chapter 1

Summary, Policy Issues, and Options for Congressional Action

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Summary, Policy Issues, and Options for Congressional Action

HUMAN BIOLOGICAL MATERIALS: QUESTIONS FOR THE FUTURE

New developments in biotechnology hold great promise for advancing knowledge about various life forms and improving human health. But with this promise come greater responsibilities for scientists and policymakers. Human biological materials—tissues and cells—can be used to develop commercial products (e.g., hybridomas and cultured cell lines]), and for diagnostic and therapeutic purposes. The use of human biological materials for therapy, research, and profit raises important legal, ethical, and economic issues (see table 1).

Many of these issues are similar to those that have been raised concerning human organ donation, which is currently regulated as a result of the Uniform Anatomical Gift Act (National Conference of Commissioners on Uniform State Laws, 1968) and the 1984 National Organ Transplant Act (Public Law 98-507). But the use of human tissues and cells in biotechnology raises questions that have not been answered in previous public policy deliberations concerning the acquisition of human organs, **Who owns a cell line-the human source of the original tissues and cells or the scientist who developed the cell line? Should biological materials be sold, and if so, what are the implications for equity of distribution? Should disclosure, informed consent, and regulatory requirements be modified to cope with the new questions raised by the increased importance and value of human biological materials?** There are no easy answers. These issues are novel and complex, and no single body of law, policy, or ethics applies directly.

Table 1.—Human Biological Materials: Many Questions, Few Definitive Answers

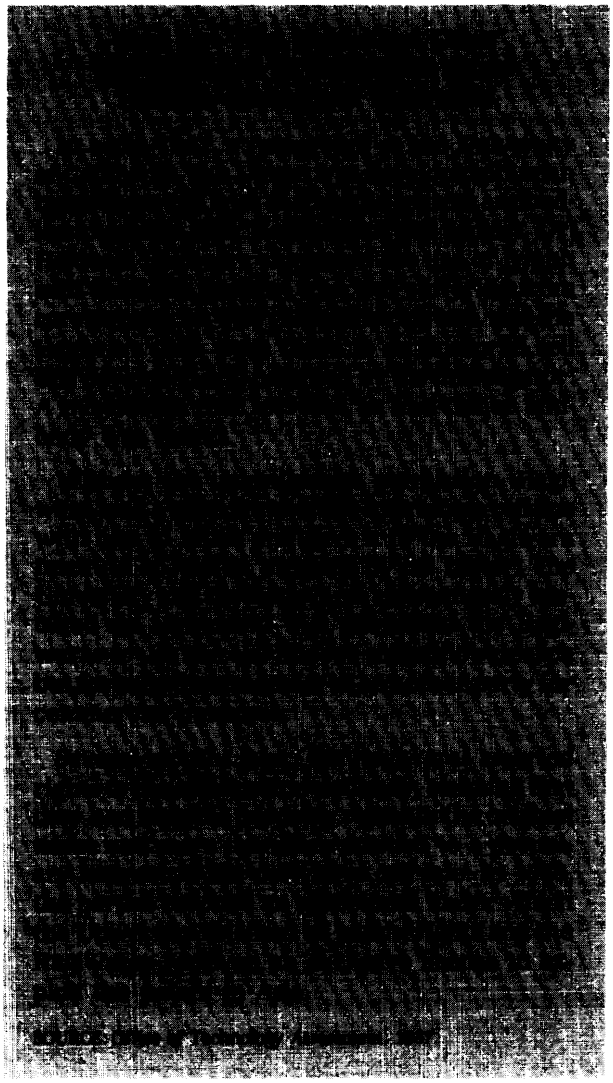
- Are bodily substances "property" to be disposed of by any means one chooses, including donation or sale?
- Do property rights to their genetic identity adhere to individuals or to the species?
- Who should make the basic decisions affecting the acquisition of tissues and cells, and under what circumstances should such acquisition be permitted or denied?
- What are patients and research subjects entitled to know about the potential for commercial exploitation of an invention that uses their bodily materials? And what is the probability that an individual's tissues and cells will end up in a commercial product?
- How is it that inventions incorporating human cells are patentable in the first place? How similar is the invention to the original biological material?
- What is the nature of the researcher's contribution versus the source's contribution to the invention?
- Who should profit from federally funded research using human tissue? To what extent are the issues raised by ownership of human biological materials related to commercial relationships between universities and companies?
- What are the implications of these issues for scientists, physicians, patients, volunteer research subjects, universities, and the biomedical product industry?

SOURCE: Office of Technology Assessment, 1987

Definitions

Human bodies contain a number of elements that are useful in biomedical research. Healthy people continually produce a variety of replenishable substances, including blood, skin, bone marrow, hair, urine, perspiration, saliva, milk, semen, and tears. Human bodies also contain nonreplenishing parts, such as organs or oocytes. Organs may be either vital (e.g., heart) or to some extent expendable (e.g., lymph nodes or a second kidney). Finally, the body can also have diseased parts. **While this report refers to all human parts-replenishing and nonreplenishing, living and nonliving beneficial and detrimental—collectively as human biological materials, it focuses**

'A hybridoma is a hybrid cell resulting from the fusion of a particular type of immortal tumor cell line, a myeloma, with an antibody producing B lymphocyte. Cultures of such cells are capable of continuous growth and specific, monoclinal antibody production. A cell *line* is a sample of cells, having undergone the process of adaptation to artificial laboratory cultivation, that is now capable of sustaining continuous, long-term growth in culture.



pr marıly on those biological mater als most frequently used in biotechnology: t ssues and cells. The e m pe imen body pa human ue flu d bod ly ub an e and b o ogi a a ea ou ed **OTA distinguishes these undeveloped human biological materials from the b o-log cal nventions developed from them (and n some cases pa en ed) such as cell l nes hybr domas, and cloned genes**

The Problem of Uncertainty

At present, there is great uncertainty about how courts will resolve disputes between the human sources of specimens and specimen users. This could be detrimental to both academic researchers and the nascent biotechnology industry, particularly if the rights of a human source are asserted long after the specimen was obtained. The assertion of rights by human sources would affect not only the researcher who obtained the original specimen, but other researchers as well because biological materials are routinely distributed to other researchers for experimental purposes. Thus, scientists who obtain cell lines or other specimen-derivative products (e.g., gene clones) from the original researcher might also be sued. Furthermore, because inventions containing biological materials can be patented and licensed for commercial use, companies are unlikely to invest in developing, manufacturing, or marketing a product when uncertainty about clear title exists.

This uncertainty about the rights of specimen sources and specimen users could have far-reaching implications as research and development progresses. Research using human biological materials could be thwarted if universities and companies have difficulty obtaining title insurance covering ownership of cell lines or gene clones, or liability insurance. Insurers would be concerned not only with suits by individuals who can be identified as the sources of specimens, but also by the potential for class action lawsuits on behalf of all those who contributed specimens to a particular research project. Researchers generally claim that the pervasive use of human cells and tissues in biomedical research makes it impractical and inefficient to try to identify the sources of various specimens or to try to value their contributions. Regardless of the merit of these claims, however, resolving the current uncertainty may be more important to the future of biotechnology than resolving it in any particular way.

THE TECHNOLOGIES

Three broad classes of basic biological techniques are of particular relevance to this report. They are **tissue and cell culture technology, hybridoma technology, and recombinant DNA technology.**

Tissue and Cell Culture Technology

Cells are the basic structural unit of living organisms. A single cell is a complex collection of molecules with integrated functions forming a self-assembling, self -regulating entity. There are two broad classes of cells: prokaryotic and eukaryotic. Prokaryotes, generally considered to be the simpler of the two classes, include bacteria. Their genetic material is not housed in a separate structure (a nucleus) and the majority of prokaryotic organisms are unicellular. Eukaryotes are usually multicellular organisms; they contain a nucleus and other specialized structures to coordinate different cell functions. Human beings are eukaryotes.

Because eukaryotes are complex, scientists often study these organisms by examining isolated cells independent of the whole organism. This reductionist approach, called tissue and cell culture, is an essential technique for the study of human biological materials and the development of related biotechnologies. **Establishing human cell culture directly from human tissue is a relatively difficult enterprise and the probability of establishing a cell line from a given sample varies, ranging from 0.01 percent for some liver cells to nearly 100 percent for some human skin cells.**

Cell cultures isolated from nontumor tissue have a finite lifespan in the laboratory and most will die after a limited number of population doublings. These cultures will age (called senescence) unless pushed into immortality by outside interventions involving viruses or chemicals. The type of donor tissue involved and culture conditions are important variables of cell lifespan. Long-term growth of human cells and tissues is difficult, often an art. Most established cell cultures have been derived from malignant tissue samples. Tissue and cell culture techniques have greatly increased knowledge about cell biology and set the stage for the development of hybridoma technology.

Hybridoma Technology

In response to foreign substances, the body produces a constellation of different substances. Antibodies are one component of the immune response and they have a unique ability to identify specific molecules. Lymphokines, sometimes called bioregulators, are also produced during an immune response.

Cell culture technology provides the tools scientists need to produce pure, highly specific antibodies. By fusing two types of cells-an antibody-producing B lymphocyte with a certain tumor cell line (a myeloma)–scientists found that the resulting immortal hybrid cells, called hybridomas, secrete large amounts of homogeneous (or monoclinal) antibodies, Monoclinal antibodies have led to a greater understanding of the intricacies of the immune response and they have become powerful and widely used laboratory tools. They also have been approved for use as therapeutic agents. **Although the production of human monoclonal antibodies has proven much more difficult than the production of rodent monoclinal antibodies, the increasing availability of large supplies of monoclinal antibodies is revolutionizing research, commerce, and medicine.**

Lymphokines (e.g., interferon) were previously available in minute and usually impure amounts—if at all. Hybridoma, cell culture, and recombinant DNA technologies now permit lymphokines to be isolated in pure form and in quantities facilitating further analysis or use. The increased production and availability of these molecules has significant therapeutic promise in the treatment of a spectrum of diseases because of their exquisite specificity and reduced toxicity.

Recombinant DNA Technology

Recombinant DNA technology, also referred to as genetic engineering, involves the direct manipulation of the genetic material (the DNA) of a cell.

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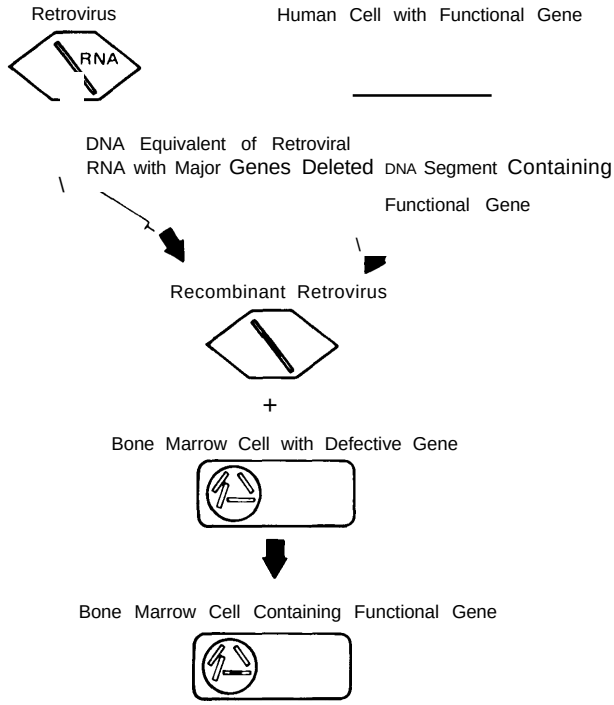
U ng h e hn que now po b e o peed he o a on e am na on and de e opmen o w de ange o b o og a ompound L ke he u e o u u e he u e o e omb nan DNA h n que ha hed fu he gh on he de a o many mpo an b o og a p o e

Gene on ng ap o e ha u e a a ety o e omb n n DNA p o edu e o p odu e mu pe ope o pa u a p e o gene nfo mation. It is an important tool that accelerates the study or production of genes. All recombinant DNA methods require the following:

- a suitable vector to move DNA into the host cell,
- an appropriate host,
- a system to select and cull host cells that have received recombinant DNA, and
- a probe to detect the particular recombinant organisms of interest.

Recombinant DNA techniques have done much to illuminate the regulation and control of important human processes. In addition, advances in this technology underlie many commercial ventures to isolate or manufacture large quantities of scarce biological commodities.

Figure 1.-The Genetic Engineering of Human Cells



SOURCE: Steve Olson, ***Biotechnology:*** *An* ***Industry*** *Comes of Age,* prepared for the Academy Industry Program of the National Academy of Sciences/National Academy of Engineering/Institute of Medicine (Washington, DC: National Academy Press, 1986)

THE INTERESTED PARTIES

Although tissues and cells can be used for diagnostic, therapeutic, research, and commercial purposes, in fact the various uses of biological materials are usually intertwined, sometimes inextricably. This means that **a variety of people, including scientists in the research community (universities and industry), plus physicians, and patient and nonpatient sources, share an interest in the acquisition and use of human tissues and cells.** All would likely benefit from a resolution of the uncertainty surrounding the uses of biotechnology.

Commercial Interest in Human Biological Research and Inventions

The government has always maintained an interest in the legal, ethical, and economic implications of the research it is funding, and this interest is magnified when such research might result in inventions that are patentable under Federal law. In addition to advances in technology, **two events occurred in 1980 to precipitate the increasing research and commercial interest in human biological materials. First, the U.S. Supreme Court held for the first time that Federal patent law applies to new life forms created by DNA recombinations-opening up the possibility that products containing altered human cells and genes might also be patentable. Second, Congress amended the patent statute to encourage patenting and licensing of inventions resulting from government-sponsored research (Public Law 96%17).**

Even though the government is the primary source of funding for basic biomedical research, no single patent policy existed for government-supported research until 1980. Instead, each agency developed its own rules, resulting in 26 different patent policies. Under this system, only about 4 percent of some 30,000 government-owned patents were licensed. Furthermore, the government policy of granting nonexclusive licenses discouraged private investment, since a company lacking an exclusive license is reluctant to pay the cost of developing, producing, and marketing a product. Thus, potentially valuable research remained unexploited. To resolve this problem, Congress passed the Patent and Trademark Amendment Act in 1980 to prompt efforts to develop a uniform patent policy that would encourage cooperative relationships between universities and industry, and ultimately take government-sponsored inventions off the shelf and into the marketplace.

The changing legal climate has provided a fertile medium for the growth of university biomedical research and development using novel biotechnologies. **From 1980 through 1984, patent applications by universities and hospitals for inventions containing human biological increased more than 300 percent (compared to the preceding 5-year period). The extent to which these and forthcoming patents will be of commercial value is difficult to assess.**

Sources of Human Tissue

There are three major sources of specimens: patients, healthy research subjects, and cadavers.

- Patients are a source of both normal and atypical specimens and these individuals may or may not be research subjects. Patient-derived specimens may be "leftovers" obtained from diagnostic or therapeutic procedures and most human tissues or cells that find their way into research protocols are of this type. Patient-derived samples can also be provided as part of a research protocol.
- Healthy volunteer research subjects may donate replenishing biological if specimen removal involves little or no risk of harm, according to generally accepted principles of human subject research.
- Cadavers are the only permissible source of normal and atypical-vital organs (including the brain, heart, and liver, but excluding kidneys and corneas). They are also the only permissible source of healthy benign organs (e.g., corneas) destined for research rather than transplantation,

While these donor classifications may seem fairly straightforward, the human relationships involved

are more dynamic than these categories suggest. In particular, the physician-patient relationship may change over the course of time into a researcher-subject relationship.

The Research Community

Research uses of human tissue are diverse and difficult to categorize. Generally, researchers are studying the characteristics and functions of healthy and diseased organs, tissues, and cells. Commercial products developed from human specimens are usually related to medical or research uses. The use of human biological is widespread; a recent survey conducted by the House Committee on Science and Technology found that 49 percent of the researchers at the medical institutions surveyed used patients' tissues or fluid in their research.

The revolutionizing effect of biotechnology on the use of human specimens is principally due to three factors:

- isolation of increasingly smaller amounts of important naturally occurring human biological factors (also known as biopharmaceuticals, bioresponse modulators, or biological mediators);
- production of virtually unlimited quantities of these factors (usually found in the body in only small amounts) using recombinant DNA methods; and
- discovery of techniques to create hybridomas, making it possible to generate large, pure supplies of specific antibodies.

At the most fundamental scientific level, human material is a source for studies designed to understand basic biological processes. From this basic research, commercial development may follow. However, **the probability that any one person's biological materials will be developed into a valuable product is exceedingly small. Thus, the issue of great potential commercial gain from donated materials is relevant to a small minority of sources.** However, in the future—as biotechnology progresses—the importance of the issue and the number of people involved could increase. The potential for commercial gain, while to date mostly a speculative consideration, could quickly become a reality. It is appropriate to consider these issues and the possible roles of the interested parties now, in advance of their becoming highly visible, so that public policy perspectives can be developed with wisdom and foresight.

Industry

The biotechnology industry is a major interested party in the controversy surrounding the use of human tissues and cells for financial gain. It is comprised of a variety of different types of organizations including the established pharmaceutical companies, oil and chemical companies, agricultural product manufacturers, and the new biotechnology companies. Of the nearly 350 commercial biotechnology firms in the United States actively engaged in biotechnology research and commercial product development, approximately 25 to 30 percent are engaged in research to develop a human therapeutic or diagnostic reagent. There is a strong international component to the biotechnology industry, with numerous research and development arrangements and partnerships between American firms and firms in Japan and Europe.

Photo credit: U.S. Department of Agriculture

Researcher withdraws a cell line sample from a freezing device.

LEGAL CONSIDERATIONS

United States law has long protected people from injury and damages. Much of this protection is afforded by the common law, the body of judge-made law built on judicial precedents. This body of legal principles has evolved over centuries *as* judges are called on to resolve disputes that have not been addressed by statute. Congress and State legislatures, however, have enacted numerous statutes to codify, modify, or overrule the common law, or to address larger societal issues that are inaccessible through the use of common law.

The common law does not provide any definitive answer to the questions of rights that arise when a patient or nonpatient source supplies biological materials to an academic or commercial researcher. Because neither judicial precedents nor statutes directly address this question, the court must do what common law judges have done for centuries: reason by analogy, using legal principles and precedent developed for other circumstances.

Three large collections of legal principles could prove relevant to the use of human tissues and cells: property law, tort law, and contract law. These three areas include a broad variety of statutes and precedents that might be relevant and thus this issue could arguably touch almost all facets of U.S. law (see table 2). **Overall, however, there is no discrete body of law that deals specifically with these human biological materials.** Because common law reacts to damages only after they have occurred, it does not anticipate possible interests that have not existed previously. In the area of the use of human tissues and cells, technology in fact has advanced beyond existing law. It is not possible to predict what principles and arguments of law might actually be used as cases of this sort come before the courts.

Table 2.—Possible Sources of Rights Relating to Human Biological Materials

Law of Patents
Law of Cadavers and Autopsies
Property rights in corpses
Emotional distress caused by wrongful acts toward cadavers
Law of Organ Transplantation
Donation of organs for transplantation
Sale of organs for transplantation
Law of Blood and Semen Sales
Sale of blood and semen
Product liability generally
Implied warranties under the Uniform Commercial Code
Specific performance under the Uniform Commercial Code
Blood as a product for tax law purposes
Law of Copyright
Law of Trade Secrets
Law of Conversion and Trespass to Chattel
Property interest
Possession
Injury to plaintiff
Abandonment
Res Nullius
Law of Accession
Cases involving crops
Specification

SOURCE: Office of Technology Assessment, 1987.

Can Human Biological Materials Be Sold Like Property?

No area of law clearly provides ownership rights with respect to human tissues and cells. Nor does any law prohibit the use or sale of human bodily substances by the living person who generates them or one who acquires them from such a person, except under certain circumstances unrelated to biotechnology research. **In the absence of clear legal restrictions, the sale of tissues and cells is generally permissible unless the circumstances surrounding the sale suggest a significant threat to individual or public health, or strong offense to public sensibility.** To date, neither deleterious health effects nor public moral outrage have occurred even though occasional reports of sales of replenishing cells have been publicized. But while the law permits the sale of such replenishing cells as blood and semen, it does not endorse such transactions and does not characterize such transactions as involving property. In this sense, **either permitting or forbidding the sale of human specimens by patients and research subjects can be claimed to be consistent with existing law.**

INFORMED CONSENT AND DISCLOSURE

> Every human being of adult years and sound mind has a right to determine what shall be done with his own body . . .
>
> –***Scholendorff v.*** Society ***of New*** York Hospital, 1914

The fundamental principle underlying the need for consent for medical or research purposes is respect for personal autonomy. Consent is a process of communication, a two-way flow of information between caregiver/researcher and patient/subject about the risks and benefits of the treatment or research.

For consent to be valid, the patient or research subject must be given an adequate amount of information with which to reach a reasoned choice. Although there are differences from State to State, the information that generally needs to be disclosed to obtain consent focuses on the nature and purpose of the treatment or research, risk-benefit information, and the availability of beneficial, alternative procedures or treatment. Consent in a research setting, like consent in a traditional treatment context, must be obtained in circumstances free from the prospect of coercion or undue influence.

There are two main sources of Federal regulations governing human research. The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) have promulgated regulations that delineate the elements necessary for informed consent to research. DHHS regulations govern research conducted or funded by DHHS, including the National Institutes of Health. FDA regulations govern clinical investigations that support applications for research or marketing permits for products such as drugs, food additives, medical devices, and biological products. Where these Federal regulations apply, disclosure requirements go beyond the accepted norms and include disclosure regarding confidentiality, compensation for research-related injuries, and the right to withdraw from research without incurring a penalty or loss of rights.

These Federal regulations are a deliberate attempt to set ethical and legal constraints on human research. A balance has been struck between the needs of researchers and the rights and safety of human subjects, The success of these regulations in achieving this balance is in no small measure a function of the integrity of investigators and the diligence of institutional review boards, which review proposed research projects for compliance with human subject research regulations.

Consent and the Prospect of Commercial Gain

The traditional view has been that in therapeutic settings, information disclosed to patients should be related to the risks and benefits of diagnostic tests or treatment, and that it should include alternative procedures. Similarly, in the research setting the disclosure of information has focused on the nature of the study and its effects on subjects. **Until recently, little thought had been given to disclosing information about the prospect for commercial gain, but with the advent of biotechnology and its potential use of human tissues and cells in valuable products, this issue merits consideration.**

Arguments can be made both for and against the idea of including information about potential financial gain in the required disclosure of information to patients and research subjects.

Arguments Favoring Disclosure of Potential Commercial Gain

If the notion of personal autonomy and the right to decide what will be done with one's body is to be given full legal recognition, then the prospect of commercial gain should be disclosed because this information may help a person decide whether or not to take part in research. Indeed, the overall trend has been toward greater disclosure of information-details about the probable impact of a procedure on lifestyle, the financial costs of one procedure over another, even the length of disability. Requiring disclosure about commercial gain can be viewed as a logical extension of the consent process.

In fact, it can be argued that the Federal regulations should explicitly require disclosure of potential commercial gain because they require dis-

closure of "significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation. " Discovery of a commercially significant tissue or cell in a subject's body may constitute a "significant new finding. "

Arguments Against Disclosure of Potential Commercial Gain

The primary argument against disclosing the prospect of commercial gain concerns the impact such information might have on the subject's ability to reach an informed choice free of undue influence. The prospect of financial gain stemming from marketable discoveries could hamper subjects from reaching informed decisions because attention to this highly speculative topic could distract attention from other important aspects of the consent process.

Disclosing information about commercial gain could sometimes jeopardize the health and safety of subjects, as well as the validity of the research itself. The hope of gain, for example, might lead subjects to give less than candid answers to questions about medical or personal history that might otherwise disqualify them from the study. It might encourage them to expose themselves to risks they would otherwise consider unacceptable. In addition, because disclosure of potential gain is so speculative, such disclosure could generate unreasonable expectations or be considered misinformation.

It can also be argued that Federal human research regulations embody a philosophy that bans participation for inappropriate reasons. DHHS regulations, for example, make it clear that parole boards should not consider participation when making prisoners' parole decisions. DHHS might consider it improper for subjects to participate in research specifically because they might profit financially. Some people thus might argue that banning reference to the prospect of financial gain is necessary to safeguard subjects from undue influence on their decisions.

Are Changes Needed in the Consent Process?

The question of disclosing potential commercial gain related to diagnostic tests or treatment is one the courts or State legislatures will need to address. However, the Federal Government funds substantial amounts of human research and will also need to consider its regulations in light of this debate. **Policymakers, institutional review boards, and researchers face these questions related to disclosure: Should potential commercial gain be disclosed? If so, what pertinent information is necessary? When is such disclosure best made? What safeguards need to be developed to minimize any detrimental impacts resulting from disclosure of probable commercial gain?**

The prospect of financial gain is a troublesome issue in terms of voluntary consent and the use of human biological materials. **It can be argued that to assure truly voluntary consent, research subjects should not be offered compensation for their time and inconvenience, let alone substantial financial gain. The counter argument is that the sources of human tissues and cells have rights or interests in marketable substances taken or developed from their bodies and so have a right to know about potential profits or to be paid outright for their tissues and cells.** Regardless of what decision is reached, care must be taken so research is not adversely affected because it becomes too complicated to get specimens.

ECONOMIC CONSIDERATIONS

The traditional relationships between donors and researchers, and among researchers at different institutions, have been informal; both information and biological materials have been exchanged freely. Today, however, the techniques of biotechnology and the potential for profits and

scientific recognition have introduced new concerns, At present, there is no widespread sentiment favoring a move toward a market system for the exchange of human tissues and cells. However, a few types of materials, such as plasma and some patented cell lines, are currently transferred within a market system. Future changes in the extent of profits generated from the biotechnology industry could force some changes in the current, primarily nonmarket system.

Two **key factors probably will determine whether a change occurs in the current system of free donation of human biological materials for use in biotechnology research and commerce. First, a change could arise from judicial decisions in present or future cases under litigation Second, a change could be initiated through greater public interest as the commercial applications of biotechnology increase and profits begin to be realized.**

There are arguments both for and against payments for donations of human biological materials. Arguments over payments for human tissues and cells used in biotechnological research echo similar debates about markets in human organs. There are five principal issues in the debate:

- the equity of production and distribution,
- the added costs of payments to sources and costs associated with that process,
- social goals (the merits of an altruistic system of donations versus a market system),
- safety and quality (both of the source and the biological materials), and
- potential shortages or inefficiencies resulting from a nonmarket system or from changing from a nonmarket system to a market system.

The factors related to social goals, safety and quality, and shortages do not now offer compelling support either for or against paying the sources of human tissues and cells. But two of the issues are central to the debate, and they seem to argue in favor of opposing approaches. **Issues of equity argue in favor of a payment system to human sources. On the other hand, the added costs of payments to sources argue against such a payment system.**

Equity of Production and Distribution

The equity of a system can be considered from both the production and distribution sides. On the production side, one issue to consider is whether any of the participants are not receiving an equitable return for their services or products. On the distribution side, the main issue is whether there is adequate access to the goods by parties who seek them.

With respect to human biological materials obtained for research, **it can be argued that sources are not entitled to the value of their donated materials because they do nothing to develop the materials into the valuable product.** To a donor, replenishable tissue is often useless, and diseased tissue is actually a threat. It is only the intervention of the researcher that gives value to these materials. Therefore, it is the researcher who should legitimately realize any economic gains from cell lines or other products developed from the original biological material.

With respect to distribution, researchers generally cooperate with each other in supplying biological materials. The main incentive to this cooperation is the scientific commitment to the free flow of ideas and materials and to date the system has operated fairly efficiently. However, as biotechnological processes and products are commercialized, this free flow of information and materials is facing increasing constraints. **Shortages of human tissues and cells for basic research could occur if the incentives to cooperate are insufficient to motivate researchers to go to the trouble of supplying fellow researchers.**

Added Costs

Two types of additional costs would be incurred if human sources were compensated for their tissues and cells or if they shared in royalties accruing from licensing agreements concerning the transfer of developed cell lines: the actual compensation to the sources and the cost of administering the program (also called ‘(transaction costs”). These costs could add significant burdens to the

process of developing biotechnology products from human materials.

The actual compensation to the human sources of original tissues and cells is unlikely to have a large economic impact on the use of human biological materials, but transaction costs are likely to dwarf the costs of payments to these individuals. Studies involving the development of cell lines can take years to complete and commercial application years longer, so the cost of keeping records of the origin of all the cell lines involved might be considerable. In addition, most of the cell lines studied are unlikely to have any commercial value so a large portion of the transaction costs would actually be unnecessary. Furthermore, under a payment system scientists would no longer exchange materials freely; they would have to negotiate over the transfer and value of property rights for cell lines and might hesitate to share materials at all. Such negotiations would further increase transaction costs.

Resolving the Payment Dilemma

From the point of view of equity, a market structure is favored because it eliminates the potential windfall realized by those who would otherwise receive free tissues and cells. On the other hand, the magnitude of the transaction costs associated with payment to human sources maybe sufficient to deter any forays into a market structure. Nonprofit organizations can play an important role in the procurement and distribution of human biological materials, just as they have played a key role in marketing blood and organs. **At present, there does not appear to be movement toward a change-in the existing system of free donations of human biological materials for use in research and commerce in biotechnology.**

ETHICAL CONSIDERATIONS

Are the human body and its parts fit objects for commerce, things that may properly be bought and sold? **There are three broad ethical grounds for objecting to or supporting commercial activities in human biological materials: respect for persons, concern for beneficence, and concern for justice.**

First, the ethical principle of respect for persons relates to the idea that trade in human tissues and cells ought to be limited if the body is considered part of the basic dignity of human beings. To the extent that the body is indivisible from that which makes up personhood, the same respect is due the body as is due persons. If the body is incidental to the essence of personhood, however, then trade in the body is not protected by the ethical principle of respect for persons.

The second ethical principle relevant to the acceptability of trade in human materials is beneficence—who would benefit. The basic question could be stated this way: would commercialization of human materials be more beneficial than a ban on such commercialization? Marketing human tissues and cells might be justified if that would lead to only good results or to a preponderance of good results over bad. Those who hold differing ethical perspectives might consider different outcomes as beneficent.

A third relevant principle is justice. Would a market setting be equitable to all members of society, including those who are financially disadvantaged? Part of the public ambivalence about a market in human tissues stems from a sense that such a market would foster inequities.

The Moral Status of Bodies and Their Parts

Ethical and religious traditions do not provide clear guidelines about the ways in which human biological materials should be developed or exchanged. The absence of established customs regarding these materials is due to the relatively new potential for conducting and profiting from the development of human cells into cell lines. **The debate about whether or not it is ethical for bodily materials to be bought and sold underlies all discussions about the commercialization of human biological materials.** In addition, there are important questions about how justice

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Two major variables are present in these Western religious traditions that affect the use of human tissues and cells: the type of materials and the mode of transfer. The significance of different modes of transfer (or acquisition, if viewed from the viewpoint of the user) and different materials hinges on various ethical principles, such as:

- respect for persons;
- benefits to others;
- Ž not harming others; and
- justice, or treating others fairly and distributing benefits and burdens equitably.

There is a distinction between ethically acceptable and ethically preferable policies and practices, Some modes of transfer and some uses may be ethically preferred—for example, tradition prefers explicit gifts and donations without necessarily excluding sales, abandonment, and appropriation in all cases. Western religious tradition prefers transfer methods that depend on voluntary, knowledgeable consent. Thus, preferred methods recognize some kind of property right by the original possessor of the biological materials.

Tomorrow's Choices

Choices about how to handle transfers of tissues and cells from patients and research subjects to doctors, teachers, and researchers are important ethical decisions in two respects. First, these choices will characterize how individuals regard the human body. If certain human parts are "dignified," then social traditions suggest that they may be given, but not sold. Second, like the choice of how to obtain blood for transfusions, the system that is chosen for obtaining human tissues and cells will convey a sense of the symbolic weight modern society places on the human body and the use of human biological materials in order to relieve suffering and enhance human health.

The dispute between those who believe that commercialization of the human body is justified and those who think it is not is in part an argument between people who accept a philosophical view that separates the body (a material, physiological being) from personhood, identity, or mind (an immaterial, rational being) and those who do not.

POLICY ISSUES AND OPTIOINS FOR CONGGRESSIONAL ACTION

Four policy issues related to the use of human tissues and cells in biotechnology were identified during the course of this study. The first concerns actions that Congress might take to regulate the commercialization of human tissues and cells. The second involves the adequacy of existing regulations covering commercialization of cell lines, gene probes, and other products developed from human biological materials. The third concerns the adequacy of existing regulations covering research with human subjects. The fourth centers on whether present practice is adequate to ensure that health care providers disclose their potential research and commercial interests in the care of a specific patient or group of patients.

Associated with each policy issue are several options for congressional action, ranging in each case from taking no specific steps to making major changes. Some of the options involve direct legislative action. Others are oriented to the actions of the executive branch but involve congressional oversight or direction. The order in which the options are presented should not imply their priority. Furthermore, the options are not, for the most part, mutually exclusive: adopting one does not necessarily disqualify others in the same category or within another category. A careful combination of options might produce the most desirable effects. In some cases, an option may suggest alterations in more than one aspect of using human tissues and cells in biotechnology. It is important to keep in mind that changes in one area have repercussions in others.

ISSUE 1: Should the commercialization of human tissues and cells be permitted by the Federal Government?

Option 1.1: Take no action.

Congress may conclude that at present, the largely nonmarket basis for the transfer of human tissues and cells is appropriate. If a commer-

cial market in human biological materials should arise, the lack of Federal regulation might result in great variability in the amounts of money paid to the sources of the original tissues and cells. If no action is taken, it is unlikely that human patients or research subjects will be routinely compensated for their tissues or cells in the near future.

Option I. L?: Mandate that donors of human tissues and cells are compensated for their donations.

Some people argue that in the interest of equity, the sources of human tissues and cells should be compensated. Congress could decide that human biological materials have a monetary value, even in their unimproved state, and that the sources of these materials have a right to this value. The amount and form of such compensation could vary. Sources could be paid for their time and trouble or paid for the actual specimen. Payment for service as opposed to substance is now standard practice in the case of sperm donation. Researchers argue that compensation for human tissues and cells in their unimproved form is impractical because the vast majority of these materials will have no ultimate value. Economists argue that the transaction costs of such compensation would outweigh any payment for the original biological material. In addition, many parties are concerned that any payment to the sources of human tissues and cells, no matter how small, would be so inefficient and inconvenient as to stifle research efforts in general. Lastly, some ethicists worry that any trade or market in human tissues and cells unacceptably alters the meaning and value of the human body.

Option 1.3: Enact a statute modeled after the National Organ Transplant Act that prohibits the buying and selling of human tissues and cells.

Congress may conclude that at present, the existing situation in which human tissues and cells are largely either donated or abandoned for research purposes is satisfactory. If Congress concludes that any for-profit market in human tissues and cells should be stifled or avoided, it could prohibit the sale of these biological materials. Such a statute would prevent patients, research subjects, or other sources from making money from providing their tissues and cells. If Congress enacted a statute modeled after the National Organ Transplant Act in particular, there would be a consistent line of Federal reasoning concerning the transfer of human organs, tissues, and cells.

ISSUE 2: Should the commercialization of cell lines, gene probes, and other products developed from human tissues and cells be modified by the Federal Government?

Option 2.1: Take no action.

At present, cell lines, gene probes, and other products developed from human tissues and cells are exchanged informally among researchers as well as by means of a market system. For the most part, profits are accrued in the form of royalties paid by those who want access to the developed products. If Congress takes no action, the use of patented inventions based on human biological materials will continue to be restricted to those who engage in licensing agreements for access to the patented products.

Option 2.2: Amend current patent law so parties other than inventors (e.g., patients, research subjects, or the Federal Government) have protected interests and access to any commercial products developed from their tissues and cells.

Within the context of current patent law, the inventor has exclusive rights to patented material and this effectively bars access by the sources to their original biological material. Some argue, however, that the patients or research subjects, particularly if they suffer from a disease, should have access to or some say in the use of patented products derived from their tissues and cells. At present, licensing agreements for the use of these patented materials do not commonly stipulate any protected interest for the original source.

Option** 2.3: **Enact a statute protecting the rights of patients or research subjects to share in profits accruing from licensing agreements for the use of cell lines or gene probes developed from their original human biological material.

The profitable features of patented cell lines and gene probes are the royalties that accrue from licensing agreements for access to these products. Congress may conclude that it is fair and equitable for the original sources of human biological materials to share in the derived profits. Such profit sharing could be in addition to or instead of a flat fee for the original unimproved tissues and cells. Some researchers argue, however, that it is often impossible to identify the source of the original material as cell lines and gene probes are developed. Many laboratory transformations over a long period of time separate the original sample from the patented invention. If Congress enacts a statute ensuring that the sources of human tissues and cells share in the profits accruing from licensing agreements, then an extensive and costly system of recordkeeping will be necessary to establish the identity and whereabouts of the original sources.

Option 2.4: Mandate that any cell line be presumed to be in the public domain unless it has been formally registered at the time the tissue was extracted or placed into culture.

The presumption that cell lines are in the public domain would bar anyone from claiming property rights to these products. While this would not directly compensate the donor or source of the unimproved tissues and cells or the researcher, it might relieve any sense of exploitation that someone else has taken over that original property right. The patent and similar systems could still apply for further inventions made in developing applications of the cell line.

Option 2.5: Enact a statute prohibiting parties other than inventors from sharing in any reimbursement for, or any profits derived from, the use of products developed from human tissues and cells.

Under the present market system, only those who have patent law protection or enter into a contractual relationship (e.g., licensing agreement) realize commercial gain from developed tissues and cells. Congress may conclude that the sources should be barred from obtaining any reimbursement for products developed from their tissues and cells. Such action would affirm that commercialization of products developed through the use of human biological materials should be limited to the patent holder and licensees, and that patients and research subjects have no right to the value of their tissues and cells in their altered forms. While such an action might serve as an economic inducement for those who would obtain human tissues and cells for the purposes of developing new inventions, it is arguably contrary to current patent and contract law (which encourages commercial negotiation between willing parties) as well as the concept of a person's autonomy over the use of bodily materials.

ISSUE 3: Are guidelines on the Protection of Human Subjects (45 CFR Part 46) issued by the Department of Health and Human Services adequate for the use of human tissues and cells in biotechnology?

Option 3.1: Take no action.

If no action is taken by the Department of Health and Human Services to alter the guidelines on the Protection of Human Subjects, it will remain unnecessary for researchers to inform subjects about possible uses of pathological or diagnostic specimens. As a result, researchers can continue to use these materials as they choose without informing the patient (see option 3.2). In addition, if the guidelines are not altered, it will not be possible for subjects to specifically waive their interests in the uses of their tissues and cells when giving informed consent because of the existing ban on the use of exculpatory language (see option 3.4).

Option 3.2: Direct the Secretary of Health and Human Services to modify or remove the exemption regarding the collection or study of existing pathological or diagnostic specimens from the regulatory requirements (46.101(b)(5)).

Current DHHS guidelines exempt research involving the collection or study of existing data, documents, or pathological or diagnostic specimens if these are publicly available or if the donor is otherwise unidentifiable. Researchers are therefore not obliged to disclose their research inter-

ests to sources of specimens when this exemption applies.

Congress could modify or remove this section of the regulations so that it becomes necessary for research subjects covered by this exemption to be informed about and have some say in the use of their tissues and cells. This option would assure that additional research subjects would be informed of the possible uses of biological specimens and related data and may be consistent with the general spirit of the guidelines to protect the interests of the research subject. Removal of the exemption, however, could restrict research on a wide variety of currently available data, documents, records, and pathological or diagnostic specimens when a researcher cannot: 1) determine the identity of the subject, and 2) assure that the subject provided an informed consent as required by the DHHS regulations. Modifying the exemption by removing only pathological specimens or diagnostic specimens could likewise curb research using currently available unidentified specimens, but would continue the exclusion for other existing data, documents, and records.

Option 3.3: ***Direct the Secretary of Health and Human Services to amend the general requirements for informed consent (46.116) to include potential commercial gain as a basic element of informed consent.***

Under the current DHHS regulations, certain information must be provided to each subject during the informed consent process. It could be decided to add a provision requiring that in seeking informed consent, a disclosure be made regarding the potential for commercial gain resulting from data, documents, records, or pathological or diagnostic specimens obtained during the research. Such a requirement could be codified as a basic element of informed consent that shall be provided to each subject (46.l16(a)), or as an additional element of informed consent to be provided to each subject when appropriate (46.l16(b)). Such a requirement would make clear that potential commercial gain is an issue that would be reviewed by the Institutional Review Board.

Option 3.4: Direct ***the*** Secretary of Health and ***Human Services to remove the ban on exculpatory language as it pertains to commercial gain (46.116).***

Under the current DHHS regulations, informed consent documents may not include exculpatory language which is used to make research subjects or their representatives waive or appear to waive any of the subject's legal rights. The intent of this provision is to safeguard subjects and to make certain that they do not relinquish any legal rights. Some subjects may not want to reap financial benefits as the result of or as a byproduct of their participation in research, and some researchers and their sponsors may be deterred from conducting important research if they must share possible financial gain with research subjects. A change in the regulations could be made to modify the prohibition on the use of exculpatory language to permit research subjects to waive any rights to commercial gain. Such a provision would need to be clearly worded. Research subjects should understand exactly what rights are being waived and that they will not be denied treatment to which they are otherwise entitled even if they decide not to waive their rights. If the regulations are amended to permit the use of exculpatory language as it relates to potential commercial gain, the Institutional Review Board will have a greater role.

Option 3.5: Under its power to regulate interstate commerce, Congress could enact a statute to permit and regulate the buying and selling of human tissues and cells.

The advantage of such a statute is that it would offer the possibility of financial compensation to the sources of human tissues and cells. In addition, such a statute would apply to the interstate transfer of these materials from all sources and therefore go far beyond any alteration in guidelines for the protection of human subjects involved in federally funded research. The disadvantage of such a statute is that it would permit commercialization of all human tissues and cells transferred interstate and extend Federal regulation into a previously unregulated area.

ISSUE 4: Is present practice adequate to ensure that health care providers dis-

close their potential research and commercial interests in the care of a specific patient or group of patients?

Option 4.1: Take no action.

Congress may decide that existing or altered DHHS guidelines concerning the protection of human subjects provide sufficient safeguards to ensure that individuals are aware of the purposes and methods of the research in which they are involved. At the present time, however, these guidelines only extend to research subjects participating in federally funded research. There are no protections for research subjects in privately funded research.

There are no guidelines to ensure that health care providers disclose their commercial interests in caring for a particular patient or group of patients. If Congress takes no action, physician/researchers will not be obliged to tell a patient about their intention to develop commercially valuable products from the patient tissues and cells. Congress may decide that the commercial interests of health care providers do not necessitate new forms of disclosure in order for patients to be adequately informed.

Option 4.2: Direct the Secretary of Health and Human Services to promulgate guidelines that require health care providers receiving any Federal reimbursement to disclose any research or commercial interests they may have in the care of a specific patient or group of patients.

If Congress acts to ensure that health care providers disclose their research and commercial interests in caring for particular patients, it will be necessary to discern what sort of commercial interests in particular merit disclosure. Physicians in private practice obviously have commercial interests in treating patients so their practice remains economically viable. It comes as a surprise to many people, however, to learn that their physician might also engage in research using a patient's tissues and cells and subsequently develop a profitable product based on these donated or abandoned materials. The relationship between physician and patient may be compromised if patients suspect that their caregivers may profit in unanticipated ways. The development of guidelines concerning this type of disclosure could promote greater trust between physicians and patients in the delivery of health care.