Chapter 4
The Interested Parties

"Biomedical research is in considerable measure so esoteric an activity that a great deal of the social control that guides it must be in the hands of the biomedical research community itself. Yet, like all other specialized and esoteric social activities, biomedical research is too important to the larger society to be left entirely to its experts. In part it needs to be effectively and continuously scrutinized and controlled by outsiders. An effective system of control, including both insiders and outsiders would better protect all the parties of interest . . ."

—Leon R. Kass
***Science,* 174:779-788, 1971**

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Why has controversy arisen over the use of human biological materials, and who are the stakeholders in this controversy? How has it even come to pass that naturally occurring substances, such as genes, plasmids, and even organisms, can be patented? While the technological advances described in chapter 3 have increased the availability and promise of new inventions and products of great importance to human health, the changing legal climate in the United States also has been a factor responsible for increasing interest in human biological materials. These events have led to an increased commercial interest in human specimens and have affected three major groups of stakeholders: the sources of human tissues and cells, the research community, and the biotechnology industry.

WHY COMMERCIAL INTEREST IN HUMAN BIOLOGICAL RESEARCH AND INVENTIONS?

The controversy that has arisen over the use of human tissues and cells can be attributed in part to two landmark events that occurred in 1980 to accelerate industry-sponsored research and 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 recombination, thus opening the possibility that products containing 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.

Patentability of Recombinant and Nonrecombinant Cell Lines

In the early 1970s, General Electric microbiologist Ananda Chakrabarty used both classical genetic selection and recombinant DNA techniques to find and develop a novel bacterial strain capable of digesting oil slicks. Chakrabarty and his employer sought patent protection under the Federal patent statute (35 U.S.C. 101). While judging the process for producing and maintaining the new bacterium to be patentable, the Patent and Trademark Office examiner rejected patent claims to the bacterium itself. The Patent and Trademark Office's Board of Appeals upheld the examiner's rejection on the ground that living organisms were ***per se*** unpatentable.

Later, the U.S. Court of Customs and Patent Appeals (CCPA) reversed this ruling (29), relying on a prior decision in In re ***Bergy*** that held "the fact that microorganisms are alive is a distinction without legal significance" (27). Bergy concerned the creation of a biologically pure culture of a naturally occurring but previously undiscovered micro-organism capable of efficiently producing an antibiotic similar to penicillin. A patent had not been sought for the naturally occurring microorganism, but one was sought for the purified sample and the processes used to create the pure culture.

A chain of related Supreme Court and CCPA decisions ultimately led to a five-to-four Supreme Court ruling upholding the CCPA's decision that genetically engineered microorganisms are within the scope of patentable subject matter defined by section 101. The high court ***Diamond v. Chakrabarty*** decision (14) makes it clear that **the question of whether or not an invention embraces living matter is irrelevant to the issue of patentability, as long as the invention is the result of human intervention.**

The court did not directly address the question of whether purified nonrecombinant cell samples are patentable since ***Chakrabarty*** dealt with a genetically recombined organism and the ***Bergy*** case was not directly considered, However, the CCPA's second ***Bergy*** decision (28) suggests that a puri-

fied strain of naturally occurring organisms is statutory subject matter unless precluded under the "product of nature" doctrine (6).

Under the product of nature doctrine, a cell or other substance occurring in nature is not patentable unless it is given a substantially new form, quality, or property not present in the original (6,46). Purification of a naturally occurring substance or organism must result in a substantial change in its characteristics, functions, or activity for the purified material or cell line to be patentable (6). If a patent examiner decides to reject patentability for an invention on grounds that it is a product of nature, he must show that the claimed product, such as a biologically pure culture, is **likely** to exist in nature as a result of natural processes and not merely that it **possibly** exists in nature (6,56).

The Patent and Trademark Office has historically taken the position that, in the absence of a Supreme Court ruling addressing the issue, higher life forms such as mammals, fish, and insects will not be considered to be patentable subject matter under section 101 (56). This position finds some support in a statement in ***Bergy*** that biologically pure cultures created and used for their chemical reactions are more similar to inanimate chemical compositions than they are to animals or plants (27). However, the rationale for this position is somewhat weakened by the Court's statement in ***Chakrabarty*** that "Congress intended statutory subject matter to include anything under the sun that is made by man" (14).

Patenting and Licensing of Government-Sponsored Inventions

The Federal Government is the primary source of funding for basic biomedical research. Yet until 1980, no single patent policy existed with respect to government-supported research. Each agency developed its own rules, resulting in 25 different patent policies, and under this system, only about 4 percent of some 30,000 government-owned patents were licensed (40). Furthermore, the government policy of granting nonexclusive licenses discouraged investment, since a company lacking an exclusive license was reluctant to pay the cost of developing a product and building a production facility. Potentially valuable research thus remained unexploited.

Congressional concern about this so-called "innovation lag" prompted efforts to develop a uniform patent policy that would encourage cooperative relationships between universities and industry, with the goal of taking government-sponsored inventions off the shelf and into the marketplace. In 1980, Congress passed the Patent and Trademark Amendment Act (Public Law 96-517) and added additional amendments in 1984 (Public Law 98-620).[1] The law allows nonprofit institutions (including universities) to apply for patents on federally funded inventions, with the Federal agency retaining a nonexclusive worldwide license. Universities are required to share royalties with the inventor and to use their own share for research, development, and education. The patent policy of the National Institutes of Health (NIH) served as a model for the uniform patent policy established by the law.

Effect of 1980 *Patent Law* Changes *on Biocommerce*

The impacts of technological breakthroughs and the changing legal climate on human biological product development is demonstrated by a 1985 survey of American medical institutions conducted by the House Science and Technology Committee's Investigations and Oversight Subcommittee. During the 5 years from 1980 to 1984, patent applications by universities and hospitals for inventions containing human biological increased more than 300 percent as compared with the preceding 5-year period and constituted 22 percent of all patent applications filed by these institutions. Forty-nine percent of all medical institutions have applied for such patents (50).

Whether these and forthcoming patents will be of commercial value is difficult to assess. The pharmaceutical industry has usually experienced a higher rate of commercial value for its patents than industry in general (10). There is reason to believe that biopharmaceuticals will have a still higher rate since they often have the potential

[1]The U.S. Department of Commerce recently requested comment on revised regulations under this statute (51 FR 22508).

to supplant an entire, well-established market occupied by a conventional drug (41). At this point, however, it is still too early to determine what pattern will be established in the biotechnology industry for the commercial value of patents.

SOURCES OF HUMAN TISSUE

Individuals who are sources of human tissues and cells are one major group of people affected by the U.S. Supreme Court and congressional actions contributing to increased development and commercialization of human biological materials. Tissues and cells can be removed from sources for medical purposes, research purposes, or both. The primary medical reasons for withdrawing human biological materials are diagnosis (removal of specimens to determine the nature and extent of a disease) and therapy (removal of diseased tissue, either permanently or for treatment and reintroduction, as in renal dialysis or homologous bone marrow transplants). Removing human specimens can involve a variety of procedures, including:

- aspiration of bodily fluids (e.g., blood, amniotic fluid) through a needle;
- examination of cells from a surface (e.g., skin or cervix cells from a Pap smear);
- surgical removal of nonsurface tissue (e.g., lymph node biopsy, tumor material); and
- noninvasive procedures to collect excretions (e.g., urine and feces) and certain secretions (e.g., semen, saliva, milk, and perspiration).

There are three major categories of sources of human tissues and cells: patients, healthy research subjects, and cadavers.

- Patients area source of both normal and atypical specimens and these individuals may or may not be research subjects. Patient-derived specimens may be ‘(leftovers” 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 organs (e.g., corneas) destined for research rather than transplantation.

While the different classifications of human sources—patient, volunteer research subject, or cadaver—may seem to be fairly straightforward, the human relationships involved between sources and physician/researchers (or another interested party) are more dynamic than these categories suggest.

For example, the distinction between an individual as a patient versus a research subject can sometimes change over the course of time. The relationship between physician and patient can also evolve from physician-patient to researcher-subject. Thus, if a patient’s specimen is removed for diagnostic or therapeutic purposes and the physician subsequently uses the specimen in research, should the patient still be considered a patient, or has he become a research subject and has the relationship become one between research subject and researcher? Or, if a patient hospitalized with a broken leg is asked to donate a blood sample, should he be considered a research subject because any risk he undergoes is for altruistic rather than selfish reasons, or is he still a patient because of the possibility that he may feel coerced to cooperate with the hospital staff on whom he is physically and psychologically dependent?

Determining whether a person is a patient or a research subject is relevant in determining the applicability of Federal regulations governing federally funded research using human biological materials. These issues are addressed further in chapter 6.

THE RESEARCH COMMUNITY

Investigators who use human tissues and cells in their research are a second stakeholder in the controversy about access, use, and profit from specimens. A recent survey conducted by the House Committee on Science and Technology found that 49 percent of the researchers at medical institutions surveyed used human tissues or cells in their research (50). According to one recent estimate, at least 500 principal investigators nationwide use human cell lines (42). NIH provides grants to about 200 individuals whose primary research focuses on human cell lines and to an undetermined number of scientists whose secondary interest is human-related (34). The use of human specimens is principally due to three factors:

- the newly emerging abilities to isolate increasingly smaller amounts of important naturally occurring human biological factors (also known as biopharmaceuticals, bioresponse modulators, or biological mediators);
- the ability to produce virtually unlimited quantities of these factors, usually found in minute amounts in the body, through recombinant DNA methods; and
- the invention of hybridomas, making possible the generation of large, pure supplies of specific antibodies (47).

Obtaining Human Biological Materials for Research

Although tens of thousands of samples of human tissue are probably used in research, detailed information on the amount and type of human biological materials used is difficult to obtain. No central records are kept on this data, and information on the source or use of human biological by biotechnology companies is often considered confidential business information. Moreover, the ways in which researchers obtain human samples vary with the type of scientist and the nature of the research.

Physicians working at a university hospital will often obtain tissue as a result of biopsies or surgery done on their patients. The physician/researcher may obtain samples directly from the operating room in cases when fresh, live tissue is needed, or receive the material after pathologists have examined it (48).

Nonphysician researchers or clinicians needing human tissues or cells that are not obtainable from their own patients or patients within the hospital obtain specimens by other avenues. Informal transfers are common among researchers at hospitals and universities around the country. Researchers and companies are becoming more cautious, however, and are moving toward a much tighter, more formal system of transferring research materials. This caution is a result of concerns over patent and ownership rights and it applies to newly isolated tissue, as well as investigator-developed cell lines and gene clones (41,43).

Researchers at some large universities and research institutes also can obtain needed material from volunteers who are asked to donate tissue samples. For example, at NIH, blood is collected by the NIH Blood Bank specifically for research purposes. Most volunteer donors are members of the NIH staff, although some outside donors are also used. Payment for blood donations for research purposes is usually about $25. Volunteers providing bone marrow for research purposes receive around $75 for a specimen (45). Generally, these types of arrangements are ad hoc, and no systematic data are available on the amounts and type of human materials collected or on payments for such material.

Researchers at biotechnology and pharmaceutical companies who need human biological also have a variety of options at hand for obtaining materials. They can pay individual volunteers for occasional specimens, usually of blood, or purchase outdated blood from the Red Cross or other blood banks. Biotechnology companies often obtain specimens as a result of their research relationships with universities and medical research centers. The biotechnology company may obtain specimens either through individual affiliations with university/hospital researchers or through research arrangements with university and hospital departments (12,25,38)41,43),

Organized repositories provide an additional avenue for both noncommercial and commercial

investigators to obtain research material. Most of the material available from these "warehouses" are not human biological as defined in this report–i.e., primary tissues or cells–but are cell lines or gene clones (containing human DNA pieces) developed and discovered by investigators and deposited at the repositories. Organizations in this field are usually funded by NIH and operated on a nonprofit basis, providing samples of tissue and genetic material to qualified researchers for a nominal processing fee. Many universities and cancer research centers maintain their own collections as well. Table 6 lists some of these facilities and indicates some of the types of material each stores.

Although no systematic survey was undertaken for this analysis, anecdotal information suggests that most university or other nonprofit researchers usually are able to obtain the samples they need for research, but individuals who need certain types of tissue must make their own arrangements. The process, however, of obtaining samples is sometimes characterized as a "scramble. " Additionally, odd samples are usually less in demand than some common types of cancer or tissue. Research popularity coupled with a higher incidence of a particular tumor can result in fierce competition for a continued supply of new specimens. Colon and bladder carcinomas are two tissues currently in high demand (1,13,23).

Table 6.— **Repositories for Human Tissues and Cells, Cell Cultures, and Cloned Genes**

Organization	Type of material collected
The American Type Culture Collection (ATCC)[a]	Cell cultures, cloned genes
The Human Genetic Mutant Cell Repository, Coriell Institute (formerly the Institute for Medical Research) .,[b]	Cell cultures
The National Cancer Institute, Biological Carcinogenesis Branch	Sera, tumor tissue (benign and malignant)
The Cell Culture Center, Massachusetts Institute of Technology	Cell cultures

[a]TheATCCis one of the largest repositories of Its type maintaining some 40000 cultures including about 1 325 human cell lines (48) These materials are providedtononprofit researchers for an average fee of $40 and to for-profit researchers at an average fee of $64 Many researchers send samples of their cell cultures to the ATCC(or other repositories) once they have been developed and reported 10 avoid the time and money required to respond to requests for samples from other researchers Samples are required to be placed in a repository if a patent application has been filedrelatingtothe sample Access to samples for which patents are pending is strictly restricted once a patent is granted [he sample is available to anyone In 1985 ATCCdistributed between 12000 and 19000 human cell cultures 10 researchers the majority of which went to universities and hospital research centers (see refs 19351

bThe Human Genetic MutantCellRepository with 3550 human celllinesinstock **responded** to 3472 requests in 1985 (see refs 52 53 I

SOURCE Off Ice ot Technology Assessment 1987

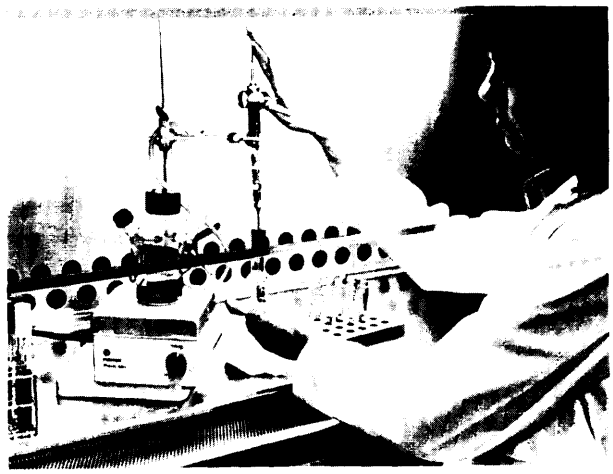


Photo credit: National Institutes of Health

Human cell lines at the American Type Culture Collection's Human Tumor Cell Bank are put into ampules for shipment to researchers.

To assist in this process, various organizations, networks, and interchanges, are undertaking more comprehensive coordinating activities. In 1980, a nonprofit organization, the National Disease Research Interchange (NDRI), pioneered the world's first retrieval/preservation/distribution mechanism for organs and tissues. NDRI makes over 100 types of tissues available to researchers studying a wide range of diseases, including diabetes, retinitis pigmentosa, cardiovascular disease, cystic fibrosis, and glaucoma (55). In response to inquiries, the National Cancer Institute (NCI) has issued a request for cooperative agreement applications to establish a cooperative network, including computer communication, to improve collection and distribution of human cancer tissues (54). The network is not a tissue bank, but will respond to requests from investigators to help them obtain the multiple fresh tumor samples they need to screen for tumor protein markers, genes, and other characteristics (1). NIH recently awarded a contract to the University of Minnesota Hospital in Minneapolis for a "Liver Tissue Procurement and Distribution System. " This program is designed to establish regional centers to collect livers removed from transplant patients and then distribute them to researchers nationwide. Finally, a project at the University of Alabama is also be-

ing designed to address shortages in the availability of tissue for research (23).

Uses of Tissues and Cells in Research

The research community uses undeveloped tissues and cells provided by sources for a wide range of purposes. Material obtained from an individual is not necessarily used strictly for research purposes, however, but can be divided for medical, research, or commercial uses. In fact, diagnostic, therapeutic, research, and commercial uses of biological are usually intertwined, sometimes inextricably. The present economic dynamics of research coupled with the proliferation of biotechnology companies have spawned a plethora of university-industry relationships that have made it increasingly difficult to separate the use of human samples in university (or other institution-based) basic research from basic and applied research in commercial settings.

Uses of human tissues and cells in basic research are diverse and thus difficult to categorize, once human biological material is provided by an individual, it is examined, manipulated, and developed by researchers. Human tissues and cells can be examined directly from the patient with limited handling (e.g., screened for a particular tumor marker) or they can be manipulated extensively to obtain a useful research tool or potentially marketable product. Generally, basic researchers use these materials to study the characteristics and functions of healthy and diseased organs, tissues, and cells.

The researcher's choice of a source of specimen is based on the type of tissue being studied and the goals of the particular research project. The material could be used for a "one-shot" experiment or used in the long-term development of something (e.g., a cell line, cloned gene, or gene probe) that expands the base of knowledge about a complex problem and advances the investigator's project. Specimens can also be used by the researcher to create cell lines that generate a continual supply of products such as monoclinal antibodies; provide insight into a patient's hereditary disease; provide the basic genetic material from which recombinant products can be produced; or serve as a medium to propagate viruses or amplify cloned DNA sequences. At the most fundamental scientific level, human material is used in experiments to examine and understand basic biological processes. This basic research can subsequently lead to other uses of human tissue, such as product development by the commercial sector.

Commercial enterprises use specimens as raw materials for both product-oriented purposes and nonproduct--oriented basic research. The use of human biological by companies for nonproduct research differs little from that just described for nonindustrial research. In product-oriented research, a specimen could be used for a one-time process to produce or test something, or it could be used as part of a long-term investigation to produce a product. Proteins might be extracted from human specimens or tissue culture cell lines derived from specimens. Similarly, genes for these useful proteins might be isolated by industrial researchers directly from undeveloped material or from an established cell line. These cloned genes can then be used to mass produce large quantities of therapeutic or diagnostic human-derived products. Human insulin, human growth hormone, and human alpha-interferon are three products produced through recombinant DNA techniques that are licensed for therapeutic use in the United States. Standardized diagnostic products (e.g., pregnancy test kits) often contain human proteins.

Companies also sometimes use human-derived material to study the efficacy of an item prior to marketing, to meet safety criteria, or to manufacture a biological product such as a viral vaccine. Specimens can be used as reagents in federally required, preclinical testing of pharmaceutical products (44). Use of such reagents is necessary to develop the potential value of the product, but is not itself the marketable item. The material used by the company for testing or manufacturing could be newly isolated specimens or standard cell lines. The new technologies, such as hybridoma technology or recombinant DNA technology, led the Food and Drug Administration (FDA) to recently amend its regulations to establish general requirements for cell lines used for manufacturing any biological product for human use (5 I FR 44451).

Some firms maintain that they do not use any original human tissue in research, concentrating their efforts on established cell lines instead. These companies obtain and manipulate generally available cell lines, resulting in new, unique, or improved cell lines.

The Research Process and Rarity of Human Tissue

To what extent are human biological materials, provided by any single (or very few) individuals), potentially profit-yielding to the research community because the material is both commercially useful and rare? Biomedical research and development using human material is a dynamic process that rarely culminates in a profit-making product. **Research results are typically a series of several joint efforts with specimens provided by several individuals.** This diversity is critical to advancing the knowledge about an area under study and the expectation of developing a commercial product at the outset of the research is often extraordinarily small. **Thus, any product developed is a consequence of many source and researcher contributions. A determination of the contribution of any single individual in the marketable product would be speculative.**

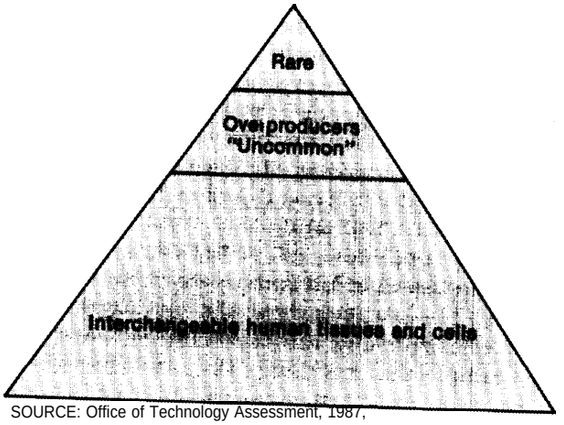
In general, the value to the researcher of certain types of tissue results more from the key issues of access and availability to the sample than from the inherent rarity or commercial potential of the tissue. Both industry and nonindustry-supported investigators usually are interested in a specified type of tissue that occurs with a known frequency in the population, but cannot be termed truly rare—such as cells from a cystic fibrosis patient; a particular type of tumor (e.g., breast, lung, liver, or other); or a collection of samples from several generations of a family. Certain types of specimens might be more easily obtained (e.g., blood instead of bone marrow), or certain samples might not be commonly removed during surgery (e.g., healthy spleens). The typical goal when obtaining human specimens is acquiring any liver tumor, for instance, not obtaining one from a specific individual that is truly rare.

Although the goal of a researcher is often to obtain many random samples of human tissue or cells, once a scientist has investigated different tissue samples it may become apparent that one or a few specimens (or the cell line the investigator has developed) "overproduces" an interesting substance. Some people might naturally produce greater than normal amounts of a substance, or some might overproduce it because of an illness. This overproduction could enable the researcher to identify a novel entity that would otherwise have gone undiscovered, or the overproduction could be useful in further research and experiments (21)—particularly if the investigator has been fortunate and able to establish a culture of the sample that continues the overproduction. Thus, once found (usually serendipitously) a novel tissue or cell can become a valuable research tool or be developed into a potential commercial product. It should be emphasized, however, that a systematic method of obtaining such unique tissues or cells does not appear to exist. **Furthermore, unique human samples do not necessarily have any actual or potential commercial value.**

It is conceivable, of course, that one person or only a handful of people are overproducers of a potential commercial substance. More likely, however, many people are overproducers but simply have not been identified by researchers (nor could they feasibly be identified). Furthermore, while some people are overproducers, nearly all persons are capable of being high, moderate, or low producers of the substance (unless an individual has a deletion in the gene for the substance—which is a rare condition itself), and once the substance has been identified with the aid of the overproducer, it usually can be detected in and isolated from anyone's tissue. Thus, while the original specimen(s) may have been useful to initially identify an interesting product, its value for commercial exploitation is diminished because the sample is not truly rare.

In a few instances, however, a specific biological substance is sought in a group of individuals to produce a specific quantity of a pharmaceutical product (which may or may not be produced with the aid of biotechnology). These sources are usually paid for their specimens; the amount paid depending on a variety of factors, including the

Figure 11.- Rarity of Human Tissues and Cells Used in Biotechnology



SOURCE: Office of Technology Assessment, 1987.

number of people who are potential sources. An example would be the bleeding of people with chronic hepatitis who have the viral antigen necessary to prepare hepatitis B vaccine from human serum (9). In these isolated instances, a reasonable attempt can be made to determine the ratio of source material to final commodity.

In summary, **the issue of rarity in human biological used in biotechnological research takes the form of a pyramid (see** figure 11). At the bottom are the vast majority of materials, relatively common and easy to obtain (though by no means does this imply an infinite supply). Much farther up the pyramid is an intermediate level, where particular samples may exhibit uncommon characteristics (e.g., the overproducers of certain substances mentioned above) or occur in the population at a low frequency (e.g., a genetic disorder like Tay-Sachs). At the top of the pyramid are the few cases of true uniqueness, which are by definition difficult, if not impossible, to identify in advance of chance discovery. **Assigning, a priori, a value to any one level is not possible since a commercial product can be developed from tissues and ceils obtained from any level.** Finally, to an increasing degree, both the "uncommonness" of cell tissue at the intermediate level and the "rarity" of some specimens at the top level can be overtaken by technology. That is, rarity of the original sample is not the only important factor because as newer techniques develop, researchers are better able to detect novel substances or purify smaller amounts of known compounds. Once the peculiarities of the tissue or ceil line have been identified and studied, biotechniques (e.g., gene cloning) provide a means to reproduce the peculiarity without further need of the material itself,

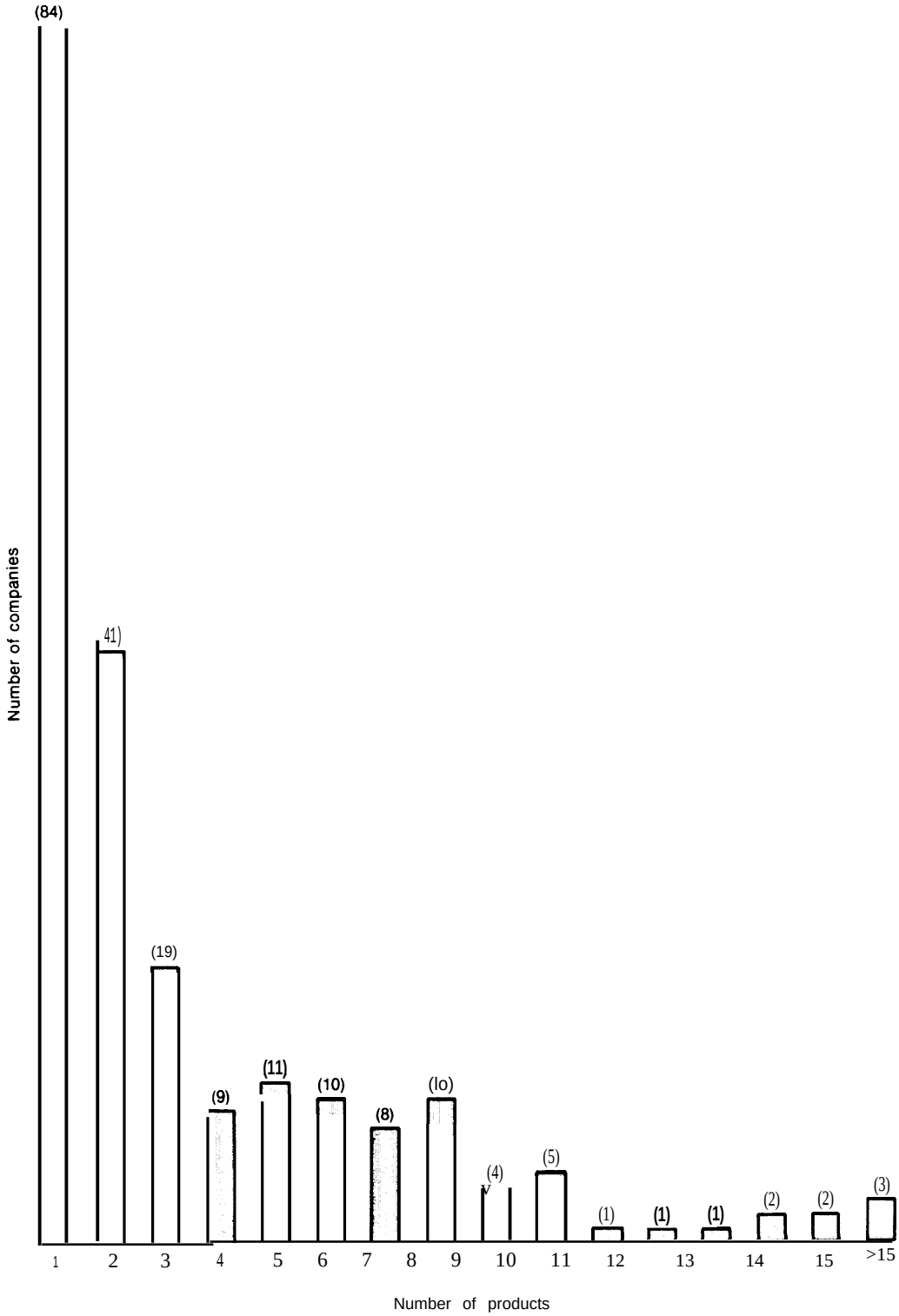
INDUSTRY

The biotechnology industry is a third major stakeholder 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, A detailed treatment of commercial biotechnology activities was published in 1984 by OTA (51); thus this section provides only a brief description of pharmaceutical. related biotechnology companies to give a sense of the current and projected levels of activity in the industry. This section also discusses the product development process.

The Companies

There are nearly **350 commercial** biotechnology firms in the United States actively engaged in—biotechnology research and commercial product development and approximately **25 to 30** percent appear to be engaged in research to develop a human therapeutic or diagnostic reagent (37), Many companies are developing several human therapeutic products (see figure 12). Most, but not all, of the human therapeutic products are derived from human tissues and cells, or human cell lines or cloned genes. (Most human diagnostic reagents are rodent-derived.)

Figure 12.—Number of Human Therapeutic Biotechnology Projects by Company



SOURCE: L I. Miller, *Biotechnology Industry 1986 Fact Book (New* York: Paine Webber, 19S6).

In addition to the commercial firms operating in the United States, 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. Recent financial statistics on the top 10 U.S. firms in the industry are provided in table 7.

Through 1985, no new biotechnology firm had reported annual sales over $100 million or net profits over $6 million. Revenues in the industry have come largely from contract research and research and development (R&.D) partnerships, rather than product sales (7). Since 1980, the biotechnology industry has raised about $1 billion in corporate and public investments, excluding about $400 million in R&D limited partnerships (5). **Nevertheless,** many business analysts consider that the human biological market has come of age in the last 2 years, as witnessed by government approval for marketing of the industry's first commercial therapeutic products.

Table 8 is a business analysis of the human therapeutic products (many using human-derived material) most likely to be marketed in this country over the next 10 years. The industry as a whole is actively researching and developing over 100 different therapeutic products with commercial potential, as demonstrated in table 9. Again, many, but not all, of these products use human-derived material.

The established pharmaceutical industry's involvement in biotechnology indicates that biotechnology is viewed as commercially valuable. These established firms provide two significant advantages to fledgling, startup companies. First, the experience and long-term funding capacities of pharmaceutical firms are believed to be needed for the extensive product testing phases that must precede any commercial marketing of a human therapeutic product (57). Second, the professional sales forces of the pharmaceutical companies are seen as necessary for immediate, successful marketing of biotechnology products. Major multinational pharmaceutical firms based in the United

Table 7.-Financial Statistics for Selected Biotechnology Companies (as of Dec. 31, 1985)

Company	Annual sales ($ millions)	Net profits ($ millions)
Genentech (CA)	89.6	5.6
Cetus (CA)	45.9	1.4
Biogen (MA)	31.4	– 19.1
Centocor (PA)	22.4	3.5
Amgen (CA)	19.8	–1.5
Genex (MD)	16.2	– 15.9
California Biotech (CA)	9.6	–0.5
Collaborative Research (MA)	8.8	4.3
Molecular Genetics (MN)	8.3	–2.5
Integrated Genetics (MA)	7.3	–3.7

SOURCE: Shearson Lehman Brothers, Inc. (reprinted in The *Economist,* Apr. 19, 1966)

Table 8.—Estimated U.S. Marketing Date for Some Human Therapeutic Products[a]

1982	**1990**
Insulin	Bone morphogenic protein
1983	Colony stimulating factor (alpha)
1984	
1985	Colony stimulating factor (GM)
Human growth hormone	
1986	Colony stimulating factor (megakaryocyte)
Interferon (alpha)	Colony stimulating factor (granulocyte)
Orthoclone OKT-3	
Hepatitis B vaccine	Colony stimulating factor (microphage)
1987	
Immunoagents	Human osteogenic protein
Immunocytotoxic agents	Interferon (gamma analogue)
Immunotoxins	
IMREG-1	Interferon (gamma fragment)
Interferon (beta)	
Interferon (gamma)	Interleukin-1 (alpha)
Pro insulin	Interleukin-1 beta blocker
Protein A	
Tissue plasminogen activator	Lipocortin
1988	Lung surfactant protein
Acylated plasminogen streptokinase complex	1991
	Factor VIIIC
Alpha-1 antitrypsin	1992
Calcitonin	Angiogenin
Epidermal growth factor	Anti-inflammatory peptide
Erythropoietin	
Immunoradiotherapeutic-S	B-cell factors
	Burst promoting activity
Interleukin-2	Colony stimulating factor (G-pluripoietin)
Superoxide dismutase	
Vitamin E microemulsion	Factor IX
1989	Fertility hormones (FSH, LH, and HCG)
Atrial natriuretic factor	
Herpes vaccine	Fibroblast growth factor
Hyaluronic acid (anti-inflammatory)	Tissue inhibitor of metalloproteinases
IMREG-2	Urokinase-antibody conjugate
Lipid emulsion	
Protein C	1993
Pro-urokinase	1994
Tumor necrosis factor	1995
	Renin inhibitors

[a]Many, but not all, of these therapeutic products contain human-derived material

SOURCE: L.I Miller, *Biotechnology Industry 1986 Fact Book (New* York: Paine Webber, 1966).

Table 9.—Some Human Therapeutic Products Being Developed by the Biotechnology Industry[a]

Immune modifiers:
- Allogeneic effect factor
- B cell growth factors
- Burst promoting activity
- Colony stimulating factor (GM)
- Colony stimulating factor (alpha)
- Colony stimulating factor (granulocyte)
- Colony stimulating factor (microphage)
- Colony stimulating factor (megakaryoctye)
- Colony stimulating factor (G-pluripoietin)
- Colony stimulating factor (other)
- D-glutamic acid, d-lysine conjugates
- Desacetylthymosin alpha-1
- lgE peptides
- IMREG-1
- IMREG-2
- Interferon (alpha)
- Interferon (alpha) receptor
- Interferon (beta)
- Interferon (gamma)
- Interferon (gamma analogue)
- Interferon (gamma fragment)
- Interferon (gamma) receptor
- Interferon analogue
- Interferon inducer
- Interferon-interleukin hybrid
- Interleukin-1 (alpha)
- Interleukin-1 (beta)
- Interleukin-1 antagonist
- Interleukin-1 receptor
- lnterleukin-2
- lnterleukin-2 analogue
- lnterleukin-2 in liposomes
- lnterleukin-2 receptor
- lnterleukin-3
- lnterleukin-4
- Lipocortin
- Microphage activating factor
- Microphage migration inhibiting factor
- Microphage peptides
- Monoclinal antibodies to T cells
- Monoclinal antibodies to HLA antigens
- Monoclinal antibodies to lnterleukin-2 receptor
- Orthoclone OKT-3
- Protein A
- Protein A analogue
- Suppressive factor of allergy
- Suppressor factor L
- Suppressor factor S
- Suppressor factors, other
- T cell suppressor inducer factor
- Tissue inhibitor of metalloproteinases
- XL factor
- XN factor

Anticancer therapy agents:
- Ampligen
- Angiogenin
- Angiogenesis inhibitor
- ÁntlCellular factors
- Cytotoxic glycoprotein
- Detox
- Human endogenous regulatory factors
- Immunoagents
- Immunocytotoxic agents
- Immunoradiotherapeutics
- Immunotoxins
- Lectin
- Lymphotoxin
- Minactivin
- OH-1
- Oncostatin
- Ovamid
- Tumor growth inhibitor factors
- Tumor necrosis factor
- Tumor necrosis factor KBS

Blood proteins/enzymes:
- Acylated plasminogen streptokinase complex
- PEG-Adenosine deaminase
- Alpha-1 antitrypsin
- Antithrombin III
- Apolipoprotein-E
- PEG-Asparaginase
- PEG-Catalase
- Coagulation agents
- Elastase
- Elastase inhibitor
- Enzyme 1
- Enzyme 2
- Erythropoietin
- Factor VIIIC
- Factor IX
- Factor Xa
- Fibrinolytic agents
- Hementin
- Hemopoietin-l
- Hirudin
- Human serum albumin
- Lipoproteins
- Lung surfactant protein
- Lysozyme
- Protein C
- Pro-urokinase
- Renin inhibitors
- Renin monoclinal antibody
- Streptokinase
- Streptokinase complex
- Superoxide dismutase
- Superoxide dismutase analogue
- PEG-Superoxide dismutase
- Extracellular superoxide dismutase
- Tissue plasminogen activator
- Trypsin inhibitor
- Urokinase
- Urokinase antibody conjugate
- PEG-U rokinase
- von Willebrand factor

Hormones:
- Angiogenin
- Angiogenic factor
- Angiogenesis factor
- Atrial natriuretic factor
- Atrial natriuretic factor analogue
- Bone morphogenic protein
- Bone growth factors
- Calcitonin
- Calcitonin analogue
- Calcitonin gene related peptide
- Calcitonin precursor
- Cartilage inducing factor (a)
- Cartilage inducing factor (b)
- Connective tissue activator protein
- CNS growth factor
- Enkephalines
- Epidermal growth factor
- Fertility hormones
- Gonadotrophin releasing hormone
- Growth associated protein
- Growth hormone releasing factor
- Human growth hormone
- Hyaluronic acid
- Inhibin
- Insulin
- Insulin receptor
- Luteinizing hormone releasing hormone
- Nerve growth factor (beta)
- Neuropeptide Y
- Neurotransmitter agents
- Neurotrophic factors
- Oxytocin
- Parathyroid hormone inhibitors
- Platelet derived growth factor
- Proinsulin
- Prolactin-release inhibiting factor
- Relaxin
- Secretin
- Somatomedin C
- Somatostatin
- Somatostatin analogue
- Somatostatin peptides
- Tetragastrin
- Thyrotropin releasing hormone
- Transforming growth factor (alpha)
- Transforming growth factor (beta)
- Vasopressin

Other products:
- Chimeric antibodies
- Encapsulated islet cells
- Monoclinal antibodies against human proteins
- Vaccines for contraception
- Vaccine for Epstein-Barr virus-induced malignant lymphoma
- Vaccine for lung cancer
- Vaccine for melanoma

[a]Many, but not all, of these therapeutic products contain human-derived material.

SOURCE: L.I. Miller, *Biotechnology Industry 19S6 Factbook (New* York: Paine Webber, 19S6).

States budget between $300 million and $400 million annually for research and development (5).

Industrial Product Development

The Food and Drug Administration (FDA) requires a biopharmaceutical product to undergo a detailed process of research, development, and testing before the product can be marketed. Studies of the conventional pharmaceutical development process have shown that only about 12 percent of the drugs that enter the human testing process reach the marketplace, and that the testing process itself is lengthy and costly (24). The

Box C.—Angiogenin: A Case History From Research to Product Development

The research and development process that may lead to the commercialization of a product derived from human tissues or cells can be lengthy and can involve many parties. The following case history chronicles the development of one such product: angiogenin.[1] The events unfold over a period of almost eight decades and the final chapter (U.S. approval for marketing) is not yet complete. The story involves a patient with a tumor (the source), researchers in many laboratories, the biotechnology industry, and an university-industry agreement. It illustrates the complex process necessary to develop a biopharmaceutical derived from human tissues or cells.

Angiogenesis is the induction of the formation of blood vessels, a function known for some time to be critical to the process of expanding the network of capillaries and blood vessels that a tumor needs to grow and spread (9,15,16,20,22,39). The master molecule responsible for the phenomenon in humans had long been sought, but until 1985 the purification and characterization of this molecule had not been achieved (16). Some 200 laboratories worldwide are involved in angiogenesis research.

In 1985, the human protein that promoted angiogenesis in vivo was isolated and characterized. The investigators called the protein angiogenin. The protein was isolated from an established human cell line (called HT-29) that had been cultured 21 years earlier from the tumor of a 44-year-old woman (17). This cell line constantly secretes minute amounts of angiogenin, although researchers believe that the protein is also secreted at certain times by normal, nonmalignant cells. Isolating angiogenin was only the first step: if inhibitors to angiogenin can now be found and produced, it is possible that they could be used to starve tumors of their blood supply.

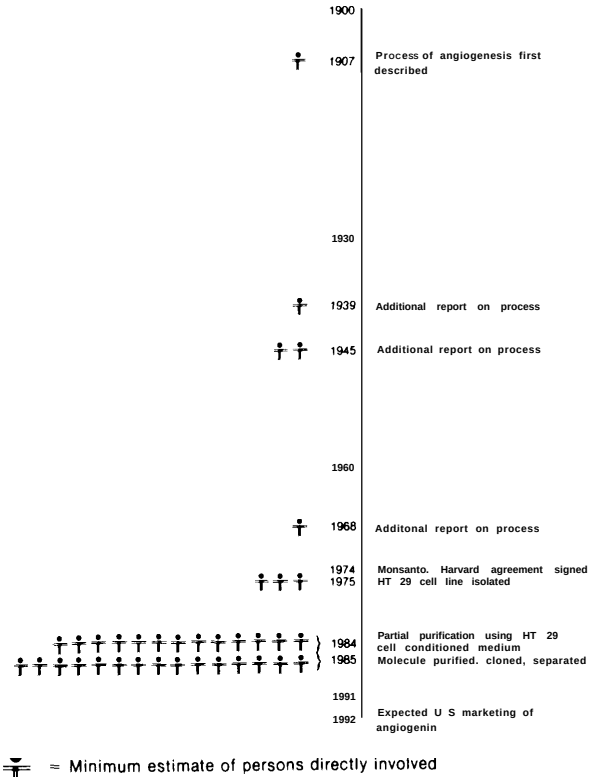
The search for the master molecule of angiogenesis was complicated. Researchers went through hundreds of liters per week of a special cell culture medium called tumor-conditioned medium. To obtain this special medium, the HT-29 cell line was grown in serum-free medium with the medium being siphoned off over time. The angiogenin was secreted into the tumor-conditioned medium at a yield of 0.5 micrograms per liter—this amounts to approximately one grain of salt in an entire liter of medium. After several months, enough purified substance was obtained to conduct a single experiment to determine the nature of the molecule. After determining the entire sequence of 123 amino acids in human angiogenin, the researchers proceeded with techniques to clone the gene for the angiogenin protein, thereby making it possible to prepare adequate quantities of the molecule.

Commercialization of an angiogenin-based product is not expected for at least 5 to 6 years (37,39). The research that resulted in the isolation and characterization of angiogenin was done at Harvard University Medical School and was commissioned in 1974 by Monsanto Co. under an 11-year, $23 million investment—through which Monsanto gains exclusive licensing rights to potential products developed under this arrangement (39).

Figure 13 traces some of the historical highlights leading to the purification of the molecule responsible for angiogenesis. Obviously, a great deal of time and the talents of many scientists were involved in solving this scientific puzzle. It is important to note that many related offshoots of angiogenesis research, including the process in nonhuman species, while not represented in the figure, were critical to the discovery of the master molecule. Additionally, such related research involved considerable manpower and money (2, 16,31,33,39,49).

[1]For a recent review, see Folkman, J. and Klagsbrun, M., "Angiogenic Factors," *Science* 235:442-447, 1987.

Figure 13.—The Development of Angiogenin



SOURCE" Off Ice of Technology Assessment, 1987

cost associated with bringing a single new product to the marketplace is on the order of $65 million to $100 million (spread over several years or two to three decades) (4). In general, the biopharmaceutical product development process includes the following steps:

- **Research:** Identification and purification of the natural protein; characterization of the molecule, often including genetic engineering technology to produce the product.
- **Research and Development:** Improvement of product yield, initial formulation, and laboratory testing.
- **Development:** Formulation of the product into a pharmaceutical; preparation and scale-up of product manufacture.
- **Preclinical Testing:** Animal testing for acute or long-term toxicity and activity of the product.
- **Clinical Testing—Physician IND:** Human patient testing at one or more clinical centers where the actual application for testing has been filed by a physician, rather than the corporation.
- **Clinical Trials-Phase I:** Patient trials to determine drug safety and appropriate dosing schedules with only modest information regarding efficacy generated.
- **Clinical Trials-Phase II:** Broadened clinical patient trials to determine drug efficacy in one or more indications.
- **Clinical Trials-Phase III:** Advanced clinical patient trials to determine drug efficacy in one or more indications.
- **Product License Approval Filing:** Materials filed with the FDA to apply for marketing approval (36).

While it is difficult to predict whether all pharmaceuticals produced by biotechnology will emulate traditional pharmaceuticals, it is likely that standard government requirements for testing of pharmaceutical products will apply to all biotechnology products (51 FR 23309).

University-Industry Relationships

A critical aspect of the controversy surrounding the use of undeveloped human tissues and cells is the increasing overlap between the spheres of two of the interested parties: the research community and the biotechnology industry. University-industry research relationships in biotechnology assume a variety of forms, and these relationships are of relatively recent vintage. One estimate indicates that the total amount of money industry supplied to universities for biotechnology research in 1984 was about $120 million, accounting for 16 to 24 percent of all funds for biotechnology R&D available to institutions of higher education that year (11).

Faculty consulting and research relationships between individual professors and corporations can include:

- single or occasional visits and interchanges, informal collaboration;
- formal collaboration with or without consulting arrangements;
- consulting arrangements with or without formal collaboration (exclusive or nonexclusive); and

- formal exclusive relationships with understood financial commitments and patent rights.

Faculty may also be involved with scientific advisory boards for biotechnology companies and may be offered some type of restricted stock or stock options not generally awarded to external consultants.

Relationships between universities and corporations can include:

- corporate contributions, directed or undirected or in the form of fellowships;
- industrial procurement of particular services, for example, education and training or contract research;
- industrial affiliates;
- cooperative research;
- privately funded research centers, with either a single funder or multicorporate sponsors;
- long-term contracts, such as those between Monsanto and Harvard or Exxon and Massachusetts Institute of Technology;
- university-controlled companies set up to develop commercial potential from university research; and
- private companies that secure patent rights for resale (30).

The implications for a market in human specimens involving researchers, universities, university-industry partnerships, and industry are discussed in detail in chapter 7.

FEE-FOR-SERVICE RESEARCH

In addition to the commercial biotechnology firms and basic research members of the research community, a novel party that uses human tissues and cells has emerged. In 1984, the first for-profit company offering personalized cancer treatments was established in Franklin, TN. Biotherapeutics, Inc., was founded by R.K. Oldham, former director and founder of NCI's Biological Modifiers Program, and W.H. West, his colleague. A second branch in La Jolla, CA, is scheduled to open soon. It is a pioneer in what has been termed '(fee-for-service" research: the company offers services to individuals who can afford to bear the costs of the research protocol involved in the cancer treatment (32).

As one part of its program, Biotherapeutics makes hybridomas producing monoclinal antibodies unique to an individual's tumor. These monoclinal antibodies are used with a mixture of other monoclinal antibodies (produced in response to tumors from other individuals) to treat the patient's tumor. The current cost of participating in the full service, not covered by conventional insurance policies, is $35,000. A $2)750 fee is charged for processing and preserving the patient's tumor for future use in therapy. Patient-funded research accounted for approximately 65 percent of Biotherapeutics' total revenues.

Biotherapeutics also uses interleukin-2, a lymphokine, to activate certain cells of the patient to become "lymphokine-activated killer cells." These cells can attack tumor cells in some individuals. The therapy regimens offered at Biotherapeutics are in use as experimental treatments elsewhere, particularly at NCI (32). Unlike other programs, however, patients at Biotherapeutics bear the cost of their individualized research/treatments. Persons contracting with Biotherapeutics waive all rights to "any cell line, reagent, product, approach, or properties that may be derived from tumor tissue, blood, or other specimens . . ," (8).

At present, Biotherapeutics is a unique combination of business, therapeutic institution, and research venture that uses human biological materials. About 200 patients have been treated at the Tennessee facility, and it is difficult to evaluate whether fee-for-service research companies will be an important interested party in the future.

SUMMARY AND CONCLUSIONS

In addition to scientific advances in biotechnology, the legal and economic considerations surrounding research on human biological have changed in the past decade. Many parties now have an interest in developing human tissues and cells: the source, the physician (or physician/researcher), the researcher, the university, and the biotechnology company. And, importantly, the spheres in which these parties operate are frequently intertwined—making resolution of conflicts difficult.

The ability to patent novel life forms created through biotechnology has spurred interest in developing human tissue and cells into marketable inventions. **The crucial element of patentability for most biological inventions in the United States, as shown in the *Chakrabarty* case, was the fact that the substance was in some way changed from the naturally occurring substance by human intervention.** This decision, coupled with technical advances in biotechnology, has resulted in increased interest in developing primary human biological material into marketable products.

Patients, healthy research subjects, and cadavers are all sources of undeveloped human tissues and cells, providing both normal and diseased specimens. As a general principle, sources of specimens are not paid for the types of samples most commonly used in biotechnology research. Volunteer research subjects, however, may be reimbursed for time or out-of-pocket expenses.

The research community, including both university and industry scientists, obtains human specimens for a broad spectrum of uses. These tissues and cells may be sought for single experiments as well as for the long-term development of cell lines or cloned genes. A sample might also be used directly to extract a commercial product. Researchers obtain human biological materials via many avenues, ranging from ad hoc agreements with local hospitals to federally supported collections.

In most cases, it is difficult to ascertain the contribution of anyone individual's sample to a final commercial product. Moreover, because the process of research is a continuum, the expectation of developing a commercial product at the outset of research is extraordinarily small. Atypical human tissues and cells are sometimes discovered, however, and can be valuable to the R&D process of a marketable human commodity.

Recently, researchers and universities have sought innovative methods to fund research. The emerging presence of the biotechnology industry has become a logical partner in such research funding, and consequently a number of university-industry or investigator-industry arrangements have developed. These arrangements range from informal col laboration to formal contracting or funding.

CHAPTER 4 REFERENCES

1. Aamondt, R. L., Division of Cancer Biology and Diagnosis, National Cancer Institute, Bethesda, MD, personal communication, April 1986.
2. Alderman, E. M., Lobb, R. R., and Fett, J. W., "Isolation of Tumor-Secreted Products From Human Carcinoma Cells Maintained in Defined Protein Free Medium," ***Proceedings of the National Academy of Science (USA)*** 82:5771-5775, ***1985.***
3. Algire, G. H., and Chalkey, H .W., "Vascular Reactions of Normal and Malignant Tissues In Vivo, I: Vascular Reactions of Mice to Wounds and to Normal and Neoplastic Transplants, "Journal *of the National* ***Cancer Institute (USA) 6:73-85, 1945.***
4. Antébi, E., and Fishlock, D., *Biotechnology: Strate@"es for Life* (Cambridge, MA: The MIT Press, 1986).
5. Behrens, M. K., "Biotechnology," 1985 *Medical* ***Conference Review*** (New York, NY: Robertson, Colman & Stephens, NOV. 8, 1985).
6. Biggart, W. A., *Patentability,* ***Disclosure Requirements, Claiming and Infringement of*** *Microorganism-Related* ***Inventions,*** reprinted in *Genetically* ***Engineered Microorganisms and Cells*** (Washington, DC: Patent Resources Group, Inc., 1981).
7. "Biotechnology's Hype and Hubris," *The* ***Economist*** Apr. 19, 1986,
8. Biotherapeutics, Inc., Franklin, TN, "Cellular Com-

ponent Development Patient Research Contract," January 1986.
9. Blumberg, B. S., Millman, I., London, W. T., et al., 'Ted Slavin's Blood and the Development of HBV Vaccine," New *England Journal of Medicine* 312(3):189, *1985.*
10. Blumenthal, D., Harvard University, Cambridge, MA, personal communication, April 1986.
11. Blumenthal, D., Gluck, M., Louis, K. S., and Wise, D., "Industrial Support of University Research in Biotechnology," *Science* 231:242-246, 1986.
12. Byers, B., Kleiner, Perkins, Caufield, & Byers, San Francisco, CA, personal communication, April 1986.
13. Der, C.J., La Jolla Cancer Research Foundation, La Jolla, CA, persona] communication, April 1986.
14. *Diamond v. Chakrabarty*, *477* U.S. 303 (1980).
15. Ehrmann, R. L., and Knoth, M., "Choriocarcinoma: Transfilter Stimulation of Vasoproliferation in the Hamster Cheek Pouch—Studied by Light and Electron Microscopy, " *Journal of the National Cancer Institute (USA)* 41:1329-1341, *1968.*
16. Fett, J. W., Strydom, D.J., Lobb, R. R., et al., "Isolation and Characterization of Angiogenin and Angiogenic Protein From Human Carcinoma Cells," *Biochemistry* 25:5480-5486, *1985.*
17. Fogh, J. (cd.), *Human Tumor Cells In Vitro (New* York: Plenum Press, 1975).
18. Folkman, J., and Cotran, R., "Relation of Vascular Proliferation to Tumor Growth," *International Review of Experimental pathology,* G.W. Richter (cd.) (New York: Academic Press, 1976).
19. Francomano, C., The Johns Hopkins Medical Institution, Baltimore, MD, personal communication, April 1986.
20. Goldmann E., "The Growth of Malignant Diseases in Man and the Lower Animals With Special Reference to the Vascular System," *Lancet 2:1236-1240, 1907.*
21. Goldstein, H., National Institutes of Health, Bethesda, MD, personal communication, April 1986.
22. Greenblatt, M., and Shubik, P., "Tumor Angiogenesis: Transfilter Diffusion Studies in the Hamster by Transparent Chamber Technique," *Journal of the National Cancer Institute (USA)* 41:111-124, *1968.*
23 Grizzle, B., University of Alabama, Birmingham, AL, personal communication, April 1986.
24 Hansen, R., "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects of Proposed Regulatory Changes, " *Issues in Pharmaceutical Economics,* R.I. Chien (cd.) (Lexington, MA: Lexington Books, 1979).
25 Henney, C., Immunex Corp., Seattle, CA, personal communication, April 1986.
26. Ide, A, G., Baker, N. H., and Warren, S. L., "Vascularization of the Brown-Pearce Rabbit Epithelioma Transplant as Seen in the Transparent Ear Chamber," *American Journal of Roentgenology and Radium Therapy* 42:891-899, *1939.*
27. *In re Bergy*, *563* F.2d 1031 (CCPA 1977).
28. *In re Bergy*, 596 F.2d 952 (CCPA 1979).
29. *In re Chakrabarty*, *571* F.2d 40 (CCPA 1978).
30. Kenney, M. F., "Biotechnology: From University to Industry," Ph.D. dissertation, Cornell University, 1984.
31. Kurachi, K., Davie, E. W., Strydom, D.J., et al., "Sequence of the cDNA and Gene for Angiogenin: A Human Angiogenesis Factor, " *Biochemistry 24: 5494-5499, 1985.*
32. Lind, S. E., '(Sounding Board: Fee-for-Service Research)" New *England Journal of Medicine 314(5): 312-315, 1986.*
33. Lobb, R. R., Key, M. E., Alderman, E. M., and Fett, J. W., "Partial Purification and Characterization of a Vascular Permeability Factor Secreted by a Human Colon Adenocarcinoma Cell Line, " *International Journal of Cancer* 36(4):473-478, *1985.*
34. McKay, C., Office for Protection from Research Risks, National Institutes of Health, Bethesda, MD, personal communication, April 1986.
35 Macy, M., American Type Culture Collection, Rockville, MD, personal communication, April 1986.
36 Miller, L. I., *Biotechnology Industry 1985 Fact Book* (New York: Paine Webber, 1985).
37. Miller, L. I., *Biotechnology Industry 1986 Fact Book (New* York: Paine Webber, 1986).
38. Mochizuki, D. Y., Immunex Corp., Seattle, WA, personal communication, March 1986.
39. "Monsanto To Reap First Fruits of Stake in Harvard: Sole Rights To 'Angiogenin', " *Biotechnology Newswatch* 3(20):3, *1985.*
40. Nelkin, D., *Science as Intellectual Property (New* York: Macmillan, 1984).
41. Ostrach, M., Cetus Corp., Emeryville, CA, personal communication, April 1986.
42. Patterson, M. K., The Noble Foundation, Ardmore, OK, personal communication, March 1986.
43. Perpich, J., Meloy Laboratories, Springfield, VA, personal communication, April 1986.
44. Rathman, G. B., "The Role of Patients, Researchers, Universities and Private Companies in the Development and Marketing of Human Biological Products, " in U.S. Congress, House Committee on Science and Technology, Subcommittee on Investigations and Oversight, *The Use of Human Biological Materials in the Development of Biomedical Products,* hearings, Oct. 29, 1985, Serial No. 99-71 (Washington, DC: U.S. Government Printing Office, 1986).
45 Read, E., and Lancono, B., National Institutes of

Health Blood Bank, Bethesda, MD, personal communication, February 1986.
46. Rosenberg, P. D., *Patent Law Fundamentals* (New York: Clark Boardman Co., 1980).
47. Spalding, B. J., "Biotech's New-wave Biological," *Chemical Week*, Dec. 18, 1985.
48. Stevenson, R., American Type Culture Collection, Rockville, MD, personal communication, April 1986.
49. Strydom, D. J., Fett, J. W., Lobb, R. R., et al., "Amino Acid Sequence of Human Tumor Derived Angiogenin," *Biochemistry* 24:5486-5494, *1985.*
50. U.S. Congress, House Committee on Science and Technology, Subcommittee on Investigations and Oversight, The *Use of Human Biological Materials in the Development of Biomedical Products,* hearings, Oct. 29, 1985, Serial No. 99-71 (Washington, DC: U.S. Government Printing Office, 1986).
51. U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology: An International Analysis*, OTA-BA-218 (Elmsford, NY: Pergamon Press, Inc., January 1984).
52. U.S. Department of Commerce, *Directory of Federal Laboratory and Technology Resources, 1986-87* (Springfield, VA: National Technical Information Service, 1986).
53. U.S. Department of Health and Human Services, National Institute of General Medical Sciences, Human Genetics Mutant Cell Repository, *Comprehensive Annual Report,* Jan. 1, 1985 to Dec. 31, 1985.
54. U.S. Department of Health and Human Services, National Institutes of Health Guide for Grants and Contracts, "Request for Cooperative Agreement Applications: RFA 86-CA-06, National Cancer Institute Cooperative Human Tissue Network," Feb. 28, 1986.
55. U.S. Department of Health and Human Services, "Research Service: National Diabetes Research Interchange," *Research Resources Reporter Reprint* 9(10):1-2, *1985.*
56. Van Horn, C., "Remarks to Association of Biotechnology Companies Symposium," *Biotechnology Law Report* 5(3):86-91, *1986.*
57. Webber, D., "consolidation Begins for Biotechnol-o@ Firms," *Chemical & Engineering News*, Nov. 18, *1985.*