chapter 2
Introduction

"I suspect at least the patient[s] should have some inherent right in the materials taken from them and any patents . . . at least for their lifetime and conceivably for their heirs' lifetimes."

—John Moore
Congressional testimony, Oct. 29, 1985

"I am lucky in that I am one of the so-called long-time survivors of [an acute leukemia research program]. If progress in the treatment of leukemia or anything else can be made through the use of my cells, then that is my contribution to mankind. I benefited from treatment which came about from years of scientific experiments, by many in and outside my particular place of treatment, funded by government grants as well as university, foundation, private and public funds."

"Human nature being such as it is, I would want to know of any breakthrough that came about as a result of my participation in research. But to those dedicated men and women in research belongs the glory. Without their endless quest, all would be for naught. "

—Mildrene C. Thomasson
Washington Post, July *23, 1986*

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> Experiment V. After evaporating two quarts of urine to dryness by gentle heat, there remained a white cake, which was granulated and broke easily between the fingers. It smelled like brown sugar, neither could it from the taste be distinguished from sugar.
>
> —Matthew Dobson, 1776

Although surely not the earliest use of a human biological material in research, this original observation concerning the urine of a diabetic patient was reported to the Medical Society of London in 1776 (12). Thus, the use of human materials in research is not a new issue. Over the past decade, however, technological advances have resulted in new, enhanced methods for studying and using human body parts—particularly tissues and cells. Using these technologies with intelligence, creativity, hard work, and a measure of serendipity, researchers have greatly increased our understanding of both human health and disease, Human samples are not only an integral part of the biomedical research process, but they are now also used as a component of (or in the production of) a variety of commercial products ranging from drugs and vaccines to pregnancy test kits.

Some of the new research and commercial uses of human biological materials have raised legal and ethical questions regarding the acquisition of bodily substances. These issues are novel; and little has been written about them. They are also extremely complex, and thus it is not surprising that there is no single body of law, policy, or ethics from which indisputable conclusions can be drawn. Questions to consider include:

- Are bodily substances "property, " to be disposed of by any means one chooses, including donation or sale?
- Do property rights to 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 the increasingly commercial relationships between universities and companies?

And, most importantly:

- What are the implications of these issues for scientists, physicians, patients, volunteer research subjects, universities, and the biomedical product industry?

This report does not address the use of tissue for the direct medical benefit of patients who need healthy human biological material—as is the case in organ transplantation, blood transfusion, or artificial insemination—except to the extent that similar legal, ethical, economic, and policy issues occur. Nor does this report explore the special concerns arising from research using special kinds of cells, such as fetal or germ cells.

DEFINITIONS

Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses—including recently developed techniques such as gene cloning and cell fusion.

What are **human biological materials?** Human bodies contain a number of parts that can be useful in biomedical research. Healthy individuals continually produce a number of replenishable substances, including blood, skin, bone marrow, hair, urine, perspiration, saliva, milk, semen, and tears. Human bodies also contain nonreplenishing parts, such as oocytes or organs, which may either be vital (e.g., heart) or to some extent expendable (e.g., lymph nodes or a second kidney). Finally, diseased examples of these body parts also exist.

While OTA refers to all human parts-replenishing and nonreplenishing, living and nonliving, healthy and diseased-collectively as **human biological materials,** this report is primarily concerned with the biological materials that are most frequently obtained from humans and used in biotechnology: **tissues and cells.** The terms **specimens, samples, body parts, human tissue, bodily substances, primary tissue,** and **biological** are also used. **OTA distinguishes these undeveloped human biological materials from the biological inventions developed from them (and in some cases patented) such as cell lines, hybridomas, and cloned genes.**[1] These inventions, and the techniques investigators use to derive them, are described in chapter 3. The issue of patentability of most biological inventions in the United States is discussed in chapters 4 and 5.

*"Products of nature," are unpatentable because they lack novelty ***(6).*** However, the biological inventions being patented today are not crude, unaltered products of nature. A claim to the entire genetic material of a single cell would probably be rejected; but one may properly seek a patent on an isolated gene encoding a protein of interest (see ch. 5).

CASE HISTORIES

Reports of sales of cells have generally aroused more public curiosity than controversy. In 1986, a Colorado company, Clonetics Corp., introduced the world's first commercial product that contains live normal cloned human skin cells (see figure 2-1). The product is sold to basic researchers who use it to study a variety of questions. Pharmaceutical, cosmetic, and other firms also use the cloned skin cells to test products. Clonetics uses samples from elective surgery (e.g., plastic surgery) that are purchased from both patients and doctors (3, 7,9).

In another instance, when hemophiliac Ted Slavin was discovered to have a high concentration of antibodies to the hepatitis B virus, he marketed his blood for up to $10 per milliliter (a milliliter is approximately 1/4 teaspoon, so this is the equivalent of more than $6,000 per pint) to commercial organizations while providing it free to noncommercial hepatitis researchers. Slavin made news when he formed a company, Essential Biological, that not only marketed his own blood but that of others with rare blood characteristics. Before his death in 1984, his blood benefited research on the development of a hepatitis vaccine and prevention of liver cancer. Recently, clinical researchers who used Slavin's blood eulogized him as a gallant man who greatly contributed to biomedical research efforts (2).

However, disputes over the acquisition and ownership of human cells have occurred. While such cases have arisen infrequently, they have great practical significance to the parties involved and have been scrutinized by the research and corporate communities for their broader implications. Four cases involving human biological materials provide insight into the complex issues that can arise.

Figure 2.—Normal Human Epidermal Cells in Culture

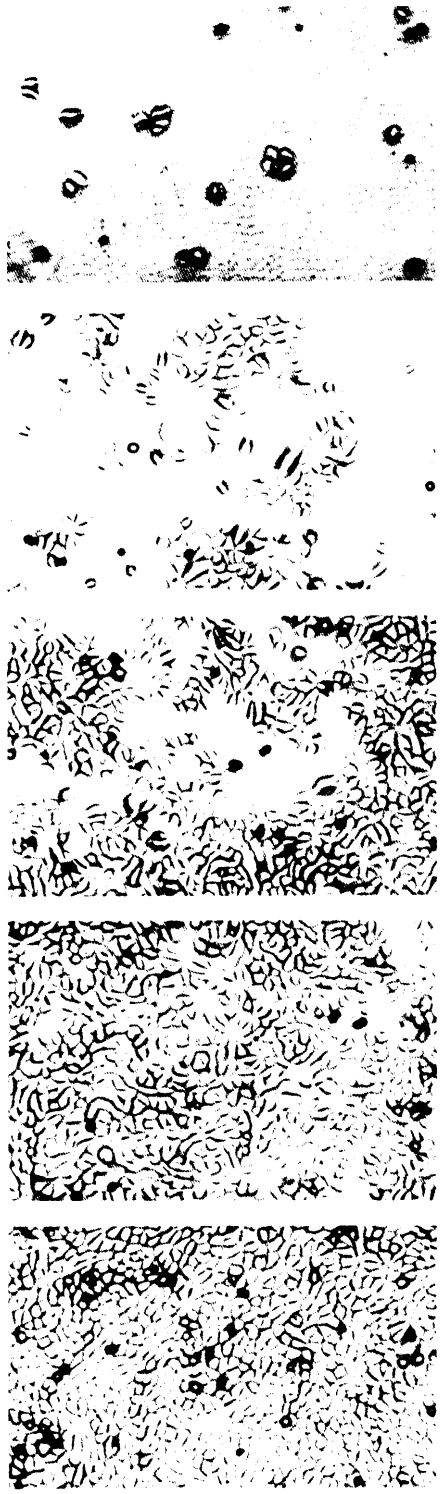
(A) 2 days after the skin samples are put into culture, clonal growth can be observed;

(B) after 4 days the colonies are developing rapidly;

(C) at 6 days the culture is ready to be shipped;

(D) after 8 days, the culture can be divided into two or more subcultures;

(E) 10 days after the first skin cells were seeded into culture, the human skin cells have multiplied to cover the surface of the growth chamber.



Normal human skin cells are supplied commercially in culture.

Photo credits: Clonetics Corp., Boulder, CO.

Case 1

In 1962, a Stanford University microbiologist working under **a** Federal research grant established the first strain of normal human cells in culture. After developing and cultivating the cell line, designated WI-38, the scientist formed a company to market the cells for use in the production of viral vaccines. The National Institutes of Health claimed that the cells were Federal property and charged him with wrongfully exploiting his federally funded research. Stanford was apparently about to take disciplinary action when the researcher resigned and filed suit seeking title to the cells. The dispute was finally settled out of court in 1981, with the scientist retaining the money from sales of the cells but with the question of ownership of the cell line still unresolved (11),

Case 2

In 1977, a man with leukemia agreed to allow a sample of his cells to be taken from his bone marrow for scientific research. Although the man died shortly afterwards, claims over who may profit from his cells continued.

Two research hematologists at the UCLA Medical Center (one of whom was also involved in case 2) succeeded in making the cells grow and divide, producing a new cell line that could be used to study leukemia. A sample of the new cell line, named KG-1, was sent to a National Cancer Institute (NCI) researcher with written instructions limiting its use. During a screening procedure, the NCI scientist noticed that the cell line produced a low concentration of interferon, a natural antiviral protein. The NCI researcher sent a sample of KG-1 to the Roche Institute of Molecular Biology, a wholly funded research arm of pharmaceutical manufacturer Hoffman-LaRoche, and they found that the cell line could be manipulated to optimally produce interferon. At Genentech, a biotechnology firm with contracts from Hoffman-LaRoche, techniques were used to isolate substantial quantities of the interferon gene from the cell line.

A dispute ensued between the University and Hoffman-LaRoche over who in fact owned the KG-1 cell line. The University, as home of the scientists who had developed the cell line, claimed

ownership and the right to royalties from the production of interferon. Hoffman-LaRoche also claimed ownership and had even filed a patent application covering both the interferon and the manufacturing process. The dispute was finally settled out of court in 1983, with the drug company retaining the right to use the cells and genes in exchange for payment of an undisclosed sum to the University (11).

Case 3

In both the Stanford and UCLA cases, claims to cell line ownership were based on the intellectual (intangible) contributions of researchers. Legal conflict over cell line ownership has also occurred based on the tangible contribution of biological materials.

In early 1981, a researcher at the University of California, San Diego, was developing human hybridoma cell lines that would secrete antibodies to cancer cells. Learning of the project, Dr. Heideaki Hagiwara suggested the use of lymph cells from his mother, who was suffering from cervical cancer. The researcher agreed, and the Hagiwara cells were fused to an immortal cell line developed and patented by the investigator. A hybridoma that secreted an anti-tumor antibody was found.

Without the investigator's permission, Hagiwara took a subculture of the hybridoma cell line with him to Japan and gave it to the Hagiwara Institute of Health, directed by his father. The university and the Hagiwaras subsequently executed an agreement that permitted the Hagiwaras to use the cell line for scientific research but forbade their transfer to any other party for commercial purposes.

Several months later, the Hagiwaras asserted rights to the cell line and antibody, claiming that they had tangible property rights in the original tissue and were therefore entitled to a pecuniary interest in the derivative cell line. In 1983, the parties reached an agreement under which the university retained all patent rights and the Hagiwaras received an exclusive license to exploit the patent in Asia (4,13).

Case 4

In 1976, John Moore was diagnosed as having a rare form of cancer, hairy cell leukemia, a condition that affects an estimated 250 Americans each year (1). The recommended treatment for Moore's condition was removal of the spleen and surgery was performed at the University of California, Los Angeles Medical Center. As a patient, Moore had signed a standard surgical consent form (providing for the postoperative disposition of the tissue) to remove his diseased spleen, which had enlarged to approximately 40 times its normal size.

After the surgery, Moore's doctor and his technician developed a cell line (designated "Mo") from a sample of Moore's spleen obtained from the pathologist. These scientists found that the cell line developed from the spleen produced high quantities of a variety of interesting and potentially useful proteins. In 1979, the university applied for a patent on the "Mo" cell line and in 1984 a patent naming the scientists as inventors was obtained and assigned to the university. In 1981, the university, on behalf of the scientists, entered into a 4-year collaborative research program with two biotechnology and pharmaceutical companies for exclusive use of the "Mo" cell line.

After his splenectomy, blood samples were obtained from Moore by the doctor over the course of several years. In 1983, Moore initially signed a research consent form waiving any claims to the results of the university's research and giving the university all rights to products. On a research consent form signed at a later date, however, Moore refused to waive his rights to any products developed from his blood.

In 1984, Moore filed a lawsuit claiming that his blood cells were misappropriated, and that he was entitled to share in profits derived from commercial uses of these cells and any other products resulting from research on any of his biological materials (the patent for the "Mo" cell line clearly states that it was derived from splenic tissue), In March 1986, the trial judge dismissed Moore's complaint as failing to state a legally cognizable claim. As this report goes to press, this ruling is being appealed (5,8)10,14,15).

THE PROBLEM OF UNCERTAINTY

Uncertainty about how courts will resolve disputes between specimen sources and specimen users could be detrimental to both academic researchers and the infant biotechnology industry, particularly when the rights are asserted long after the specimen was obtained. The assertion of rights by sources would affect not only the researcher who obtained the original specimen, but perhaps other researchers as well,

Biological materials are routinely distributed to other researchers for experimental purposes, and scientists who obtain cell lines or other specimen-derived products, such as gene clones, from the original researcher could also be sued under certain legal theories (see ch. 5), Furthermore, the uncertainty could affect product developments as well as research. Since inventions containing human tissues and cells may be patented and licensed for commercial use, companies are unlikely to invest heavily in developing, manufacturing, or marketing a product when uncertainty about clear title exists.

Research using human biological materials could be thwarted if universities and companies have difficulty obtaining title insurance covering ownership of cells or genes, as well as liability insurance for related disputes. Insurance carriers will likely be concerned not only with suits by individuals who are identifiable as the specimen sources, 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 tissues and cells in biomedical research makes it highly impractical and inefficient to identify the sources of the various specimens for purposes of valuing individual contributions. These concerns are addressed in chapter 7.

SUMMARY AND CONCLUSIONS

The government has always maintained an interest in the legal, ethical, and economic implications of research it is funding, and this interest is magnified when such research results in inventions that are patentable under Federal law. This report considers each of these aspects, as they apply to research and product development using human biological materials—undeveloped tissues and cells. The report also examines the scientific techniques that serve as the foundation of the boom in biotechnology and the parties interested in the boom.

This report does not address the use of tissues for the direct medical benefit of patients who need healthy human biological material—as is the case in organ transplantation, blood transfusion, or artificial insemination-except to the extent that similar legal, ethical, economic, and policy issues occur. Nor does this report explore the special concerns arising from research using special kinds of cells, such as fetal or germ cells.

Advances in technology and increased use of human biological materials for therapy, research, and commerce has raised a number of important questions that likely will need to be addressed in the immediate future. There are no easy answers. The issues are novel and complex and no single body of law, public policy, or ethics directly applies. But regardless of the merit of claims by the different interested parties, resolving the current uncertainty may be more important to the future of biotechnology than resolving it in any particular way.

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