardians or medical surrogates should make these decisions, and some were vocal that the preferences of the individual should be considered to the extent possible (e.g., for children).

3.3.5 Sponsorship of Research

Exhibit 3-6 presents findings on issues related to sponsorship of research. Participants discussed how they felt about researchers accessing their stored tissue and if it mattered who was sponsoring the research—i.e., a for profit company, a university, or the federal government. Most participants felt that researchers should be able to gain access to stored tissue samples, although a few believed that there were differences between research conducted by different entities. Some participants in Cleveland, Boston, and Miami felt that the profit motives of biotechnology and pharmaceutical companies differentiated their research from academic research. Most participants in Richmond, Mililani, and San Francisco felt that there were no differences between the various sponsors of research.

Across mini-hearings, it did not matter to many participants if firms could profit from research on stored tissue. A few participants in the Boston and Miami mini-hearings, however, expressed some discomfort about the profit motives of these firms. A few participants in Honolulu and Miami felt that they would want to share in profits that may result from research on their stored tissue, while overall, most participants felt it was unimportant or impractical.

3.3.6 Safeguards

Participants were asked about issues related to safeguards for research and medical information. These findings are presented in Exhibit 3-7. Across locations, people felt that researchers should have to receive approval from a committee or other entity that oversees the ethics of research prior to conducting research on stored tissue. When asked who should review and oversee research, participants identified individuals that typically comprise IRBs. In addition, some felt that representatives of the groups being studied and ethical people (regardless of profession) should be included.

When asked what group they trusted to protect medical information that is available about them, no group was categorically identified. Some participants in San Francisco, Cleveland, Boston, and Miami said that they trusted their personal physicians.

Exhibit 3-1 Knowledge About Tissue Storage

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
What is human tissue? Describe some ways that human tissue can be collected from you.	In general, participants understood what constitutes tissue, although they mentioned or asked questions about tears, milk, urine, saliva, and feces.						
What do you think your human tissue can reveal about you?	Participants understood that cells contain DNA and that DNA may reveal characteristics, disease propensity, or actual disease conditions.						
What do you think happens to blood and other tissue after it's been used for a test or removed from you?	Most participants had never considered what happens to tissue.						
		Knew that tissue was kept for retesting. Mentioned case of laboratory with errors on Pap smears.			Most participants had not thought about whether tissue could be stored and used for research.	Most participants thought that tissue samples were destroyed or disposed of after initial use.	"I would be very surprised to find out that tissue that was taken from me after it was tested wasn't just dumped."
How many of you have ever signed a consent form for medical treatment or a surgical procedure? What issues are usually discussed or covered in a consent form for medical services or a surgical procedure?	A couple in each group had had tissue removed. Not all recalled signing a consent form.						
	Group agreed it was not knowledgeable about what is or is not in a consent form.	"They won't even touch you with a ten foot pole until after you have signed it."	Doctors may explain about the procedure, but they don't explain that the tissue may be used for research. Participants felt that patients do not give true informed consent to do research.		A few had signed consent forms, but no one remembered being informed as to storage or future use of tissue.	Half of the group was unsure about whether medical/ surgical consent forms that they had signed in the past covered tissue storage.	Many in the group were unsure about whether medical/ surgical consent forms that they had signed in the past covered tissue storage.

Exhibit 3-2 Ownership and Consent

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
Who owns tissue removed from the body for medical purposes, such as in this scenario for a breast biopsy? Is it the personal property of the person from whom it was taken? Should it be considered a gift to medical research and to teaching? How long should a facility be able to keep the tissue?		Physicians, Department of Health, Patients	Hospital should own it, but agreed that patient should own the information that is revealed.	Most felt that if the consent was signed the hospital owned it.	Some thought individuals should own it, while others thought hospitals should own it after consent is given. "You know, it's mine until I say you could have it and then do what you want with it, but, you know, give that option."	Participants felt that providers should own tissue samples if consent is provided. One participant wanted to personally own her sample if the tissue was determined cancerous so she could take it to other providers for evaluation or allow it to be used for other research.	Some felt that hospitals or providers could own their tissue if was used for research purposes. One person disagreed and stated, "I feel personal about it; I feel like it's mine."
Should specific consent be obtained from the patient by the hospital to use residual tissue for research?	Consensus that use of anonymous tissue for research was acceptable and necessary for the public good.			Varying opinions about whether consent should be obtained. One individual thought a blanket consent form for all future research would be appropriate.	Some participants wanted to be aware of research done on their tissue. One assumed that research would be for finding a cure and therefore did not desire to be informed.	Members of the group had questions and concerns regarding the law, consent, and stored tissue samples. One participant wanted to consent for specific research on her stored tissue to ensure that it is used appropriately.	Some participants wanted to consent to specific research on their stored tissues. Others felt that general, one-time consent for research was enough. One person felt it was difficult to consent for research when the potential uses of the research are not known. Another questioned the practicality of obtaining consent for research years after tissue samples are taken.

Exhibit 3-2 Ownership and Consent *continued*

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
If the opportunity arises for research to be conducted on your stored [tissue], would you want to be able to specifically consent to or decline to participate in that research study? Would it make a difference if the research is done with or without any identifying information about you?	While a number of members in the group stated that they have no real concerns about the use of their own stored tissue for research, they believed that other people do.	Most did not care whether research was done on their stored tissue without their active consent. Most felt that additional consent for research on their stored tissue was not needed: "There's no need, because it might just, you know, hold things up." One person disagreed: "And maybe it's a manner or a type of activity that I don't agree with philosophically, so I would like to be told so maybe I could say yes or no don't use it in that manner."	Some participants stated that researchers should not have to obtain additional consent to do research on stored tissue.	Opinions varied regarding the provision of consent for research on human tissue samples. One person thought that a blanket consent form for all future research would be appropriate. "Maybe you should sign a release form, a blanket release form, for giving tissue so in the event that you do have any surgeries—sort of like a will."	Most participants wanted to be able to specifically consent to research.	One participant wanted to consent for specific research on her stored tissue. Others were not concerned. One person stated, "If you consent to have some part of your body given up, and in doing that you are helped, you are cured, they find out what you have, all right, why do you care where it goes?"	Some wanted to specifically consent to research. Others had no concerns about research if they had given their general, one-time consent for future research.

Exhibit 3-3 Privacy and Confidentiality

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
How would you feel if your insurance company had access to the results of the research on your grandfather?	Participants were somewhat concerned about the potential for insurance companies to use this type of information to deny or increase the cost of coverage.	Firmly believed that insurance companies should not have access to their records. "Is it a criteria that they have to know just what you are made up of? I mean, every detail all the way down to your tissues in order for them to cover you or not cover you?"	Most participants did not want insurance companies to have access to information that might be revealed from their stored tissue. One participant asked whether keeping information from insurance companies constituted fraud.	There may be concerns about insurance companies finding out information if physicians are involved in the process.	The group felt strongly that insurance companies should not have access to findings.	The group felt that insurance companies should not have access to findings.	Participants were very concerned about the protection of their privacy rights. They felt strongly that insurance companies should not have access to research on stored tissue.
How do you balance the advantages of research into genetic diseases against possible abuses of your privacy?	Contemplated need for medical commission to ensure that medical research is ethical (similar to the FCC). Had no real concerns about use of their stored tissue, but thought other people did.	Participants were not concerned about privacy and confidentiality.	In general, participants valued research and were reluctant to impose restrictions that would impede medical research.	In general, participants valued research and were reluctant to impose restrictions that would impede medical research.	Some felt privacy was more important than their desire to be informed if future research revealed information about them.		Participants felt that checks and balances needed to be in place to ensure that there were no abuses to privacy.
How would you feel about the hospital pathology department keeping your [tissue] without directly telling you? What if the sample were totally anonymous, without any link to your name?	Agreement that use of anonymous tissue for research was acceptable and necessary for the public good.	"What's the big deal about taking the tissue out of a human body and studying it without their knowledge?"	See above.	See above.	Agreement that use of anonymous tissue for research was acceptable and necessary for the public good.		Most had no concerns about anonymous research, although some wanted to specifically consent to research, even if it is anonymous.

Exhibit 3-3 Privacy and Confidentiality *continued*

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
Is it OK that other facts about you may be known to the researcher, such as age, sex, and ethnic group? How crucial is it for confidentiality of your relationship to the tissue specimen be maintained? (Confidentiality here means that your name is stored with your tissue, but is not given out.)	Some argued that there should be no discussion between employers, insurers, and researchers based on identifiable information.	Participants in the group were not concerned about privacy and confidentiality issues and their stored tissues.	Participants felt that both anonymous and linked research are acceptable.	Participants wanted their name linked to stored tissue, so that they would be informed of relevant findings. On dissenter said there should be no links. “The sample should just be generic.”	Other facts were recognized as being important in research and were not a concern.	Participants were not concerned about the linking of their personal characteristics with their stored tissue.	Participants were not concerned about research that links personal characteristics to stored tissue. Participants were adamant that they wanted their privacy maintained.
What do you think would happen if your name was mistakenly given out?	Many participants did not think that privacy and confidentiality could be ensured in today's commercial health care environment						
					Participants stated that there is a need to ensure that tissue is not misused. One participant said the Tuskegee Experiment was not so long ago, while another countered that researchers today do not resemble the Tuskegee researchers.		Participants were cynical about whether privacy was really protected anyway in “the age of computers.”

Exhibit 3-3 Privacy and Confidentiality *continued*

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
What if, during later research, a researcher finds out medically useful information about you from a stored tissue sample (for example, that you might benefit from a new drug)? Would you want the researcher or a physician to notify you?	Most participants would want to be notified.	All members of the group stated that they would want to know if a researcher discovered relevant information about them from their tissue. Links to stored tissue with personal identifiers were necessary for this purpose.	Most members of the group stated that they would want to be informed if a researcher discovered clinically relevant information about them from their stored tissue or the tissue of family members.	Some participants felt that if research revealed information about them then they would want to be informed. Others only wanted to know if they could act on the information in some way. Several participants didn't think the researcher should be burdened with having to inform tissue donors of results.	Some participants would want to be informed, but others agreed that indirect benefits of research might be enough and that loss of privacy would not be counterbalanced by personal benefit.	Some wanted to be notified if research revealed relevant information about them or their family members. Others did not want to hear about research findings that indicate propensity for disease.	
How would you feel if information about your stored tissue was linked to your medical history? Should there be a time limit to the linkage after which identifying information is deleted? If yes, how long? Would you feel more comfortable about the sample's link to your medical history if it was associated with a scrambled identifier? If yes, who should have access to the key to the scrambled identifier?	The group actively contemplated the advantages and disadvantages of linking individuals and their medical history to stored tissue. Some in the group differentiated between performing research at one point in time versus the need to track research subjects over time.	All agreed that they thought that links to stored tissue with personal identifiers were necessary.	Most felt that both anonymous research and research that is linked to individuals' names was appropriate.	Given the choice, participants wanted links between tissue samples and their identity so that they could be informed of relevant findings. One person disagreed, stating, "I think once you sign the consent form, they should throw your name away."	Some participants felt they did not want to have links from their stored tissue to their names or medical record.	There were mixed feelings among participants regarding whether they wanted links between their stored tissue and their medical history.	Most felt that both anonymous research and research that is linked to individuals' names was appropriate.

Exhibit 3-4 Stigmatization

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
How do you feel about a researcher studying specific groups of people, such as ethnic or racial groups? Do you see any positive or negative issues from this kind of research (for example, the potential for stigmatizing certain groups if research points out higher incidence of certain diseases in the ethnic group versus the positive effect of being able to screen and provide better treatments for the group).	Members of the group contemplated both potential positive and negative implications from performing research on specific groups such as ethnic or racial groups. While one person pointed out that there is no history of "disease discrimination" among employers and insurers in relation to diseases commonly linked to certain groups (e.g., Tay Sachs Disease), another mentioned there is a history of discrimination related to diseases linked to specific groups (e.g., AIDS).	Members were not concerned about the potential for stigmatizing certain ethnic or racial groups or families with research on stored tissue. One participant stated, "So what's the big deal about taking the tissue out of a human body and studying it without their knowledge?"	Some thought that there could be negative impacts from studying diseases that could be linked to certain ethnic groups, and cited the example of Japanese sterilization of the mentally retarded. Participants mentioned that insurance companies, employers, and the government could misuse this information. Members considered how to balance the importance of research on specific groups versus the potential to misuse the information obtained from it. Participants viewed research on specific groups as positive, and gave the example of research on sickle cell disease.	Participants stated that there could be negative implications from researching specific groups. One person felt that there was the potential to disseminate information to people prematurely since the body of knowledge about diseases continually evolves. Another stated, "You don't want to create a scare on the populace nor do you want to create a scare among health care providers as well." Potential employment discrimination were also mentioned. While participants acknowledged these potential implications, they were not concerned about the stigmatization of groups due to such research.	There was disagreement regarding research on specific ethnic or racial groups. One participant felt there would be negative consequences from research that publicized that a disease belongs to certain groups. Another person said that information gained from such research is valuable and that ethnic and racial groups are better off when more is known about diseases that may affect them.	Participants were not concerned about research conducted regarding certain ethnic groups.	The group discussed that there were potential positive and negative impacts from conducting research that focuses on certain ethnic groups. Some thought that such research was positive because it could help the group. One participant stated that there could be issues with insurance coverage based on this research. One participant stated that she is an Ashkenazi Jew and that confidentiality and privacy were very important to her.

Exhibit 3-5 Third Party Concerns

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
When findings from a study of human tissue reveal something about family members, do you think the family members should be informed? Is the issue any different if the tissue comes from a person who is alive? Can you think of reasons why family members shouldn't be informed?	There were mixed feelings as to whether and under what circumstances relatives should be informed. No distinction if person is alive. It would create strife if some wanted to be informed and others did not.	All participants agreed that family members should be informed if genetic research reveals information about them.	One participant was concerned about doing research that could reveal information about family members. Others were not concerned. Most participants said they would want to be informed.	Participants were somewhat concerned about family information. Some of them were concerned with who would pass on the information. A few participants didn't see a need for researchers to share genetic information if the tissue donor was dead.	Most participants felt that family members have a right to know if research reveals something about them, though one remarked that, "And perhaps some of us don't want to know that."	Participants felt positively about research that could benefit family members. Participants wanted to tell family members if research on their stored tissue revealed information about family members.	Some felt strongly that family members should be informed about research results, while others felt that their family members might not want to know about the existence or genetic propensity for a disease. One participant stressed that there are emotional considerations when families are involved.
Should family members be provided the opportunity to consent to a study of their relative's tissue if there is the potential that they could be linked to findings?	In general, most participants agreed that this would be operationally difficult.						
	There were mixed feelings about who should consent for research.				No.	No.	Participants had mixed feelings about research on stored tissue that may reveal information about family members.
Are there any potential negative consequences from studying diseases that may run in families? If yes, what are they?	Participants found it difficult to articulate any negative consequences specific to families.						
					Potentially false [positive] results and heightened anxiety among family members especially if at issue is propensity versus actual disease.	No.	One participant felt that her family members might not want to know if there was a familial history of a disease, such as Alzheimer's, which has no cure.

Exhibit 3-5 Third Party Concerns *continued*

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
For those who are unable to make decisions about their own human tissue storage (e.g., someone in a coma, the mentally impaired), who do you think should be given the authority to make those decisions?	Not asked.	Not asked.	Participants thought that a legal guardian should be given the authority to make decisions about tissue storage for those who are unable to make such decisions.	Participants stated that decisions about tissue storage and research should be made by legal guardians. One person suggested that the preferences of people with limited competence should be taken into account whenever possible (e.g., for children).	Participants thought that a close relative or legal guardian would be asked in these cases.	Not asked.	Participants felt that medical surrogates should make decisions about human tissue storage for those who are unable to make such decisions. They also felt that individuals' wishes should be considered.

Exhibit 3-6 Sponsorship of Research

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
Should a medical researcher be able to access stored tissue if it is available, such as your neighbor's blood samples?	Some said they were not concerned about the use of their stored tissue for research, although they thought that other people would be. Many thought that research using anonymous tissue is acceptable and appropriate.	Participants said that research on human tissue was needed.	Yes.	Yes.	Yes.	Participants felt positively about research conducted on stored tissue.	Yes.
Would it be any different if the researcher was a professor at a medical school versus a researcher for a drug or biotechnology company? Would it matter if the sponsor of the research were the federal government or a drug company?	Participants felt there was no distinction.	Most believed that research conducted on the university level or by the public sector was for the public good.	Participants were not concerned about whether research was sponsored by the government or by private firms.	Two felt that academic- or government-sponsored research was more valid than research sponsored by a for-profit or biotechnology firm. Others felt positively about for-profit firms.	Some felt there is a difference between research conducted in a university setting versus a for-profit company. Others felt that if research is used to find better treatments, then sponsorship does not matter.	One individual felt positively about using stored tissue for health research but was concerned about its use for cosmetic research. Some had concerns about the ethics of pharmaceutical company research.	Participants saw for-profit and academic research as different, although they felt positively about both types. The group saw no difference between government and privately sponsored research.
How do you feel about a company profiting from another person's stored tissue? Do you feel that the company has an obligation to tell the research subjects? Should the research subjects be able to share in the profits? If yes, would you trade your privacy for the potential profits from the research?	It did not matter to most participants whether researchers or drug companies could profit from research using stored tissue, although they would object to tissue samples being bought and sold.	Participants thought that if private companies profited from using stored tissue, the companies should have to pay for the tissue. One person argued, however, that even research by private companies benefits society, so there was no need for payment.	Most members of the group were not concerned about firms profiting from research on stored tissue samples.	When asked if research subjects should share in profits from human tissue research, one participant said no, stating, "Our names and demographics are sold everyday, and we don't profit from that."	It did not matter to most participants whether researchers or drug companies could profit from research.	There were mixed feelings regarding whether organizations should profit from research on stored tissue.	Participants had mixed feelings about individuals sharing in profits that result from research on their stored tissue.

Exhibit 3-7 Safeguards

ISSUE	**Richmond, VA 9/16/97**	**Honolulu, HI 9/25/97**	**Mililani, HI 9/29/97**	**San Francisco, CA 10/1/97**	**Cleveland, OH 10/21/97**	**Boston, MA 10/23/97**	**Miami, FL 11/5/97**
Do you think researchers should require approval by a committee like this that oversees the ethics of research, before doing the research on the stored tissue?	Some thought that an independent commission is needed to ensure that medical research is ethical.	Yes.	Yes.	One person thought that additional review might stifle the research initiative.	Participants agreed that researchers should have to receive approval from an IRB.	Yes.	Participants felt that checks and balances are needed to ensure that research is conducted ethically.
Who do you think should serve on a committee that oversees research? (members of a community group, physicians, hospitals/institutions, other researchers, representatives of the groups being studied, the government)		Researchers, doctors, and medical lawyers should oversee research. IRBs should include members with backgrounds in philosophy, bioethics, and psychology; elected officials; clergy; and representatives from groups being studied.	Those who would benefit and those who would not profit from the research should be represented, as should the FDA, the AMA, someone from outside the research organization, and someone who is knowledgeable about medicine.	Two participants said those who conduct or would benefit from the research should not be on an IRB. Many said that membership should be as diverse as possible. One person said that those who are trained in or have knowledge of ethics should be included.	IRB members should include ethical researchers and exclude members with political motivations or those affiliated with the research sponsor. If research is conducted on ethnic or racial groups, members of those groups should be represented.	An IRB should include ethical people who have knowledge about ethics, individuals from various disciplines, representatives from different religions, and nurses. Politicians and lawyers should be excluded.	IRBs should include individuals with high ethical standards and integrity, individuals with ethics or medical backgrounds, representatives from the general population, theologians, and people with legal backgrounds.
Who do you trust to protect medical information that is available about you and your human tissue?	No group was nominated who categorically could be trusted.						
	Some stated that legal restrictions were needed to limit how research can be used and/or confidential information disclosed.			Personal physician.	Group members stated that they trusted physicians and surgeons to protect medical information that is available about them.	Participants stated that they trusted their physicians and hospitals to protect their medical information, although one person stated, "I wouldn't say I trust them 100 percent."	Some said they trusted their doctors to protect medical information; those who had participated in research studies said they trusted the researchers and the sponsoring institutions to do so.

4. Conclusions

4.1 Introduction

This chapter presents conclusions based on findings from the mini-hearings on tissue storage issues. Conclusions are presented regarding the participants' knowledge, beliefs, and attitudes about tissue storage. We have also provided a discussion of some potential directions for future research in this area.

4.2 Knowledge About Tissue Storage

The mini-hearings indicated that participants were generally knowledgeable about what constitutes human tissue. However, many people are not aware that tissue may be stored and later used for research. Greater efforts to educate the public and increase awareness regarding uses of stored tissue may be desirable.

4.3 Beliefs and Attitudes About Tissue Storage

Several conclusions resulted from participants' beliefs and attitudes about tissue storage. These conclusions are discussed below in sections on consent and ownership, privacy and confidentiality, stigmatization of ethnic groups, third party concerns, sponsorship of research, and safeguards for privacy and research.

4.3.1 Consent and Ownership

Conclusions regarding consent for research and ownership issues:

- Participants did not fully understand the consent process. They often feel pressured to consent to procedures without fully understanding the forms they are signing because of time pressures or fear of being denied care.
- The disposition of tissue is not routinely discussed with patients.
- Participants wanted to retain the right to specifically consent to future use of their tissue, but usually they were willing to relinquish ownership at the time of consent.
- Consent for the future use of stored tissue should be separate from consent for the procedure.

4.3.2 Privacy and Confidentiality

Conclusions regarding participants' views on privacy and confidentiality:

- Participants were comfortable with the confidential use of stored tissue including linkages with demographic information such as sex, age, and ethnic group.
- Participants did not want insurance companies to have access to findings from research on stored tissue.
- There is a need for public education regarding the management of sensitive medical information and the protection of privacy and confidentiality in research.

4.3.3 Stigmatization of Ethnic Groups

Conclusions pertaining to the potentially stigmatizing impact of research on specific ethnic:

- Participants were not concerned about the stigmatization of ethnic groups, although they recognized the potential for this to happen.
- Participants felt that the potential benefits of group-specific genetic research outweighs any potential harm.

4.3.4 Third Party Concerns

Conclusions regarding the rights of family members and those with limited competence regarding tissue storage issues:

- Participants believed it is the right of the research subject to choose whether or not to disclose to anyone, including family members, findings from research on their stored tissue.
- Participants believed that the legal guardian should be responsible for providing consent for persons with limited competence to do so for themselves.

4.3.5 Sponsorship of Research

The following conclusion pertains to sponsorship of research:

- Participants saw the benefit of genetic research to society regardless of who sponsors or who conducts the research.

4.3.6 Safeguards

Conclusions regarding safeguards for privacy and research:

- Participants did not have an abiding faith in any one group to protect medical information.
- Participants identified desirable categories of IRB members similar to those typically found on IRBs.
- Participants felt that IRBs should include at least one representative of the group being researched.

4.4 Directions for Future Research

While this project was not designed to draw conclusions about how the public in general feels about stored tissue research, in this report, we have identified many common themes that surfaced time and again during the mini-hearings. NBAC may want to consider commissioning a formal survey to determine if any of the findings of the mini-hearings are generalizable to the American public. A survey could be designed using the same basic research framework that was developed for the mini-hearings. Of course, questions would need to be reworked to be suitable for a questionnaire and to ensure that they captured the information that is most important to the Commission. In order to ensure that the results would give a true measure of the knowledge, beliefs, and attitudes of the general public, the study would have to be designed to collect responses from a sample that is widely representative of our citizenry.

Based on feedback gleaned from the mini-hearings, two additional areas have been identified for potential future research and evaluation by NBAC. First, the consent process was not well understood by the general public. Many participants were not aware of the content of procedure consent forms, and some felt that they had no choice but to sign consent forms. It is suggested, therefore, that the following topics could be evaluated regarding the consent process:

- the content of treatment and research consent forms at different institutions,
- the interaction between providers and patients concerning consent,
- appropriate timing of consent,
- patients' comprehension of consent issues, and
- whether separation of consent to use stored tissue increases comprehension and satisfaction with the process.

In addition, it is recommended that public education materials be developed for NBAC concerning the management of information and the protection of the public's privacy and confidentiality in research. As mini-hearing participants contemplated the potential uses of stored tissue, they raised questions and had concerns based on their heightened awareness. The general public will continue to have questions and concerns regarding their privacy protections as technology in medicine continues to advance. Therefore, NBAC needs to be able to readily advise the public regarding these issues.

APPENDIX A

Moderator Guide

Issues in Human Tissue Storage
Mini-Hearing Moderator Guide

These questions focus on what you know about human tissue storage and medical research.

1. What is human tissue? Describe some ways that human tissue can be collected from you.
   - How many of you have had a surgical procedure in which something was removed from you (e.g., appendectomy)?
   - How many of you have ever participated in a research study as a research subject?
   - How many of you have ever given a blood sample?

2. What do you think your human tissue can reveal about you?
   - DNA
   - genetic predisposition for certain diseases
   - body's reaction to and/or the existence of diseases and organisms

3. What do you think happens to blood and other human tissue after it's been used for a test or removed from you?

4. How many of you have ever signed a consent form for medical treatment or a surgical procedure? What issues are usually discussed or covered in a consent form for medical services or a surgical procedure?

The following questions ask how you feel about a number of issues regarding human tissue storage and research. Questions will be based on how you feel about certain hypothetical scenarios.

5. *Your friend goes to the doctor because she finds a small lump in her breast. The physician removes the lump and studies the tissue (i.e., performs a biopsy) to determine if it is cancerous. The study reveals that the lump is cancerous. Some of the tissue taken from your friend is kept by the hospital's Pathology Department as part of routine policy. Sometimes the laboratory uses tissue samples to audit the accuracy of the department's procedures. Also, the tissue might be useful even years later should your friend have a similar problem again. The hospital is required for clinical and medicolegal reasons to store a small amount of tissue. In this instance, a larger sample is stored than is needed.*
   - Who owns tissue removed from the body for medical purposes, such as in this scenario for a breast biopsy?
   - Is it the personal property of the person from whom it was taken?
   - Should it be considered a gift to medical research and to teaching?
   - How long should a facility be able to keep the tissue?
   - Should specific consent be obtained from the patient by the hospital to use residual tissue for research?

6. *Your grandfather, who died in 1956, was treated at a university hospital. During his autopsy, the pathologist decided to keep and preserve slides of his brain tissue. Recently, physicians at the hospital have studied the brain tissue, and they have determined that he had a disease that tends to run in families, although it may skip one or more generations. Therefore, the disease could potentially affect you, your brothers and sisters, your cousins, and future generations of your family.*

   - When findings from a study of human tissue reveal something about family members, do you think the family members should be informed?
   - Is the issue any different if the tissue comes from a person who is alive?
   - Can you think of reasons why family members shouldn't be informed?
   - Should family members be provided the opportunity to consent to a study of their relative's tissue if there is the potential that they could be linked to findings?
   - If an individual's tissue can reveal genetic information about someone else (such as a parent, child, or sibling), do you feel that the third party has any control of the tissue sample?
   - Are there any potential negative consequences from studying diseases that may run in families? If yes, what are they?
   - How would you feel if your insurance company had access to the results of the research on your grandfather?
   - How do you balance the advantages of research into genetic diseases against possible abuses of your privacy?

7. *You are in the hospital and your physician tells you that you need to have your gallbladder removed. He discusses the procedure with you and you sign a consent form for the surgery. Afterwards, you experience a speedy recovery and go home. Without your direct knowledge, the hospital pathology department decided to keep your gallbladder. Later, a researcher approaches the department about a gallbladder study and asks for access to stored gallbladder tissue.*

   - How would you feel about the hospital pathology department keeping your gallbladder without directly telling you?
   - What if the sample were totally anonymous, without any link to your name? An anonymous sample would be one that is totally and irreversibly unlinked to your name.
   - Would it make a difference if your name or other identifying information was linked to your gallbladder for storage purposes?
   - How important is it, for research like this, that all identifying information has been stripped from the tissue sample?
   - How would you feel if your identity was linked to your gallbladder during storage, but the person conducting research was unaware of your identity?
   - Is it OK that other facts about you may be known to the researcher, such as age, sex, and ethnic group?
   - How crucial is it for confidentiality of your relationship to the tissue specimen be maintained? (Confidentiality here means that your name is stored with your tissue, but is not given out.)
   - What do you think would happen if your name was mistakenly given out?
   - If the opportunity arises for research to be conducted on your stored gallbladder, such as in this scenario, would you want to be able to specifically consent to or decline to participate in that research study? Would it make a difference if the research is done with or without any identifying information about you?
   - What if, during later research, a researcher finds out medically useful information about you from the gallbladder sample (for example, that you might benefit from a new drug)? Would you want the researcher or a physician to notify you?

- How would you feel if information about your stored tissue was linked to your medical history? Should there be a time limit to the linkage after which identifying information is deleted? If yes, how long? Would you feel more comfortable about the tissue sample's link to your medical history if it was associated with a scrambled identifier? (A scrambled identifier would use numbers and letters to identify you. A key that matches the identifier to the person would be kept apart from the medical information.) If yes, who do you think should have access to the key to the scrambled identifier?

8. *While visiting his physician, a blood sample was taken from your neighbor as part of a routine check-up. As is routine policy, the laboratory retained his blood sample. A few months later, a medical researcher approaches the laboratory with a request for access to stored blood samples for individuals with certain characteristics (sex, age, ethnic group). Your neighbor's stored blood sample happens to meet the criteria for the researcher's study.*

   - Should a medical researcher be able to access stored tissue if it is available, such as your neighbor's blood samples?
   - Would it be any different if the researcher was a professor at a medical school versus a researcher for a drug or biotechnology company?
   - Would it matter if the sponsor of the research were the federal government or a drug company?
   - How do you feel about a company profiting from another person's stored tissue? Do you feel that the company has an obligation to tell the research subjects? Should the research subjects be able to share in the profits? If yes, would you trade your privacy for the potential profits from the research?
   - In this scenario, recall that the researcher wanted to access stored samples for individuals with certain characteristics. Let's say that the researcher was doing a study of people of Asian descent. How do you feel about a researcher studying specific groups of people, such as ethnic or racial groups? Do you see any positive or negative issues from this kind of research (for example, the potential for stigmatizing certain groups if research points out higher incidence of certain diseases in the ethnic group versus the positive effect of being able to screen and provide better treatments for the group).

9. *Think about any of the scenarios we have been discussing. Researchers want to use stored tissue for medical research. Now, researchers must present their proposed research to a board that reviews protections of human subjects from physical, social, and economic harm including protection of privacy. Often these review boards consist of doctors, lawyers, religious leaders, ethics experts, and community members.*

   - Do you think researchers should have to receive approval by a committee like this that oversees the ethics of research, prior to doing the research on the stored tissue?
   - Who do you think should serve on a committee that oversees research? (members of a community group, physicians, hospitals/institutions, other researchers, representatives of the groups being studied, the government)
   - Who do you trust to protect medical information that is available about you and your human tissue?
   - For those who are unable to make decisions about their own human tissue storage (e.g., someone in a coma, the mentally impaired), who do you think should be given the authority to make those decisions?

10. Let's take some time now to look back on the self assessment forms you completed at the beginning of the forum to see if any of your thoughts and feelings have changed about tissue storage.

APPENDIX B

Mini-Hearing Protocol

Mini-Hearings on Issues in Human Tissue Storage
Mini-Hearing Protocol

1. Welcome, Project Overview, and Introductions

   - The moderator will self introduce and make the participants comfortable.
   - The moderator will ask participants to complete a self-assessment form.
   - The moderator will describe the project and its purpose. The moderator will explain that the purpose of the project is to provide NBAC with information about the public's understanding, beliefs, and feelings about genetic tissue issues. The moderator will explain that findings will be used by NBAC to assist in its development of a report to the President and the Nation, due in 1998.
   - The moderator will introduce the attending Commissioner, NBAC staff, and CHPS staff.
   - Participants will self-introduce.
   - The moderator will describe the format for the mini-hearing and provide ground rules for discussion (e.g., all participants are encouraged to talk, only one person speaks at a time, respect for differing viewpoints, no right or wrong answers).
   - Mini-hearing participants will be encouraged to ask questions when clarification is needed.
   - The moderator will explain that the mini-hearing will last approximately 90 minutes, followed by public comment.

2. Mini-Hearing Discussion

   - The moderator will lead the discussion using the moderator guide.
   - The moderator will ask for clarification and probe for additional information when appropriate.
   - The mini-hearing will be audio taped. Audio-tapes will be transcribed upon completion of the mini-hearing. Note-takers will also record key points of the discussion.

3. Closure

   - The moderator will ask mini-hearing participants if they have any questions or additional comments. The moderator will answer questions as appropriate.
   - Upon completion of the mini-hearing, the moderator or a Commissioner will invite the public to comment. Individuals will be asked to limit their comments to five minutes and/or to submit written comments to NBAC.
   - The moderator will refer participants to NBAC should participants or the public have additional questions or comments about the project.
   - The moderator will adjourn the mini-hearing.

APPENDIX C

Self-Assessment Tool

National Bioethics Advisory Commission
Self-Assessment Tool for Group Discussion Participants

Thank you for agreeing to participate in a discussion of issues dealing with stored body tissues. Please take a few minutes to fill out these questions. There are no right or wrong answers and you will not be asked to give the completed tool to anyone. We are interested in your thoughts and feelings about stored human tissue, research uses of stored tissue specimens, and what concerns you may or may not have about privacy and informed consent in genetic research.

We are especially interested in whether or not your thoughts and feelings change as a result of the discussion we will be having. Towards the end of the discussion you will be asked to review these questions again and enter any changes to your previous answers. Then we will spend a few minutes discussing the changes that participants in the discussion group made.

Respond as best you can to each question, checking your answer in the row marked "before discussion." After you have finished the "before" questions, put these papers away until later when you will be asked to check answers in the row marked "after discussion." Thank you.

Self-Assessment Questions

1. Have you ever provided a tissue sample which might have ended up being used in medical research?

Before Discussion: YES ___ NO ___ DON'T KNOW ___
After Discussion: YES ___ NO ___ DON'T KNOW ___

2. If your answer to the first question above was "yes", do you know or have you ever had any concerns about the potential uses which might be made of your tissue sample?

Before Discussion: YES ___ NO ___ DON'T KNOW ___
After Discussion: YES ___ NO ___ DON'T KNOW ___

3. Suppose you were ill and went to a doctor who asked you to give a tissue sample. In general, for which of the following purposes would it be O.K. with you that the tissue sample be used? (Place a check in the box next to each purpose indicating whether it is O.K., Not O.K., or you Don't Know.)

Before Discussion: PURPOSE	O.K.	Not O.K.	Don't Know
a) for treating me for my specific disease.			
b) for determining if I may be especially susceptible to another disease.			
c) for medical research on the disease that I have, but which may or may not ever benefit me.			
d) for medical research on genetic causes of diseases among my family.			
e) for medical research on genetic causes of diseases in general.			

After Discussion: PURPOSE	O.K.	Not O.K.	Don't Know
a) for treating me for my specific disease.			
b) for determining if I may be especially susceptible to another disease.			
c) for medical research on the disease that I have, but which may or may not ever benefit me.			
d) for medical research on genetic causes of diseases among my family.			
e) for medical research on genetic causes of diseases in general.			

4. Please indicate how much you trust each of the following people or organizations to protect your privacy and rights regarding the uses of your tissue samples and the information that can be learned about you by studying the samples. Place a check in the box next to each group indicating whether your degree of trust is low, medium, or high.

	Before Discussion			*After Discussion*		
Person or Organization	Low Trust	Medium Trust	High Trust	Low Trust	Medium Trust	High Trust
a) doctors						
b) the government						
c) the hospital research ethics committee						
d) lawyers						
e) religious organizations						

APPENDIX D

Mini-Hearing Summary Reports

Mini-Hearing Report

Richmond, Virginia, September 1997

Mini-Hearings on Issues in Human Tissue Storage
Report on Pilot Test— Richmond, Virginia—September 1997

Overview

The Center for Health Policy Studies (CHPS) is assisting NBAC to explore public knowledge, beliefs, and feelings about human tissue storage issues. Six mini-hearings will be held across the country to ascertain what the American public believes and feels about uses of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Findings from the mini-hearings will be used by NBAC as it develops its reports to the President and the nation.

In September 1997, CHPS piloted questions and protocols for the mini-hearings on the campus of Virginia Commonwealth University (VCU) in Richmond, Virginia. Eleven representatives from the community actively participated in the mini-hearing, which lasted 90 minutes. A moderator from CHPS led the discussion. Questions and hypothetical scenarios were used to prompt the group to discuss their thoughts and feelings about issues regarding human tissue storage. The discussion addressed ownership, privacy, sponsorship of research, notification of affected relatives, and potential stigmatization of groups or individuals. In addition, each participant completed a self-assessment prior to and following the discussion to see if his or her thoughts and feelings about human tissue storage changed as a result of the discussion. Self-assessments were used for discussion purposes only and were not collected. The general public was invited to observe the discussion, and time was allotted for public comment following the mini-hearing.

Summary of Substantive Findings

The participants in the Richmond group actively shared their thoughts and opinions about human tissue storage. The mini-hearing stimulated the thoughts of the group, and all participants acknowledged after the mini-hearing that their ideas and opinions about human tissue storage had evolved and changed over the course of the discussion. It was notable that participants in the group raised a number of issues regarding privacy, confidentiality, and disclosure of information to health insurers. Summarized below are several general findings from the mini-hearing:

- Participants in the group demonstrated that they were knowledgeable about what items qualify as human tissue and what it can reveal.
- A number of individuals in the group stated that they had never considered that human tissue would be stored after being used for a test or after removal.
- The group was not knowledgeable about what is (and what is not) generally included in a medical or surgical consent form.
- There was consensus that use of anonymous tissue for research was acceptable and necessary for the good of the public.

- Members of the group contemplated both potential positive and negative implications from performing research on specific groups such as ethnic or racial groups. While one person pointed out that there is no history of "disease discrimination" among employers and insurers in relation to diseases commonly linked to certain groups (e.g., Tay Sachs Disease), another mentioned there is there is a history of discrimination related to diseases linked to specific groups (e.g., AIDS).
- Participants questioned whether confidentiality of medical records could be ensured in today's commercial health care environment.
- Members of the group contemplated the need for an independent commission (similar to the FCC) to ensure that medical research is ethical, while others stated that legal restrictions were needed to limit how research can be used and/or confidential information disclosed.
- It did not matter to most participants whether researchers or drug companies could profit from research using stored human tissue, although they would object to tissue samples being bought and sold.
- The group actively contemplated the advantages and disadvantages of linking individuals and their medical history to stored tissue. Some in the group differentiated between performing research at one point in time versus the need to track research subjects over time.
- While a number of members in the group stated that they have no real concerns about the use of their own stored tissue for research, they believed that other people do.
- There were mixed feelings regarding who should consent for research related to the study of familial diseases and whether (and under what circumstances) relatives should be notified.

Overall, members of the group expressed that they were happy to provide their input regarding human tissue storage. Individuals in the group stated that, although they are not currently worried about how human tissue is stored and used, there is the potential for misuse in the future with changes in the health care system. As one person summarized, "I'm glad someone is thinking of this."

Process Findings

Recruiting Participants

Participants in the group were identified and personally invited to participate in the mini-hearing by someone who was interested in human tissue storage issues. Participants also received a letter of invitation to the mini-hearing and a follow-up phone call the day before the mini-hearing. It is felt that these strategies were essential to the successful turnout of the mini-hearing members.

Advertising to the Public

Advertising flyers for the mini-hearing were distributed in residential areas around Richmond and were posted on campus bulletin boards around VCU. The mini-hearing was also advertised on a public radio station on the morning of the mini-hearing. In spite of these efforts, only one representative from the general public came to the mini-hearing, likely due to the short time period between the planning of the mini-hearing and its completion. It is felt that advertising in community newspapers and with specific community organizations will help to increase public turnout for future mini-hearings.

Holding the Mini-Hearing

In general, the mini-hearing was completed in an effective manner. Suggestions for improving the delivery of future mini-hearings are as follows:

- The hypothetical scenarios (without the questions that follow) should be provided to mini-hearing participants. This will allow group members to refer back to the scenarios after contemplating specific issues. Scenarios should also be written on flip charts so that the public will be able to refer to the scenarios.

- Self-assessment forms should be made available to the public so that they will be able to follow mini-hearing members' discussion of their forms.
- Question number four on the self-assessment form should be rephrased for clarity (see attached form for the revised question).
- The availability and use of findings from the mini-hearings should be discussed with participants and the public.

Modifications to the Moderator Guide

Based on issues that emerged from the pilot mini-hearing, the following modifications will be made to the moderator guide:

- There will be additional discussion and education about what is written in medical and surgical consent forms.
- Questions regarding the linking of stored tissue to individuals' medical histories will be added. Issues related to the use of scrambled identifiers for individuals will be discussed including who, if anyone, should keep or have access to the key.
- Participants will be educated about who typically sits on an IRB.

Mini-Hearing Report

San Francisco, California, October 1, 1997

Mini-Hearings on Issues in Human Tissue Storage
Mini-hearing Report—San Francisco, California—October 1, 1997

Overview

The Center for Health Policy Studies (CHPS) is assisting NBAC to explore public knowledge, beliefs, and feelings about human tissue storage issues. Six mini-hearings will be held across the country to ascertain what the nonexperts participants believe and feel about uses of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Findings from the mini-hearings will be used by NBAC as it develops its reports to the President and the nation.

On Wednesday, October 1, 1997, CHPS held a mini-hearing on the campus of the University of California, San Francisco. Nine individuals from the San Francisco area participated in the mini-hearing which lasted two hours. A moderator from CHPS led the discussion. Questions and hypothetical scenarios were used to prompt the group to discuss their thoughts and feelings about issues regarding human tissue storage. The discussion addressed ownership, privacy, sponsorship of research, notification of affected relatives, and potential stigmatization of groups or individuals. In addition, each participant completed a self-assessment prior to and following the discussion to see if his or her thoughts and feelings about human tissue storage changed as a result of the discussion. Self-assessments were used for discussion purposes only and were not collected. The general public was invited to observe the discussion, and time was allotted for public comment following the mini-hearing.

Summary of Substantive Findings

The participants in the group actively shared their thoughts and opinions about human tissue storage. The group had five women participants, most of whom were in their 20s and 30s. Three of the women were white, one was Hispanic, and one was Asian. There were also four men who participated in the mini-hearing, three of whom were in their early 30s and one who was in his 40s. Three of the men were white, and one was Hispanic. All of the participants were college educated, and some had completed graduate work. Almost all participants did not know each other prior to the mini-hearing. Three of the participants had been recruited by an NBAC Commissioner. The findings from the mini-hearing are summarized below:

- Participants in the group were knowledgeable about what items qualify as genetic tissue and what it can tell about individuals.
- Most participants felt that if they signed a consent form for a surgical procedure, the hospital had legal ownership of their tissue. One person commented that patients usually do not sign consent forms when blood samples are taken, in most cases.
- Opinions varied regarding the provision of consent for research on human tissue samples. One person thought that a blanket consent form for all future research would be appropriate.
- There was strong opinion among participants that if future research on their tissue revealed information about them then they would want to be informed. They recognized that this may place a heavy burden on the researcher.
- Most stated that they wanted to hear the information from their physician and not the researcher. One participant stated that insurance companies may find out this information if physicians are involved in the process.
- Given the choice between anonymous and linked information, participants stated that they wanted the linkage between their stored tissue samples and their identity to be managed so that they could be informed of relevant findings. One person disagreed, stating, “I don’t feel there should be any linkage.

Researchers are there to do research and not relay information back to the people. The [tissue] sample should just be generic. They [the researchers] would be on the phone all of the time."

- One person thought that patients should be able to track research using their tissue as opposed to requiring that the researcher or physician contact the patient. The system would be analogous to a professor posting grades after an exam so that students have the option of viewing (or not viewing) the results. Several participants acknowledged that some people would not want to know if research revealed that they had a certain disease or genetic predisposition to disease, but some participants thought that people should have the right to know if they wanted the information.
- One member of the group stated that human tissue can be a "gold mine" of information about a person, especially as technology advances.
- One person stated that he would not want genetic information obtained from research recorded in his medical record. Another suggested having two separate records when research is being conducted: the medical record and a research record. Participants stated that links were still needed between the research record and the medical record so that researchers could access necessary information from their medical record. One participant felt that only definitive information about an individual obtained from research such as the actual presence of disease (as opposed to genetic predisposition for disease) should be put into the medical record.
- Two participants felt that research was more valid if done by a university or government researcher rather than a for-profit or biotechnology firm. Other participants felt positively about research conducted by private, for-profit firms. One person stated, "There is always someone who is going to benefit, so if you could increase the body of knowledge, it doesn't matter where it's being done."
- One participant stated that ethics committees should have jurisdiction over both private and public research.
- When asked if research subjects should share in profits from human tissue research, one participant said no, stating, "Our names and demographics are sold everyday, and we don't profit from that."
- Participants stated that decisions about human tissue storage and research should be made by legal guardians for individuals who cannot make decisions for themselves. One person suggested that the preferences of people with limited competence should be taken into account whenever possible (e.g., for children, people with schizophrenia).
- Participants stated that there could be negative implications from conducting research on specific groups. One person stated that there was the potential to disseminate information to people prematurely since the body of knowledge about diseases continually evolves. Another stated, "You don't want to create a scare among the populous or among health care providers." Insurance and employment discrimination were also mentioned as potential negative implications. While participants acknowledged these potential negative implications, they were not concerned about the stigmatization of certain groups because of such research.
- When asked who should be on an IRB, two participants stated those who are conducting the research or those who could benefit from the research should not be on the IRB. Many stated that IRB membership should be as diverse as possible, "just like you pick a jury." One person stated that people who are trained in ethics and have a knowledge of ethics should be included on a review board.
- Many participants changed their answers on their self-assessment forms after the discussion. Four individuals realized that they had, in fact, provided human tissue samples in the past. For one participant, the discussion created more concerns regarding the use of human tissue samples. Another participant changed an answer to state that it was OK to do general research using her tissue whereas before the discussion she didn't know. For three people, their overall trust of professionals and institutions to protect their privacy rights decreased after the discussion. One participant reported, however, that her trust in the government increased.

Mini-Hearing Report

Miami, Florida, November 5, 1997

Mini-Hearings on Issues in Human Tissue Storage
Mini-hearing Report—Miami, Florida—November 5, 1997

Overview

The Center for Health Policy Studies (CHPS) is assisting NBAC to explore public knowledge, beliefs, and feelings about human tissue storage issues. Six mini-hearings will be held across the country to ascertain what the American public believes and feels about uses of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Findings from the mini-hearings will be used by NBAC as it develops its reports to the President and the nation.

On Wednesday, November 5, 1997, CHPS held a mini-hearing at the Radisson Mart Plaza Hotel in Miami, Florida. Ten individuals from the Miami area participated in the mini-hearing which lasted two hours. A moderator from CHPS led the discussion. Questions and hypothetical scenarios were used to prompt the group to discuss their thoughts and feelings about issues regarding human tissue storage. The discussion addressed ownership, privacy, sponsorship of research, notification of affected relatives, and potential stigmatization of groups or individuals. In addition, each participant completed a self-assessment prior to and following the discussion to see if his or her thoughts and feelings about human tissue storage changed as a result of the discussion. Self-assessments were used for discussion purposes only and were not collected. The general public was invited to observe the discussion, and time was allotted for public comment following the mini-hearing.

Summary of Substantive Findings

The participants in the group actively shared their thoughts and opinions about human tissue storage. The group was comprised of ten women who were in their 40s and 50s. Several participants were Jewish. Two women were African American and one woman was Latina. The women were recruited for the mini-hearing because of their activism and involvement in the community. The findings from the mini-hearing are summarized below:

- Participants in the group were knowledgeable about what items qualify as genetic tissue and what it can tell about individuals. Two individuals had participated in a research study (the Women's Health Initiative) prior to the mini-hearing.
- Most participants did not realize that tissue samples may be stored after initial use. One person stated, "I would be very surprised to find out that tissue that was taken from me after it was tested wasn't just dumped."
- Many in the group were unsure about whether medical/surgical consent forms that they had signed in the past covered tissue storage. One person questioned whether there is a law about disclosure of the potential to store tissue.
- When asked who should own stored tissue samples, one participant stated, "I feel personal about it; I feel like it's mine." Others disagreed and felt that hospitals or providers could own their tissue if was used for research purposes. One person wanted to ensure that researchers weren't given all of her stored tissue in case her tissue was needed for comparison purposes in the future.

- One participant stated that she is an Ashkenazi Jew and that confidentiality and privacy were very important to her. She stated that if research was to be conducted on her stored tissue then she would want to consent to the research first, and she would want no links to her name or identity.
- Participants felt strongly that insurance companies should not have access to results from research on their stored tissue. There were concerns that insurance companies would financially penalize individuals who have propensity for diseases.
- Participants had mixed feelings about research on stored tissue that may reveal information about family members. One person felt that research into familial diseases was important so that early detection and treatment interventions could be undertaken. She stated that her family has a history of diabetes, which she felt was important information for the family to know. Another person stated that members of her family would not want to know if there was a familial history of Alzheimer's disease because there is no cure.
- One person stated that individuals should tell their own family members about the existence of a genetic disease or propensity for disease, "not a governmental entity or medical person." Another stressed that there are emotional considerations when families are involved.
- Some participants wanted to consent to specific research on their stored tissues while others felt that their general, one-time consent for research was enough. One person stated that it is difficult to consent for research on stored tissue when the potential uses for the research are not known. Another felt that consent for specific research was a good idea, but questioned the practicality of researchers tracking down individuals to obtain their consent for research conducted years after tissue samples were taken.
- Some participants were very concerned about the protection of their privacy rights. Participants were cynical about whether their privacy was protected in "the age of computers." One person stated, "The research is going so fast that soon they will be able to punch in your name and pull up your whole DNA." One participant stated that there is a need to feel trust that someone is protecting individuals' privacy.
- One person suggested that consent forms should address the protection of individuals' privacy during research.
- Participants felt there was a difference between research conducted by for-profit organizations versus academic institutions because of the financial motives of for-profit companies, although they felt positively about research conducted by for-profit companies. One person stated, "I don't think ethics are any better in the academic world than they are in the pharmaceutical world."
- Participants did not feel differently about research conducted by the government versus that conducted by for-profit companies.
- Participants had mixed feelings about individuals sharing in profits that result from research on their stored tissue. One person stated that she would want a share of the profits, while another pointed out that there was the potential for exploitation of certain individuals when money is offered in exchange for tissue.
- Participants stressed the need to inform the community about uses of stored tissue and that checks and balances are needed for research conducted on stored tissue.
- Some participants stated that they had concerns about research being conducted on stored reproductive tissue. One participant stated that it sounded similar to "the genetic testing done by the Germans." One participant felt, however, that research into genetic engineering and cloning was "scary, but a little wonderful."

- Participants had no concerns about research that focused on individuals with certain characteristics if there were no links to individuals' identities. Some participants felt that consent was unimportant for research on stored tissue when research is anonymous.
- The group discussed the potential positive and negative impacts of conducting research that focuses on certain ethnic groups. Some participants thought that such research was positive because it could help the group. Some stressed the need for oversight of such research to make sure that it was conducted ethically. One participant stated that there could be issues with insurance coverage based on this research.
- Participants thought that IRBs should include individuals with high ethical standards and integrity; individuals with ethics or medical backgrounds; representatives from the general population; theologians, and people with legal backgrounds.
- Members of the group stated that they trusted their physicians to protect their medical information. Participants who had participated in research studies stated that they trusted the researchers and their sponsoring institutions to protect their privacy.
- The group felt that medical surrogates should make decisions about human tissue storage for individuals who are unable to make such decision for themselves. Participants stated that individuals' wishes about use of tissue should be taken into account.
- Two participants stated that, after the mini-hearing, they were more aware about uses of human tissue for research.
- Many participants stated that they did not trust religious organizations, lawyers, or the government to protect their privacy rights. Some stated that they trusted hospital ethics committees and physicians to protect their privacy rights.
- Public comment was provided by one member of the audience following the discussion. He stated that he thought about ownership of stored tissue in a similar manner to ownership of old car parts after his car has been repaired. He was not concerned about what happened to the old car parts or his stored tissue because they had little use to him. He also thought that consent for research on stored tissue was very important. He stated that he would want to consent for research on his stored tissue just as he would want to provide consent for the taking of his fingerprints, because it could reveal information about him.

Mini-Hearing Report

Mililani, Hawaii, September 29, 1997

Mini-Hearings on Issues in Human Tissue Storage
Mini-hearing Report—Mililani, Hawaii—September 29, 1997

Overview

The Center for Health Policy Studies (CHPS) is assisting NBAC to explore public knowledge, beliefs, and feelings about human tissue storage issues. Six mini-hearings will be held across the country to ascertain what the American public believes and feels about uses of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Findings from the mini-hearings will be used by NBAC as it develops its reports to the President and the nation.

On Monday, September 29, 1997, CHPS held the second of two Hawaiian mini-hearings at the Mililani Elementary School in Mililani, Hawaii. Eleven representatives from the Mililani Mauka/Launani Valley and the Mililani/Waipio/Melemanu Neighborhood Boards participated in the mini-hearing, which lasted nearly two hours. A moderator from CHPS led the discussion. Questions and hypothetical scenarios were used to prompt the group to discuss their thoughts and feelings about issues regarding human tissue storage. The discussion addressed ownership, privacy, sponsorship of research, notification of affected relatives, and potential stigmatization of groups or individuals. In addition, each participant completed a self-assessment prior to and following the discussion to see if his or her thoughts and feelings about human tissue storage changed as a result of the discussion. Self-assessments were used for discussion purposes only and were not collected. The general public was invited to observe the discussion, and time was allotted for public comment following the mini-hearing.

Summary of Substantive Findings

The participants in the Mililani group shared their thoughts and opinions about human tissue storage. Some of the participants in the mini-hearing knew each other, as the group represented two community neighborhood boards. The group was made up of seven women, four of whom were white. The remaining women were Asian and Pacific Islander. There were also four men who participated in the mini-hearing, all of whom were white. Most men were in their 40s and 50s. Women ranged in ages from late 20s to early 70s. The findings from the mini-hearing are summarized below:

- The group was less than confident of the government's ability to protect the privacy of specific information about themselves gleaned from genetic research conducted on stored tissue.
- The majority of participants stated that they had had a surgical procedure in which tissue was removed.
- Most participants thought that the hospital that takes a tissue sample should own it. All agreed that the patient should own the information that is revealed from that tissue.
- The majority of participants felt that patients typically do not give true informed consent to do research when signing a medical or surgical consent form. As one person stated, “Doctors may explain about the procedure, but they don't explain that the tissue may be used for research.”

- Some participants stated that researchers should not have to obtain additional consent to do research on stored tissue after the original medical or surgical consent form has been signed.
- Most stated that they did not want insurance companies to have access to information that might be revealed from their stored tissue.
- One participant was concerned about performing research on stored tissue that may reveal information about family members. Other participants expressed that they were not very concerned about the impact of genetic research on families.
- Most members of the group stated that they would want to be informed if a researcher discovered clinically relevant information about them from their stored tissue or the tissue of family members.
- Some thought that there could be a negative impact from studying diseases that could be linked to certain ethnic groups. Participants also mentioned that insurance companies, employers, and the government could misuse this information, and cited the example of Japanese sterilization of the mentally retarded.
- Members considered how to balance the importance of research on specific groups versus the potential to misuse the information obtained from it.
- Most felt that anonymous and anonymized research was useful and appropriate.
- Participants were not concerned about whether research was sponsored by the government or by private firms.
- Most members of the group were not concerned about firms profiting from research on stored tissue samples. As one participant stated, “For them to profit, somebody somewhere profits [from the research], so, therefore it's useful.”
- Some participants viewed research on specific groups or ethnicities as positive, and gave the example of research on sickle cell disease.
- Individual participants in the group mentioned that the following groups should be represented on an IRB: people who would not profit from the research, people who would benefit from the research, the Food and Drug Administration, the American Medical Association, someone outside research organizations, and someone who is knowledgeable about medicine/research.
- Participants thought that a legal guardian should be given the authority to make decisions about human tissue storage for those who are unable to make such decisions.
- Three participants changed their answers on the self assessments, stating that after the mini-hearing, they were less concerned about the government's ability to protect their privacy and rights.

Mini-Hearing Report

Honolulu, Hawaii, September 25, 1997

Mini-Hearings on Issues in Human Tissue Storage
Mini-hearing Report, Honolulu, Hawaii, September 25, 1997

Overview

The Center for Health Policy Studies (CHPS) is assisting NBAC to explore public knowledge, beliefs, and feelings about human tissue storage issues. Six mini-hearings will be held across the country to ascertain what the American public believes and feels about uses of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Findings from the mini-hearings will be used by NBAC as it develops its reports to the President and the nation.

On Thursday, September 25, 1997, CHPS held the first of two Hawaiian mini-hearings at the Hale Po'ai in Honolulu, Hawaii. Twelve representatives from the Kalihi-Palama Neighborhood Board participated in the mini-hearing, which lasted nearly two hours. A moderator from CHPS led the discussion. Questions and hypothetical scenarios were used to prompt the group to discuss their thoughts and feelings about issues regarding human tissue storage. The discussion addressed ownership, privacy, sponsorship of research, notification of affected relatives, and potential stigmatization of groups or individuals. In addition, each participant completed a self-assessment prior to and following the discussion to see if his or her thoughts and feelings about human tissue storage changed as a result of the discussion. Self-assessments were used for discussion purposes only and were not collected. The general public was invited to observe the discussion, and time was allotted for public comment following the mini-hearing.

Summary of Substantive Findings

The participants in the Honolulu group shared their thoughts and opinions about human tissue storage. All of the participants in the mini-hearing knew each other, as they serve together on a community neighborhood board. The group represented a number of ethnic groups including whites, Asians, and Pacific Islanders. Most members of the group were in their 50s. There were also some participants in their 20s and 30s. One participant was a retired physician. General findings from the mini-hearing are summarized below:

- Participants in the group demonstrated that they were knowledgeable about what items qualify as human tissue and what it can reveal.
- A number of individuals in the group stated that they had never considered that human tissue would be stored after being used for a test or after removal.
- There were diverse answers regarding who owns human tissue. Answers included physicians, the Department of Health, and patients.
- Members of the group stated that they believed they had no choice but to sign medical or surgical consent forms that included consent for research. One person stated, “They won't touch you with a ten foot pole if you don't sign it.”
- Participants stated that they thought that research on human tissue was needed. Most felt that they did not care whether research was done on their stored human tissue without their active consent. One person stated, “Take whatever you need, as long as you help me.”

- All members of the group stated that they would want to be informed if a researcher discovered clinically relevant information about them from their stored tissue. All agreed that they thought that links to stored tissue with personal identifiers were necessary for this purpose.
- Members of the group firmly believed that insurance companies should not have access to their medical records. Participants did not know how much information insurance companies already know. As one participant stated, "Do they have to know everything about me, down to my cells?"
- Members were not concerned about the potential for stigmatizing certain ethnic or racial groups or families with research on stored tissue. One participant stated, "What's the big deal about taking a tissue out of the body and studying it without your knowledge?"
- Most believed that research conducted on the university level or by the public sector was for the public good. Participants also thought that if private companies profited from using stored tissue, that the companies should have to pay for the stored tissue. One person argued, however, that even research by private companies benefits society, so there was no need for payment.
- Most members felt that researchers did not need to ask for additional consent for research on their stored tissue. As one person stated, "It could hold up the research." One person disagreed and said, "I would like to be told so maybe I could say yes or no. Maybe they are doing something that I don't agree with."
- Participants in the group were not concerned about privacy and confidentiality issues and their stored tissues.
- All participants agreed that family members should be informed if genetic research reveals information about them.
- Participants in the group agreed that researchers, practicing physicians, and medical lawyers should review and oversee medical research. Other people that participants thought should be represented on an IRB included: someone with philosophy background who is educated in bioethics, elected officials or their representatives, clergy, someone with a psychology background, and representatives from the groups being studied. Some participants mentioned that selecting a member of the clergy could be difficult given religious differences.

One person from the public made a statement after the mini-hearing. He stated that more education about human tissue storage was needed for the general public and that he was glad that this series of mini-hearings is being conducted.

Mini-Hearing Report

Cleveland, Ohio, October 21, 1997

Mini-Hearings on Issues in Human Tissue Storage
Mini-hearing Report—Cleveland, Ohio—October 21, 1997

Overview

The Center for Health Policy Studies (CHPS) is assisting NBAC to explore public knowledge, beliefs, and feelings about human tissue storage issues. Six mini-hearings will be held across the country to ascertain what the American public believes and feels about uses of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Findings from the mini-hearings will be used by NBAC as it develops its reports to the President and the nation.

On Tuesday, October 21, 1997, CHPS held a mini-hearing at Mount Zion Congregational Church in Cleveland, Ohio. Seven individuals from the Cleveland area participated in the mini-hearing which lasted two hours. A moderator from CHPS led the discussion. Questions and hypothetical scenarios were used to prompt the group to discuss their thoughts and feelings about issues regarding human tissue storage. The discussion addressed ownership, privacy, sponsorship of research, notification of affected relatives, and potential stigmatization of groups or individuals. In addition, each participant completed a self-assessment prior to and following the discussion to see if his or her thoughts and feelings about human tissue storage changed as a result of the discussion. Self-assessments were used for discussion purposes only and were not collected. The general public was invited to observe the discussion, and time was allotted for public comment following the mini-hearing.

Summary of Substantive Findings

The participants in the group shared their thoughts and opinions about human tissue storage. Four women and three men participated in the mini-hearing. Participants were in their 20s and 30s with the exception of one man who was in his 60s. All group members were African-American. The findings from the mini-hearing are summarized below:

- Participants in the group were knowledgeable about what items qualify as genetic tissue and what it can tell about individuals.
- Prior to the mini-hearing, some participants had not thought about whether human tissue could be stored and used for research.
- Some participants thought that the individuals from whom tissue is taken should own it. Others thought that if consent was given to a hospital for a test or procedure, then the hospital owns the tissue. One person stated, “It's mine until I say you can have it.”
- Opinions varied regarding whether participants wanted to be asked to consent for specific research on stored tissue. Some participants wanted to be aware of research before it is done. One person assumed that if the tissue was being used for research then it was being used for “finding a cure.” Therefore, he did not desire to be informed of the research.

- The group discussed issues of mistrust with the medical profession and the research that may be performed by them. One participant stated the Tuskegee Experiment was not that long ago, while another stated that medical researchers today do not resemble the medical researchers of the Tuskegee Experiment. One member said that the average person needs to know how his or her stored tissue is being used and that there was a need to ensure that tissue is not misused.
- Most participants felt that family members have a right to know if research reveals something about them. One participant remarked, however, "Some of us don't want to know." Participants thought that there could be negative consequences from notifying individuals about research findings from genetic studies. These consequences could include notifying people of potentially false results and heightened anxiety of family members, especially if the research reveals a propensity for disease rather than the actual presence of disease.
- The group felt strongly that insurance companies should not have access to findings that result from research on their stored tissue.
- Some participants felt that there was a significant difference between research conducted in a university setting and research conducted by a for-profit/biotechnology company. One person stated that university-sponsored research is more acceptable because it is being used to teach someone rather than for money. Another disagreed and stated that if the research is being used to find better treatments, it doesn't matter who sponsors it.
- Some participants felt that they did not want links from their stored tissue to their names or medical record. They felt that their privacy rights were more important than their desire to be informed if future research revealed information about them. One person stated that since, generically, findings from research are communicated back to providers (e.g., through published studies), she would hear about and benefit from research findings on her stored tissue anyway, without the link to her name. One person disagreed and stated that as long as his name was not "publicized," then he was comfortable with research being linked to his name.
- There was some disagreement among group members regarding research on specific ethnic or racial groups. One participant stated that there are negative consequences from research that publicizes that diseases "belong" to certain groups. Another person said that the information gained from such research is valuable and that ethnic and racial groups are better off when more is known about diseases that may affect them.
- Participants agreed that researchers should have to receive approval for research from a committee or IRB. One person wondered, however, what other alternatives there could be to ensure that research is ethical and appropriate.
- Members of the group thought that IRBs should include researchers who are ethical and exclude individuals with political motivations for being on the IRB and individuals in the sponsoring party's organization. Group members stated that they trusted surgeons and physicians to protect medical information that is available about them. Participants also thought that if research is being conducted on certain ethnic or racial groups, then members of that group should be aware that such research is being conducted.
- Participants agreed that a legal guardian or a person with a legal Power of Attorney should make decisions about human tissue storage for an individual who is unable to make such decisions.
- After the discussion, one individual stated that she was more aware that tissue samples may be used in medical research than before the mini-hearing. Another participant felt more positively about medical research being conducted on the genetic causes of diseases, while another felt more negatively about such research. One person felt that her trust had increased in hospital research ethics committees and lawyers for protecting her privacy rights from the discussion. Some members of the group had little trust in the government for protecting their privacy rights both before and after the discussion.

Mini-Hearing Report

Boston, Massachusetts, October 23, 1997

Mini-Hearings on Issues in Human Tissue Storage
Mini-hearing Report—Boston, Massachusetts—October 23, 1997

Overview

The Center for Health Policy Studies (CHPS) is assisting NBAC to explore public knowledge, beliefs, and feelings about human tissue storage issues. Six mini-hearings will be held across the country to ascertain what the American public believes and feels about uses of tissue samples, the ethical obligations of those who may learn significant health risk information from tissue samples, and privacy protections. Findings from the mini-hearings will be used by NBAC as it develops its reports to the President and the nation.

On Thursday, October 23, 1997, CHPS held a mini-hearing at the Sheraton Boston Hotel in Boston, Massachusetts. Fourteen individuals from the Boston area participated in the mini-hearing which lasted two hours. A moderator from CHPS led the discussion. Questions and hypothetical scenarios were used to prompt the group to discuss their thoughts and feelings about issues regarding human tissue storage. The discussion addressed ownership, privacy, sponsorship of research, notification of affected relatives, and potential stigmatization of groups or individuals. In addition, each participant completed a self-assessment prior to and following the discussion to see if his or her thoughts and feelings about human tissue storage changed as a result of the discussion. Self-assessments were used for discussion purposes only and were not collected. The general public was invited to observe the discussion, and time was allotted for public comment following the mini-hearing.

Summary of Substantive Findings

The participants in the group actively shared their thoughts and opinions about human tissue storage. The group was comprised of twelve women and two men, most of whom were in their 60s and 70s. Two of the women were in their 40s. Participants were identified and recruited for the group through their membership in the Retired and Senior Volunteer Program, a program sponsored by the City's Commission on Affairs of the Elderly. The findings from the mini-hearing are summarized below:

- Participants in the group were knowledgeable about what items qualify as genetic tissue and what it can tell about individuals. Three individuals had participated in a medical research study prior to the mini-hearing.
- Most participants thought that tissue samples were destroyed or disposed of after initial use.
- Half of the group was unsure about whether medical/surgical consent forms they had signed in the past covered tissue storage. Two participants stated that they had chosen not to sign consent forms or had crossed out/initialed items to which they did not consent.
- Participants stated that the hospital should own tissue samples if consent is provided, as long as the person who signs the consent understands that the tissue may be stored and used later.
- One participant stated that she wanted to personally own her tissue sample if it was determined that the tissue was cancerous. She felt that this ownership would allow her to take the tissue to other providers for further evaluation or allow it to be used for other research.
- Many participants felt positively about research conducted on stored tissue. One member of the group was a colon cancer survivor who felt grateful that research was done on stored tissues, especially since it could potentially help a family member in the future. Another member of the group stated that her son had needed a kidney transplant and felt that research on stored tissue was needed to develop new treatments. She stated, "You can't get [tissue samples] back, so what do you care [how it is used]?"

- Members of the group had questions and concerns regarding the law, consent, and stored tissue samples. One individual wondered if the law that applies to decisions about tissue storage was similar to the law for organ donation in which family members could override individuals' decisions. Another person had concerns about how privacy and confidentiality issues were covered by the law. Other participants wondered what legal limits there were for research on tissue samples and discussed concerns regarding the potential to clone their stored tissue.
- There were mixed feelings among group members regarding whether organizations should profit from research on stored tissue. One person thought that "people close their eyes to a lot of things" when money is involved. One individual felt positively regarding stored tissue used for research on diseases but had concerns about its use for research on cosmetics. There were some concerns about the ethics of research done by pharmaceutical companies and the need to regulate how and under what circumstances stored tissue can be used.
- One participant felt that if hospitals could profit from selling stored tissue samples then there would be an incentive to take as much tissue as possible from patients.
- Many participants thought that it would be impractical for individuals to share in any profits that may result from research on their stored tissue, especially considering the volumes of tissue samples that exist. One person suggested that lower health insurance premiums might be appropriate for individuals who donate their stored tissue for research.
- Some participants had no concerns with stored tissue being linked with their names while others did not want a link between their names and the tissue. The participants were not concerned about researchers knowing other types of information such as personal characteristics.
- One participant wanted to consent for specific research that is conducted on her stored tissue to ensure that it is used appropriately.
- When asked who should be on an IRB, participants gave the following responses: individuals who are ethical and knowledgeable about ethics, individuals from various disciplines, people who represent society as a whole, representatives from different religions, and nurses. Participants thought that politicians and lawyers should not be on IRBs.
- Participants stated that they trusted their physicians and hospitals to protect their medical information, although one person stated, "Not 100 percent."
- Some participants wanted to be notified if research on their stored tissue revealed medically relevant information about them or their family members. Other participants did not want to hear research findings that indicate propensity for disease. As one person stated, "I could get hit by a bus, too." One participant did not want to hear information that revealed that she had an incurable disease, although she wanted to know about the disease if there was an available cure.
- Participants wanted to tell affected family members if research on their stored tissue revealed information about the family members. Participants stated that individuals' privacy rights would be taken away if providers told family members directly without consulting the individuals from whom the tissue was taken.
- After the discussion, a few participants had less trust in physicians and hospital research ethics committees to protect their privacy rights than before the discussion. One person indicated that she felt that it was not okay for research to be conducted on her stored tissue after the discussion, although before the discussion she felt positively about such research.

APPENDIX E

Evaluation of Tissue Sample Storage Focus Group Methodology

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Introduction

In an ideal world where time and money are not an issue, social science researchers will use both quantitative and qualitative methodologies to study a given topic as they gather systematic and important data that complement each other. Quantitative methodologists, utilizing sophisticated sampling techniques and large survey samples, tend to concentrate on structure, context and the regularity of patterns of relationships and interactions in which people lead their lives. Qualitative methodologists endeavor to get "inside" members of the society as they interact with each other and encounter new situations assuming that individuals are as likely to shape social structure as to be shaped by it (Mead, 1934; Blumer, 1954; Strauss, 1978). Therefore qualitative techniques such as participant observation, interviewing and focus groups are often used as the initial exploratory step, particularly when little is known about an area. This exploration then generates questions or hypotheses to be tested by a large scale quantitative survey. Answers to surveys also raise questions that have not been answered by the initial phrasing of the questions, so it is nice to have the luxury of going into the field once more in order to elaborate on and clarify the questionnaire answers.

Social science researchers try to use different types of data collection techniques to examine the same topic. This is based on the premise that measurement improves when diverse indicators are used and that the data thus collected has greater validity (Neuman, 1994). While in many cases it is not warranted or possible to use several methods, it is also true that circumstances prevent the carrying out of any one method in its ideal form, e.g., the response rate on a survey is too low for one category of respondents, the weather is bad and too few focus members turn up, the time or money allotted is insufficient.

Knowledge grows out of replication, and each study can add to this knowledge base provided that its weaknesses and strengths are duly noted so that researchers and policy makers have some idea of how valid and reliable the previous research is. This is particularly true of social science research when direct educational and policy applications of the findings were the reasons the study was conducted. Therefore, it is a good idea to compare the conduct of any given research project with a gold standard, to analyze the weaknesses and strengths of the findings of any one study in order to determine the appropriate methods of "filling in the missing pieces" and in order to assess the kinds of educational programs that will be effective and social policy decisions that reflect public deliberations.

Ethicists, lawyers, and biomedical researchers understand that privacy, confidentiality, informed consent, and ownership are important issues for the public to be aware of as the development of DNA analysis changes clinical and research applications in a way not possible before. Now individuals' identities as persons and their life chances in society may be enhanced by the new frontier or negatively affected by misapplication of DNA analysis by third parties. Therefore it is in the public interest to be informed in order to eventually achieve a societal consensus on these matters. Meanwhile protective guidelines have been developed and these also should be open to public scrutiny. Academics and policy makers believe that it is in the public interest to be informed; however, the public's interest in being informed may not be as great. Compared to corporate downsizing, worries about affording health care, paying off their credit card debts, or trying to save money to send their children to college, DNA tissue banking may seem like a very esoteric issue that has low priority in their lives.

In the following discussion, I will highlight in bold those section that pertain specifically to the research design for the tissue sample storage focus groups and the implications that can be drawn from the findings.

The National Bioethics Advisory Commission is a complex client—really a conglomerate of clients representing different constituencies who are not necessarily unified in their views and values. In the case of the hybrid focus group/mini-hearings/forum on tissue samples, the Commission, as it is well aware, is operating under two additional constraints: 1) a population who knows little about the subject (This alone raises a number of questions as to why they know little about the subject matter; what and how much they want to know; and how important it is to them to be informed.) and 2) the truncated timeframe which necessitated recruiting procedures which may affect the validity and reliability of the data collected.

The strength of focus group research lies in allowing the researcher to find out not only the whether, but the how and why behind people's beliefs and attitudes. However, if individuals do not have any prior beliefs or attitudes because they have never heard about the issues or never thought about them, then the researchers may derive from the questions either 1) good base line data or 2) data given in response to the agenda driven questions felt to be important by the client or researchers, but not reflecting the real feelings and attitudes of the participants. An emerging social desirability criterion is to give at least partial control or agenda setting to research participants, clients and patients (Krueger and King, 1998; Kenen and Smith, 1995; Mishler, 1986;) An example of this is physician/patient consultations in which the patients only respond to what they perceive to be the physician's questions and do not put forth their own agendas for fear of being ignored or considered antagonistic (Anspach, 1988).

Advantages and Disadvantages of Focus Group Research

The focus group design is the best methodology for the subject in question. Every methodology, however, has strengths and weaknesses. The focus group design provides many advantages and a few disadvantages. (Merton, Fiske, and Kendall, 1990; Stewart and Shamdasani, 1991; Morgan, 1998).

Advantages include:

1. Focus groups are useful in identifying cognitive (thinking) or affective (emotional) processes associated with a particular viewpoint or outcome.
2. Focus groups use principles of group dynamics to explore variations in individual responses. This interaction may enable participants to recall details of experiences that otherwise might not come into their minds.
3. Focus groups use purposive sampling in order to gain understanding and insight by hearing in depth from the people you are interested in.
4. Focus group responses have a certain ecological validity, not typical of survey research; participants can qualify their responses or identify important reasons or events that helped account for their answers.
5. Focus groups are conducted using open-ended questions allowing for a wider range of responses. Probing and follow-up questions elicit situations, examples, symbols and original words, thus providing specificity of responses.
6. Focus groups utilize guided discussion allowing participants to fully express in their own words and definitions their affective, cognitive, and situational experiences, which provides depth of analysis.
7. The focus group approach encourages cross-fertilization of interpretations, brainstorming and creativity. Nondirective moderation of the process supports a free association of concepts within the topic outline, allowing expression of words and images, at progressively deeper levels (called “laddering”).

Disadvantages include:

1. The sample is of necessity small and is not random, and therefore the results are not generalizable.
2. The interaction sometimes causes interruptions and generates irrelevancies that are due more to personality factors and status claims than to the study questions being investigated.
3. The development of a leadership effect—where a strong, articulate person structures the discourse and others either support his/her position or keeps quiet when they otherwise would have contributed alternative views.
4. The possible inhibiting effect of the group with regard to certain attitudes, behaviors and experiences that the participants feel may elicit disapproval from some group members. This is usually stronger with controversial and emotionally sensitive issues.
5. A set agenda that does not allow sufficiently for the members to express feelings about the issue not covered by the agenda.

In the following sections, I discuss recruitment criteria, size, and number of focus groups and the interview/moderator's guide. The issues raised are not meant as a criticism of the hybrid mini-hearing/focus group chosen. Given the constraints posed by a multi-constituent client group and abbreviated timeframe, the design was appropriate. In an area that is as complex as that of tissue sample storage, where the knowledge base is so meager and the public's attitudes just evolving, several studies need to be carried out before firm policy recommendations can be based on the results. Any one study can only uncover a small part of what ideally needs to be known for informed policy making decisions. Therefore, questions about the limitations of the interpretation of the data derived from this mini hearing/focus group study need to be addressed.

Recruitment Criteria

Individuals participating in the focus groups need to 1) reflect the population being studied (Stewart and Shamdasani, 1990); 2) have experienced the situation being investigated (Merton, Fiske, and Kendall, 1990); or 3) be waiting to experience the situation in the future (Morgan, 1998).

The degree of homogeneity within focus groups is determined by the size and nature of the sample from which they are drawn and the purpose of the focus group study. Therefore, age, gender, occupation, ethnicity, etc., need to be considered. For the purpose of many studies, educational homogeneity is crucial; without it many of the problems stated above as the weaknesses of focus groups may become exacerbated. For controversial or sensitive areas, it is better that the focus group participants do not know each other. In cases of evaluation of a specific program, recruiting participants who know each other is nearly inevitable and may even be valuable.

This study concerning the public's opinions about the use of tissue samples falls under the third criterion above—individuals will be influenced by the situations being discussed. The fact that just about every American has had, or will have, at least a blood test makes everyone a potential focus group participant. This is the kind of tissue sample most people have experienced. Many or even most individuals, however, do not connect blood with tissue, most probably have not even thought about the issue and have not directly experienced the scenarios presented. Even if the participants are told that blood is a tissue, the new information may not be processed quickly enough for a focus group member to develop a truly informed opinion in the time allowed. This new information may also compete with previously held long-term assumptions about blood and thus is not assimilated completely. New information needs to be processed by individuals and integrated into their cognitive and emotional frames. Emotions must not be neglected, and they too often are. As genetic counselors

have discovered, emotions color much of individuals' attitudes, knowledge and behavior. Furthermore, individuals bombarded with information often resort to heuristics (short-cuts which usually serve the purpose) but which may in specific cases lead them astray (Tversky and Kahneman, 1974). For these reasons, sufficient time is needed to consider the criteria by which members of the public should be chosen as participants in the various focus groups, e.g., extent of prior knowledge of subject as well as demographic factors. The Commission's timeframe did not allow for this.

The recruitment procedures used were as good as any in the timeframe available, but they resulted in a possible bias which can be called the "polite" factor. Social life is based on the norm of reciprocity and people's attachments to significant others in their lives and their investments and involvements in activities they deem important (Stark, 1996). Some of the participants chosen were either friends or acquaintances of a Commissioner or members of a community group. It is as likely that they participated as a favor for someone, rather than they were interested in the issue. Thus, they may adhere to expectations by expressing an interest in the topic in order to be "polite" rather than feeling free to express other opinions. This "polite" factor may have been exacerbated by the audience present. While audiences are more likely to influence expression of attitudes on controversial issues and ones that have strong emotional content, not the case here, they may have swayed participants to feign interest in the use of tissue sample storage in their lives that were not truly felt.

Size and Number of Focus Groups

Optimally, a focus group needs to be large enough to ensure interaction and expression of a variety of opinions yet small enough to allow everyone to participate and prevent engagement in side conversations. There is general agreement that a minimum of 6 and maximum of 10 individuals meets this requirement best in most cases (Morgan, 1998).

There is no ideal number of focus groups to be held. If money and time allow, the researchers should try and hold as many focus groups as necessary until they do not obtain any new information—in technical terms until the researchers reach saturation. In general practice, a minimum of 2 for each homogenous group, e.g. women, men, blacks, whites for a total of 6 to 8 focus groups is usual. If the focus groups are being held strictly for the purpose of making sure that questions in a survey are comprehensive, then a couple of groups may be adequate. Findings based on designs based on a single group for each category of participant are more suspect, as it is difficult to separate content from group dynamics and composition. Furthermore, this only allows for among group comparisons, not within group comparisons and hinders the ability to discern patterns (Krueger, 1998).

The number and size of the focus groups were standard. Because of time and money constraints, a decision was made to maximize breadth (the number of different homogeneous subgroups) over depth (more than one focus group for each). For the purpose involved, the decision to interview various different subgroups was the better one. It was particularly important to include subgroups of the public likely to be directly affected and who have had a history of stigmatization, e.g., African-American and Jewish women. Yet, when the design requires only one focus group for each category, e.g., students, senior citizens, it is difficult to determine whether the findings are idiosyncratic of the membership of that particular focus group or that they reflected opinions held by many other members in that category. For example, the University of San Francisco concentrates on scientifically oriented graduate programs and is a medical and research center. Students and young adults working there may reflect more of the attitudes of the scientific community than they do other students. A sample selected at Berkeley may have expressed different views. There is no way of knowing unless two focus groups of each subgroup are conducted. If diverse opinions are expressed, it would be necessary to conduct additional focus groups or the findings would have to be qualified.

The Moderator/Interview Guide

The interview guide sets forth the major areas of inquiry and conceptual criteria pertaining to the data collected in the group interview (Morgan, 1988). The questioning is focused on the subjective experiences of the participants exposed to a particular situation or idea in order to ascertain their personal definitions of the situation.

Each topic in the guide should be examined beforehand in terms of sub-topics likely to evolve, amount of elaboration (additional explanations, reasons and perspectives) likely to occur as the interview proceeds and the time needed). Often four or more drafts of the guide are developed before wording and order of the questions are finalized. Usually a pilot focus group is conducted and the moderator's guide is revised in light of those findings.

The core of the guide is kept the same for all groups to ensure the comparability of the data across groups. A few additional questions can be tailored for different focus groups in the series. These can be designed in advance or can emerge from unanticipated responses given in a prior focus group session. This is a major advantage of conducting a series of focus groups.

Moderator guides can be loosely structured, moderately structured, or tightly structured in reference to both predetermined questions and group dynamics. Each kind of guide is geared to a different kind of goal. The more structured groups are used to produce answers to the researcher's questions. This approach assumes that you already know the right questions to ask and achieves a maximum of highly targeted information at the expense of limiting your ability to know whether you have missed some crucial issues. Less structured groups are most useful for exploratory purposes which enable the participants to reveal their perspectives on the topic and are the best choice when you are uncertain about what you need to know. This approach, however, means that groups can vary considerably in how much valuable information they produce and the between group analysis becomes more difficult (Morgan, 1998).

This focus group study used a tightly structured guide which was consistent with the Commission's mandate. It was important to learn the public's attitude toward confidentiality, privacy, ownership, and informed consent. The question of agenda, though, remains an important one. Obtaining members of the public's opinions on questions thought by members of the Commission to be important is not necessarily the same as what members of the public think is important. Many questions were asked on very complex issues in an hour and one-half timeframe. It is unlikely that participants had prior views on these issues. This was realized in the design of the study. In order to offset this, self-assessments before and after-focus-group participation were included. It would be interesting to investigate these self-assessments in more depth prior to designing future educational efforts.

In addition, if a “polite” effect (discussed earlier in the paper) existed, it could carry over to participants' responses by their indicating that they felt the focus group discussion was more valuable to them than it really was. Further time to think about the issues raised, talking to other important people in their lives, plus additional exposure to information could alter the opinions expressed in the focus group. This might be particularly true with regard to this study where so many questions were raised for discussion all at once.

No one moderator's guide can, or necessarily should, raise all issues pertaining to the subject and this guide is no exception. This study was primarily cognitively oriented, though a few questions explicitly asked about feelings and the vignettes were intended to evoke feelings as well. Future research should include additional questions about feelings which may have as strong an influence on attitudes and behavior than logical deductions based on fact (Kessler, 1980; Ubell and Loewenstein, 1997). Questions about the use of DNA information by for-profit companies should also be included.

Summary

Issues of informed consent, privacy, confidentiality, and ownership are of prime concern when patients, donors, and research participants have become sources of tissue samples of great value to biomedical research and to biotechnology firms, pharmaceutical companies, and genetic testing enterprises as well. The public is largely unaware of the complexities involved until they or friends and relatives face such a request for the use of their tissues, and even then they are probably unaware of many of the possible ramifications. The extent of lack of information, misinformation, or disinterest needed to be ascertained, and focus group methodology is particularly suitable for exploratory studies.

Ethicists, lawyers, clinicians, and researchers realize the importance and necessity of airing these issues in the public arena and discussing them until some kind of societal consensus emerges on the above issues. Until this is achieved, and it may take a long time, guidelines have been developed to protect individuals and the public needs to be informed of what these are and the reasoning behind them. The potential for large economic gain needs also to be presented to the public. The public's attitude toward "helping science" and helping those with economic motives are quite different.

It was particularly important to ascertain how privacy, confidentiality, and ownership issues were viewed by the public as compared to informed consent, as the latter may involve a good deal of emotional baggage and unpleasant experiences due to the way informed consent has been implemented in medical settings. The forms are obtuse and patients feel that they have no choice but to sign them and usually do not feel that they offer them any protection anyway. They are often seen as protection for the doctor or hospital. The bureaucratic way they are presented, often along with all the other forms to be filled out, including insurance information, furthers this impression. It may be useful to have some focus groups just on this issue. Other groups are investigating informed consent, and this may not be in the purview of this Commission, although the way informed consent is used in other areas influences the way informed consent is perceived with regard to tissue storage.

This focus group/forum hybrid is a good start in pointing out areas that need further study and possible ways of addressing the issues. Because it is a hybrid, certain caveats discussed previously need to be kept in mind if actual educational or policy decisions are based on the findings. The main ones are listed below.

- Recruitment by friends or acquaintances may introduce bias.
- Questions about emotions should be included.
- More than one focus group should be used for each subgroup.
- Agenda-setting by client may prevent participants from raising questions not thought about by client.
- Having an audience may inhibit responses.

The Commission's report should include these caveats and, if requested, supply future researchers whose studies have been approved by IRB boards with the tapes to use as comparison data. If money is available, the tapes should be entered into a computer program such as Ethnograph so that further analysis of the findings can be made and themes elucidated. This level of sophistication is not necessary for the writing of the immediate report, but could be valuable for the future.

The storage of cord blood raises some additional issues as well. As most families have children or wish to have them in the future, the ethical issues involved will impinge on many people. High-quality children (health being a main component) are greatly valued in our society. Using this as a topic might identify cognitive or affective (emotional) processes associated with a particular viewpoint or outcome related to storage of tissue samples and provide the depth of analysis which makes focus group methodology such a useful tool.

References

Anspach, R. 1988. Notes on the sociology of medical discourse: The language of case presentation. *Journal of Health and Social Behavior* 29:357–375.

Blumer, H. 1954. What is wrong with social theory? *American Sociological Review*: 19:3–10.

Glaser, B. and Strauss, A. 1967. *The Discovery of Grounded Theory: Strategies for Qualitative Research*. New York, Aldine.

Greenbaum, T. 1988. *The Practical Handbook and Guide to Focus Group Research.* Lexington, MA., Lexington.

Kenen, R. and Smith, A.C.M. 1995. Genetic counseling for the next 25 years: Models for the future. *Journal of Genetic Counseling* 4:115–124.

Kessler, S. 1980. The psychological paradigm shift in genetic counseling. *Social Biology* 27:167–185.

Krueger, R.A. 1988. *Focus Groups: A Practical Guide for Applied Research*. Newport, CA., Sage Publications.

Krueger, R.A. 1998. *Analyzing and Reporting Focus Group Results*. Newport, CA., Sage Publications.

Krueger, R.A. and King, J.A. 1998. *Involving Community Members in Focus Groups.* Newport CA., Sage Publications.

Mead, G. 1934. *Mind, Self, and Society*. Chicago, University of Chicago.

Merton, R. Fiske, M. and Kendall, P. 1990. *The Focused Interview: A Manual of Problems and Procedures (second edition)*. New York, The Free Press.

Mishler. E.G. 1986. *Research Interviewing*. Cambridge, MA, Harvard University Press.

Morgan, D. 1988. *Focus Groups as Qualitative Research*. Newport, CA., Sage Publications.

Morgan, D. 1998. *Planning Focus Groups*. Thousand Oaks, CA., Sage Publications.

Neuman, W.L. 1994. *Social Research Methods: Qualitative and Quantitative Approaches (second edition)*. Boston, Allyn and Bacon.

Stark, R. 1996. *Sociology (sixth edition)*. Belmont, CA., Wadsworth.

Stewart, D. and Shamdasani, P. 1991. *Focus Groups: Theory and Practice*. Newbury Park, CA., Sage Publications.

Strauss, A. 1978. *Negotiations: Varieties, Contexts, Processes, and Social Order*. San Francisco, Jossey-Bass.

Strauss, A. and Corbin, J. 1990. *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. Newbury Park, CA., Sage Publications.

Tversky, A. and Kahneman, D. 1974. Judgment under uncertainty: Heuristics and biases. *Science*, 185:1124–1131.

Ubel, P.A. and Lowenstein, G. 1997. The role of decision analysis in informed consent: Choosing between intuition and systematicity. *Social Science and Medicine* 44:647–656.