sen, G. Dudek-Wojciechowska, H. Claeys, in *Proteolysis and Physiological Regulation*, D. W. Ribbons and K. Brew, Eds. (Academic Press, New York, 1976), pp. 189–202; L. Sottrup-Jensen, H. Claeys, M. Zajdel, T. E. Petersen, S. Magnusson, in *Progress in Chemical Fibrinolysis and Thrombosis*, J. F. Davidson, R. M. Rowman, M. Samama, P. C. Desnoyers, Eds. (Raven, New York, 1978), vol. 3, pp. 191–209; F. J. Castellino, *Trends Biochem. Sci.* **4**, 1 (1979).
40. B. San Segundo, M. C. Martinez, C. M. Cuchillo, F. X. Aviles, *Biochim. Biophys. Acta* **707**, 194 (1982); F. X. Aviles, B. San Segundo, M. Vilanova, C. M. Cuchillo, C. Turner, *FEBS Lett.* **149**, 257 (1982).
41. M. Trexler and L. Patthy, *Proc. Natl. Acad. Sci. U.S.A.* **80**, 2457 (1983); M. Trexler, L. Banyai, L. Patthy, N. D. Pluck, R. J. P. Williams, *FEBS Lett.* **154**, 311 (1983).
42. W. Gilbert, *Nature (London)* **271**, 501 (1978); C. C. F. Blake, *ibid.* **273**, 267 (1978); *ibid.* **277**, 598 (1979); C. S. Craik, S. Sprang, R. Fletterick, W. J. Rutter, *ibid.* **299**, 180 (1982).
43. S. J. Friezner Degen, R. T. A. MacGillivray, E. W. Davie, *Biochemistry* **22**, 37 (1983).
44. C. Quinto *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 31 (1982).
45. K. W. Jackson and J. Tang, *Biochemistry* **21**, 6620 (1982).
46. W. Kisiel, W. M. Canfield, L. H. Ericsson, E. W. Davie, *ibid.* **16**, 5824 (1977); G. A. Vehar and E. W. Davie, *ibid.* **19**, 401 (1980).
47. K. Katayama *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 4994 (1979).
48. P. Fernlund, J. Stenflo, A. Tufvesson, *ibid.* **75**, 5889 (1978).
49. B. Furie, D. H. Bing, R. J. Feldmann, D. J. Robison, J. P. Burnier, B. C. Furie, *J. Biol. Chem.* **257**, 3875 (1982).
50. F. van der Graaf, G. Tans, B. N. Bouma, J. H. Griffin, *ibid.*, p. 14300.
51. F. van der Graaf, J. S. Greengard, B. N. Bouma, D. M. Kerbiriou, J. H. Griffin, *ibid.* **258**, 9669 (1983).
52. G. Kreil, *Annu. Rev. Biochem.* **48**, 317 (1981); M. Zimmerman, R. A. Mumford, D. F. Steiner, Eds., *Precursor Processing in the Biosynthesis of Proteins* (vol. 343, *Annals of the New York Academy of Sciences*, New York, 1980).
53. M. O. Lively and K. A. Walsh, *J. Biol. Chem.* **258**, 9488 (1983).
54. S. N. Thibodeau, R. D. Palmiter, K. A. Walsh, *ibid.* **253**, 9018 (1978); G. Scheele and R. Jacoby, *ibid.* **258**, 2005 (1983).
55. M. Laskowski, Jr., I. Kato, T. R. Leary, J. Schrode, R. W. Sealock, in *Proteinase Inhibitors*, H. Fritz, H. Tschesche, L. J. Greene, E. Truscheit, Eds. (Springer-Verlag, New York, 1974), pp. 597–614.
56. C. A. Ryan, *Annu. Rev. Plant Physiol.* **24**, 173 (1973); Y. Birk, *Methods Enzymol.* **45**, 695 (1976).
57. D. Kowalski, T. R. Leary, R. E. McKee, R. W. Sealock, D. Wang, M. Laskowski, Jr., in *Proteinase Inhibitors*, H. Fritz, H. Tschesche, L. J. Greene, E. Truscheit, Eds. (Springer-Verlag, New York, 1974), pp. 311–324.
58. C. Nelson, M. Walker-Simmons, D. Makus, G. Zuroske, J. Graham, C. A. Ryan, in *Mechanism of Plant Resistance to Insects*, P. Hedin, Ed. (ACS Monograph, 1983), p. 103; P. Bishop, D. J. Markus, G. Pearce, C. A. Ryan, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 3536 (1981).
59. H. Holzer, in *Metabolic Interconversion of Enzymes 1975*, S. Shaltiel, Ed. (Springer-Verlag, New York, 1975), pp. 168–174.
60. J. Travis and G. S. Salvesen, *Annu. Rev. Biochem.* **52**, 655 (1983).
61. K. Kurachi *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 6826 (1981).
62. T. Chandra, R. Stackhouse, V. J. Kidd, K. J. H. Robson, S. L. C. Woo, *Biochemistry*, in press.
63. L. Sottrup-Jensen, T. E. Petersen, S. Magnusson, *FEBS Lett.* **121**, 275 (1980); S. R. Mortensen, L. Sottrup-Jensen, H. F. Hansen, S. Magnusson, *ibid.* **135**, 295 (1981).
64. A similar thiol ester occurs in the C3, C4, and C5 components of complement [J. B. Howard, *J. Biol. Chem.* **255**, 7082 and 7084 (1980)].
65. H. Neurath, in *Protein Folding*, R. Jaenicke, Ed. (Elsevier/North-Holland, New York, 1980), pp. 501.
66. W. C. Barker and M. O. Dayhoff, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 2836 (1982); K. Titani, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **42**, 2256 (1983); S. Shoji, L. H. Ericsson, K. A. Walsh, E. H. Fischer, K. Titani, *Biochemistry* **22**, 3702 (1983).
67. M. G. Rossman, in *The Enzymes of Glycolysis: Structure, Activity and Evolution*, C. C. F. Blake, D. C. Phillips, H. C. Watson, Eds. (Royal Society of London, London, 1981), p. 191.
68. W. F. Bodmer, in *ibid.*, p. 173; J. S. Richardson, *Adv. Protein Chem.* **34**, 168 (1981).
69. M. Eigen, *Naturwissenschaften* **58**, 465 (1971).
70. J. D. Robertus, R. A. Alden, J. J. Birktoft, J. Kraut, J. C. Powers, P. E. Wilcox, *Biochemistry* **11**, 2439 (1972); J. D. Robertus, J. Kraut, R. A. Alden, J. J. Birktoft, *ibid.*, p. 4293; D. A. Matthews, R. A. Alden, J. J. Birktoft, S. T. Freer, J. Kraut, *J. Biol. Chem.* **256**, 8875 (1977).
71. J. Drenth, J. N. Jansonius, R. Koekoek, B. G. Walthers, *Adv. Protein Chem.* **25**, 79 (1971).
72. E. N. Baker, *J. Mol. Biol.* **115**, 263 (1977).
73. M. N. G. James and A. R. Sieleck, *ibid.* **163**, 299 (1983).
74. J. Tang *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 3437 (1973); N. S. Andreeva, A. A. Fedoroc, A. E. Gushchina, R. R. Riskulov, N. E. Shutskever, M. G. Safro, *Mol. Biol.* **12**, 922 and 936 (1978).
75. E. Subramanian *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 556 (1977).
76. R. Bott, E. Subramanian, D. R. Davies, *Biochemistry* **21**, 6596 (1982).
77. T. Blundell, B. L. Sibanda, L. Pearl, *Nature (London)* **304**, 273 (1983).
78. R. G. Bradshaw, L. H. Ericsson, K. A. Walsh, H. Neurath, *Proc. Natl. Acad. Sci. U.S.A.* **63**, 1389 (1969); B. L. Vallee, J. F. Riordan, D. S. Auld, S. A. Latt, *Philos. Trans. R. Soc. London Ser. B* **257**, 215 (1970); J. A. Hartsuck and W. N. Lipscomb, in *The Enzymes*, P. D. Boyer, Ed. (Academic Press, New York, ed. 3, 1971), p. 1; B. L. Vallee, A. Glades, D. S. Auld, J. F. Riordan, in *Zinc Enzymes*, T. G. Spiro, Ed. (Wiley, New York, 1983), p. 26; W. N. Lipscomb, *Annu. Rev. Biochem.* **52**, 17 (1983).
79. K. Titani, *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 1666 (1975); M. F. Schmid and J. R. Herriott, *J. Mol. Biol.* **103**, 175 (1976).
80. K. Titani, M. A. Hermodson, L. H. Ericsson, K. A. Walsh, H. Neurath, *Nature (London) New Biol.* **80**, 35 (1972); B. W. Matthews, J. N. Jansonius, P. M. Colman, B. P. Schoenborn, D. Dupourque, *Nature (London)* **238**, 37 (1972); W. R. Kester and B. W. Matthews, *J. Biol. Chem.* **252**, 7704 (1977); *Biochemistry* **16**, 2506 (1977); M. G. Holmes and B. W. Matthews, *ibid.* **20**, 6912 (1982).
81. Supported by NIH grant GM-15731. I thank Drs. K. A. Walsh and E. W. Davie for valuable suggestions and critical reading of the manuscript.

Biotechnology as an Intellectual Property

Reid G. Adler

One of the most significant issues created by the emergence of modern biotechnology has been the legal characterization and treatment of biotechnological industrial products. Advances in most other technologies have been readily assimilated by the patent system and routinely licensed and marketed. Because of the tremendous potential impact of biotechnology on many diverse areas, however, it has received an unusual amount of attention and generated a variety of public policy issues and legal uncertainties. This article focuses on biotechnology as an intellectual property.

The term property is generally associated with physical objects, such as household goods or land for which ownership and associated rights are guaranteed and protected by the government. Intellectual property, on the other hand, is intangible. It includes patents, trade secrets, copyrights, and trademarks—rights (which can be bought, sold, or licensed) to exclude others from making, copying, or in some instances using or selling tangible embodiments of the proprietary subject matter.

Although microorganisms have been used for industrial purposes such as baking or fermenting for millennia (*1*), the recent use of restriction enzymes to create recombinant DNA has fueled interest in developing genetic engineering techniques and encouraged the creation of a host of new processes and products. The characterization of these research results as intellectual properties encourages industry to allocate labor, research and development, and funding to facilitate the production of commercially marketable items. As is similarly becoming evident in several other areas, including gene therapy (*2*) and environmental dissemination of organisms (*3*), biotechnology as an intellectual property has also challenged legal and public policies and will continue to catalyze change for several years.

Reid G. Adler is an attorney and is a technical law clerk to the Honorable Giles S. Rich, U.S. Court of Appeals for the Federal Circuit, Washington, D.C. He also teaches "Science and the Law: Biotechnology" at the Graduate School at the National Institutes of Health.

This article first evaluates various types of biotechnological intellectual properties in the context of their underlying legal requirements. While the general discussion of these property types is applicable to other technologies, greater emphasis is placed on the patent system because it appears to play the major role in protecting biotechnology and has received the largest amount of legal and public attention. Next, other matters that affect intellectual property, such as international competition, relations between universities and industry, and uncertainties over the ownership of cell lines and genes, are considered.

Summary. Recent advances in biotechnology have created many public policy and legal issues, one of the most significant of which is the treatment of biotechnological industrial products, particularly under the patent system. Patents represent one of several types of intellectual property; their ownership confers the right to exclude others from benefitting from the tangible products of a proprietary subject matter. Intellectual property law and its protections will play a major role in the rate at which biotechnology develops in the United States. In this article biotechnological intellectual property issues are reviewed in the context of their underlying legal requirements. The implications of other factors, such as international competition, research funding, and gene ownership, are also considered.

Patents

The granting of exclusive rights as a way of encouraging innovation is an ancient practice (*4*). For example, the doges of Venice and kings of England granted monopolies (from the Greek *monopōlion*, right of exclusive sale) to inventors as an inducement for them to trade new articles that would be of benefit to society.

A less beneficial practice of the English sovereigns involved the granting or selling of monopolies to favored subjects, thereby conferring an exclusive right to sell already-traded commodities (such as salt, iron, vinegar, or playing cards) or to engage in a trade (such as the transportation of beer or the importation of Spanish wool). Monopolies to inventors or merchants were awarded in the form of "letters patent" (from the medieval Latin *litterae patentes*, open letters) addressed to the public at large (*5*). The later use of such patent monopolies, however, restrained professions and commerce in items that previously had been freely enjoyed by the public, typically at lower prices (*6*). Eventually, Parliament enacted the Statute on Monopolies to make all monopolies illegal, except those awarded to inventors (*7*).

Under U.S. law, a patent represents a federal grant of the "right to exclude others from making, using or selling" an invention or discovery for a 17-year period (*8*), issued through the Patent and Trademark Office (PTO) of the Department of Commerce. A patent holder (patentee) may exercise this right by suing an infringer to obtain an injunction against continued infringement and to recover compensatory damages (*9*).

The patent grant is not an unconditional, affirmative right to make, use, or sell an invention (*10*). Other federal or state laws may restrict the practice of an invention: a patented pharmaceutical is still subject to the regulatory purview of the Food and Drug Administration before its clinical use is permitted; genetically engineered microbial pesticides require Environmental Protection Agency permits under the Federal Insecticide, Fungicide, and Rodenticide Act (*11*) before they are disseminated; and the use of excessively noisome genetically engineered inventions might be curtailed under local nuisance ordinances. In addition, although a patent may be obtained for an improved version of a patented device, the improvement may not legally be practiced without permission of the basic device's patentee.

The U.S. Constitution authorizes Congress to enact laws "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive rights to their writings and discoveries" (*12*). The patent system achieves this progress in several ways. First, it encourages inventions that advance the state of the "technological arts" or enrich our knowledge of alternative means for accomplishing a given task, even though the particular alternative is not better than what was known before (*13*). Patents are published weekly by PTO and become references in the technical literature. Disclosure encourages competitors to design around or improve a patented invention, further advancing technology. The patent system's most important purpose may be its "inducement to risk an attempt to commercialize" an invention (*14*), which thereby maximizes society's benefit. Progress is attained through the proliferation of ideas, with the marketplace ultimately determining which patented inventions are commercially successful (*15*).

Statutory requirements. By law, a patent contains a statement of the invention's title and of the grant of rights to the patentee, to which a copy of the specification is attached (*8*). The patent specification (*16*) resembles most scientific journal articles in that it usually contains an abstract, a general discussion of the problem, related developments in the field, a "preferred embodiment" of the invention, and a written description that includes specific examples setting forth materials, methods, and conditions necessary to recreate the invention. The specification is also the patent application as originally filed, together with any amendments made to it during "prosecution"—the period in which an application is examined by PTO to ensure compliance with statutory provisions. Excerpts from the patent statute are found in Table 1.

The specification concludes with one or more "claims" (*17*). These are various legal descriptions of the invention, defining subject matter over which the patentee is entitled to assert his or her property right. A claim is analogous to a description in a deed of the location and dimensions of a tract of land. In short, they define the scope of protection afforded by the patent (*18*). Selected claims from several key biotechnology patents are reproduced in Table 2. The claims and specification are first judged during prosecution against the standards set forth in the patent statute, the basic provisions of which follow. Note that patents carry only a rebuttable presumption of validity (*19*), so their allowance by PTO may be challenged and effectively second-guessed through litigation.

Patentable subject matter. Section 101 of the patent statute sets forth three requirements for patentability: utility, novelty, and statutory subject matter (Table 1) (*20*). Utility has been broadly interpreted, and essentially excludes only things that are "mischievous or immoral" (*21*). The requirement of novelty, although mentioned here, is applied under section 102. Defining the limits of statutory subject matter as applied to biotechnological products has been problematic.

In 1980 the Supreme Court's landmark opinion in *Diamond* v. *Chakrabarty* (*22*) decided the question of whether certain claims to a microorganism (excerpt 1 in Table 2) defined patentable subject mat-

ter under section 101. The issue, as characterized by the majority in this 5 to 4 decision, was a narrow one of statutory interpretation to determine whether the claimed microorganism constitutes a "manufacture" or "composition of matter" within the meaning of the statute. PTO's primary argument against the patenting of microorganisms, given the "great complexity" of the "social, economic and scientific questions" involved was that Congress had not specifically authorized the extension of the patent law into such new subject areas (*23*). However, the Court found that, in choosing the expansive language of section 101, Congress had plainly contemplated that the patent laws would be given wide scope, and held that the claims at issue defined patentable subject matter (*24*). Other considerations, including the possibility that encouraging genetic research might spread pollution or disease, were noted by the Court but were not factors in its decision.

In a previous patentability appeal in 1975, PTO had ruled that animals (chickens, in that case) did not constitute patentable subject matter under section 101 (*25*). This position apparently has been unofficially maintained by PTO even after *Chakrabarty*. However, eukaryotes such as plants expressing recombinant DNA or the novel mouse that expressed a rat growth hormone gene (*26*) should—assuming that they and others of their genetically engineered ilk are otherwise patentable—satisfy section 101 under the rationale of *Chakrabarty*. Reticence by PTO in issuing patents may adversely affect the rate at which some areas of biotechnology develop. The *Chakrabarty* opinion recognized that "the grant or denial of patents on microorganisms is not likely to put an end to genetic research or to its attendant risks," but "may determine whether research efforts are accelerated by the hopes of reward or slowed by want of incentives" (*22*, p. 317).

Novelty. Section 102 (Table 1) sets forth criteria by which the novelty of claimed inventions within the defined classes of statutory subject matter may be determined. Their purpose (and that of the nonexcerpted provisions of section 102) is to prevent the granting of patents on applications claiming subject matter that already belongs to the public and to encourage the prompt filing of patent applications after their substance has become known.

Any claim in an application that encompasses ("reads on") something already in the public domain ("prior art"), such as machines, organisms, processes, conference abstracts, or published articles, is "anticipated" and thus unpatentable. In contrast, claims to novel "pure cultures" of isolated naturally occurring microorganisms may be allowable (*27*) if the purified culture has some quality or performs a function not available from the organisms as found in nature. The claims in the Isaacs and Lindenmann patent (excerpt 2 in Table 2) encompass interferon in its naturally occurring and purified extract forms. These claims are presumed valid (*19*), but they might not be upheld if challenged in litigation. More proper claims would have been limited to purified interferon.

Unobviousness. Section 103 (Table 1) sets forth the criterion of "unobviousness" by which useful and novel inventions are determined to be patentable. This provision is intended to preclude patent protection for those inventions that are so closely related to the prior art that their production is within the skill of a hypothetical person of ordinary skill in the pertinent field.

As interpreted by the Supreme Court (*28*), section 103 requires that the scope and content of the prior art be determined and the differences between this prior art and the claimed subject matter be ascertained. If the invention as a whole, notwithstanding these differences, would have been unobvious to an ordinary worker in the pertinent field at the time the invention was made, then the claimed invention is patentable. The determination of unobviousness is a subjective one, but the statute provides the procedures and the standard by which the decision must be made (*29*). As an illustration, the prior art references cited against the claims for producing recombinant DNA in the Cohen and Boyer patent (excerpt 3 in Table 2) are partially reproduced in excerpt 5 of Table 2. They include one patent and 15 articles and represent the closest prior art considered by PTO. The allowed claims were found to be unobvious to an ordinary worker aware of this art.

Enablement. The first paragraph of section 112 (Table 1) includes the "enablement" provision of the statute. Its purpose is to require that the specification contain sufficient "written" information at the time it is filed to enable "any person skilled" in the pertinent art (not

Table 1. Selected statutory excerpts.

Patent Statute, Title 35 *U.S. Code*:

Section 101—Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Section 102—Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless—

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or. . . .

Section 103—Conditions for patentability; non-obvious subject matter

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. . . .

Section 112—Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. . . .

Copyright Statute, Title 17 *U.S. Code*:

Section 102—Subject matter of copyright: In general

(a) Copyright protection subsists . . . in original works of authorship fixed in any tangible medium of expression, now known or later developed, from which they can be perceived, reproduced, or otherwise communicated, either directly or with the aid of a machine or device. . . .

(b) In no case does copyright protection for an original work of authorship extend to any idea, procedure, process, system, method of operation, concept, principle, or discovery, regardless of the form in which it is described, explained, illustrated, or embodied in such work.

the general public) to make and use the claimed invention without undue experimentation (*30*). Enablement makes the patent understandable by those in its field to avoid infringement; provides the public with the ability to practice the invention after the patent expires; and secures the continuous disclosure of novel, useful, and unobvious technical advances (*31*). Section 112 also requires the disclosure of the "best mode" that is contemplated of practicing the invention at the time the application is signed, thus proscribing concealment of an inventor's preferred embodiment (*32*). The best mode requirement is satisfied by not withholding information (*33*). Satisfying the enablement requirement is more difficult and represents a particular area of uncertainty for patents on multicellular organisms.

A legally sufficient disclosure of a machine or chemical composition may easily be made through figures and text. In contrast, it is difficult to explain the production and use of a genetically engineered organism or a method for using a novel pure culture of a rare but naturally occurring microorganism unless the organism itself is available. For example, claim 2 of the Jackson *et al.* application (excerpt 4 in Table 2), which also encompasses unisolated species, was rejected by PTO because isolation of other such organisms from soil samples was held to involve undue experimentation (*34*). One way to satisfy section 112 is to deposit a microorganism (*35*), before the patent application is filed (*36*), with independent depositories such as the American Type Culture Collection. The United States is a signatory to the Budapest Treaty, which specifies deposit, maintenance, and distribution standards for patent purposes for depositories in member nations. These repositories will provide cultures to requestors after a patent is issued thus rendering the organism equivalent to a "stock reagent" that may be used as described in writing. For this reason, a more restrictive version—claim 3—of Jackson *et al.* was allowed (excerpt 4 in Table 2).

An important problem with enablement concerns multicellular organisms. Depositories for genetically engineered mice or larger creatures could be created; however, the logistics, maintenance, and distribution costs involved may be prohibitive. Unless a claimed invention is capable of adequate enablement in words alone, some deposit will be necessary. Perhaps the deposit of frozen embryos could simplify this matter. However, it may be impossible to know within a reasonable time whether a new genetically engineered organism infringes a claim to a related patented organism thus enabled, particularly for animals with long gestation and maturation periods. Accordingly, the length of time needed for comparison testing and other difficulties with an embryo deposit practice might represent undue experimentation in the view of the courts. It may become necessary for Congress to modify the disclosure requirements of section 112 to specifically authorize the deposit of frozen embryos, or to ease the requirement as was done in the Plant Patent Act, which requires disclosure to be only "as complete as is reasonably possible" (*37*).

The general concept of enablement also applies to references used as prior art to determine patentability under sections 102 and 103. For example, although antibody-producing human-mouse and mouse-mouse hybridomas were reported in the early 1970's (*38*), their disclosures are not necessarily enabling as to human-human cell fusion for which hybridization conditions are not set forth. Even a statement that human-human hybridomas will likely be produced in the near future would not qualify these two articles as prior art, since workers of ordinary skill could not produce such hybridomas on the basis of their teachings. Several other hybridomas have indeed subsequently been patented (*39*). A different enablement issue concerns a withdrawn-from-issue application for a widely known plasmid owned by Stanford University and the University of California that is being reevaluated by PTO to determine, in part, whether the specification is enabling (*40*).

Infringement. A claim is literally infringed when it encompasses something. Infringement is also found when an accused object is physically different from but legally equivalent to the subject matter claimed. Under the doctrine of equivalents, "devices, processes or compositions of matter which do the same work, in substantially the same way, and accomplish the same results . . . are equivalent even though they differ in name, form or shape" (*41*).

Thus, claim 1 of Chakrabarty (excerpt 1 in Table 2), which is directed to the genus *Pseudomonas*, would not literally

Table 2. Excerpts from selected U.S. patents.

1) *Chakrabarty*—No. 4,259,444, "Microorganisms having multiple compatible degradative energy-generating plasmids and preparations thereof," issued 31 March 1981
Claim 1: A bacterium from the genus *Pseudomonas* containing therein at least two energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway.

2) *Isaacs and Lindenmann*—No. 3,699,222, "Production of viral interfering substances," issued 17 October 1972
Claim 1: Interferon.

3) *Cohen and Boyer*—No. 4,237,224, "Process for producing biologically functional molecular chimeras," issued 2 December 1980
Claim 1: A method for replicating a biologically functional DNA, which comprises: transforming under transforming conditions compatible unicellular organisms with biologically functional DNA to form transformants; said biologically functional DNA prepared in vitro by the method of: (a) cleaving a viral or circular plasmid DNA compatible with said unicellular organism to provide a first linear segment having an intact replicon and termini of a predetermined character; (b) combining said first linear segment with a second linear DNA segment, having at least one intact gene and foreign to said unicellular organism and having termini ligatable to said termini of said first linear segment, wherein at least one of said first and second linear DNA segments has a gene for a phenotypical trait, under joining conditions where the termini of said first and second segments join to provide a functional DNA capable of replication and transcription in said unicellular organism; growing said unicellular organisms under appropriate nutrient conditions; and isolating by means of said phenotypical trait imparted by said biologically functional DNA.

4) Application Serial No. 008,378 of Jackson, Theriault, Sinclair, Fager, and Karwowsky—
Claim 2: A process for producing the antibiotic AX-127B-1 which comprises culturing a microorganism belonging to the species *Micromonospora pilosospora* having the ability to produce antibiotic AX-127B-1 in a nutrient medium including a carbon and nitrogen source and accumulating the antibiotic in said medium.
Claim 3: A process according to claim 2 wherein said microorganism is selected from the group consisting of *Micromonospora pilosospora* NRRL 11415, *Micromonospora pilosospora* NRRL 11416, and *Micromonospora pilosospora* NRRL 11417, and mutations thereof.

5) References cited against the Cohen and Boyer patent (3) include
U.S. Patent No. 3,813,316 of Chakrabarty (1974)
Morrow *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, vol. 69, pp. 3365–3369, November 1972
Morrow *et al.*, *ibid.*, vol. 71, pp. 1743–1747, May 1974
Hershfield *et al.*, *ibid.*, vol. 71, pp. 3455 *et seq.*, 1974
Jackson *et al.*, *ibid.*, vol. 69, pp. 2904–2909, October 1972

be infringed by an analogously prepared bacterium of the genus *Bacillus*, but might nevertheless be infringed by the *Bacillus* if it were held to be equivalent. In contrast, a *Pseudomonas* having one recombinant DNA plasmid providing both degradative pathways expressed by the two nonrecombinant plasmids of Chakrabarty may do the same work and produce the same result but do so in a different way and thus avoid infringing.

The courts generally allow a broader scope and a wider range of equivalents to patents that represent a new field or a distinct step in the progress of an art (*42*). A countervailing doctrine, however, recognizes that the behavior of chemical or biochemical compounds is not always predictable as conditions vary, and this should limit the scope of claims to what the patent's disclosure reasonably teaches (*43*). In addition to these opposing doctrines of legal interpretation, patent litigation is an inexact science. Infringement suits in biotechnology, when infringement can be detected (*44*), will often be reduced to debates between opposing expert witnesses (*45*). Uncertainties as to the scope of attainable patent coverage will be a factor in business decisions to file patent applications or to preserve inventions in secrecy until the courts ultimately rule on these matters.

Trade Secrets

Trade secrets encompass private proprietary information or physical materials that afford a competitive advantage to the owner (*46*). The classic example of a trade secret is the Coca-Cola brand syrup formula. Biotechnological trade secrets might include hybridization conditions, cell lines, corporate merchandising plans, or customer lists. Unlike patents, trade secrets have a potentially unlimited duration, are primarily regulated by state law, and need not satisfy the more stringent requirements for patentability. Courts will enjoin disclosure of a trade secret and compensate the owner for its unauthorized use when the secret has been discovered by improper means, such as breach of confidence (*47*). The trade secret, however, is no longer protectable when it becomes public knowledge through independent discovery, reverse engineering, or through disclosure, for example, at an open session of the National Institutes of Health Recombinant DNA Advisory Committee (RAC).

Biotechnology is characterized by certain unique aspects that affect reliance on trade secrets. Because present and former university researchers still play major roles in developing the basic research necessary to commercialize this technology, publication of research results is usually expected and is often an important aid in recruiting individuals from a limited pool of talent (*48*). Additional risks to the secrecy needed to protect this type of intellectual property include the tendency of scientists to share information at conferences during informal gatherings, mobility of graduate students and employees, and computer theft of trade secret data bases containing sequencing or restriction map data (*49*). Some disclosure is also required by the federal government; because environmental impact statements may become required for some genetically engineered projects (*3*) and certain recombinant DNA experiments are reviewed by the RAC (*50*), there is an enhanced risk of leaks, and potential access to trade secrets by competitors who use the Freedom of Information Act (*51*).

Reliance on trade secrets, however, may be prudent notwithstanding the risks of disclosure. The rapid pace of development in biotechnology suggests that much patentable work may become outdated before a patent would be issued (generally about 2 years or longer after an application is filed). Moreover, certain types of products might be more appropriately protected in this manner. Trade secret protection may be more actively utilized for sequence data bases rather than for plasmids or other tangible creations.

Copyrights

A copyright protects the expressed form of an idea but not the idea itself. This differs from patent and trade secret protection, which can encompass the substance of the idea behind a particular object (*52*). The purpose of the copyright law is to secure public benefit by encouraging the efforts of those who create "original works of authorship" (section 102 in Table 1) (*53*). The copyright owner is granted the exclusive right to reproduce and distribute the work (*54*); however, the actual use of a copyrighted work is not protected. To be copyrightable, the work must be "fixed in a tangible medium of expression, now known or later developed," such as print, painting, or other media including those in which the work cannot be directly perceived by the human senses, such as film or videotape (*55*). Copyright has evolved with the growth of technology since the invention of movable type; for instance, Congress recently amended the copyright statute to explicitly recognize the copyrightability of computer software (*56*).

It has been suggested that copyright protection extends to original DNA sequences—works that arguably may embody creative, and indeed artistic, expression (*57*). This argument is made by analogy; a cell's DNA is a compilation of instructions to cellular machinery like the computer instructions embodied in software. The analogy does not fit precisely, however. Alternative computer programs can accomplish the same result through equivalent but different instructions. In contrast, the limited redundancy in the genetic code permits fewer ways to specify particular amino acids. This might preclude protection under copyright, since the judiciary is reluctant to protect works in which the underlying idea is capable of expression in only a few ways (*58*). Furthermore, the value of a copyrighted DNA sequence would be minimal. Once a gene has been disclosed, it would be a relatively simple matter to prepare an analog, without copying, to express the underlying idea by taking advantage of the code's wobble.

A work may also be denied copyright protection if its appearance has "an intrinsic utilitarian function" (*59*). Because particular codons may ultimately determine the higher order structure necessary for effective transfer RNA functioning during translation, DNA sequences may be inherently useful and noncopyrightable for this reason as well. Computer data bases, photomicrographs of DNA, or instruction manuals related to biotechnology can be copyrighted, as is this issue of *Science*. But again, copyright protection is limited. This issue of *Science* cannot be reproduced but all the ideas in it may be freely used (*60*).

Trademarks

A trademark is a word or symbol "adopted and used by a manufacturer or merchant to identify his goods and distinguish them from those manufactured or sold by others" (*61*). Laboratory equipment useful in biotechnology already bears trademarks that are well known to workers in the field, just as trademarked sports equipment or frozen foods have become known to their respective purchasing populations. Certain vectors useful in recombinant research may become known by various trademarks, just as pharmaceuticals are similarly known and advertised. This area of

intellectual property, of the four considered in this article, has not presented any particular legal or business issues, but is an important and valuable member of an industrial portfolio of properties.

Choice of Intellectual Property Protection

Biotechnological products and processes are protectable by the various property rights discussed above. These properties can be bought, sold, and licensed like any other type of property. Their worth depends on what the market will bear and on the value placed on protection from competition by the property owner. Selection of the most appropriate mode of protection is a business judgment based on several factors that differ from case to case. These include the pace of technological development (if rapid, then a trade secret approach may be preferable to patenting), associated costs (the costs of secrecy may exceed those of obtaining a patent but perhaps not the costs of trying to enforce it), security considerations (it may be impossible to prevent disclosure of a trade secret or its reverse engineering), the need to show patents to investors or venture capitalists as a measure of success, or the basic, pioneering nature of a discovery (patents that grant broad rights may be more valuable). Also, the type of subject matter sought to be protected is a determining factor—for example, instruction manuals can be copyrighted and protected as a trade secret but are not patentable.

International Competition and Related Issues

An authoritative study recently issued by the Office of Technology Assessment (OTA) reports that, although the United States is the world leader in the basic science and commercial development of biotechnology, continued preeminence is not assured (*62*). In the face of mounting interest by foreign governments in their own biotechnology industries, OTA evaluated several factors that may be critical to our international competitiveness. It found that the most important factors are the availability of start-up financing and tax incentives for business, increases in federal funding of basic and applied research, and the continued availability of trained scientific and technical personnel. Factors of moderate importance are the ultimate regulatory umbrella of health, safety, and environmental laws; intellectual property law; and university-industry relations.

Several of these factors are interrelated. Thus, in this era of decreasing federal research subsidies, changes in the funding and licensing interactions of the federal government, private industry, and universities merit attention (*63*). Research strategies and directions may be affected as a result of these changes, in part because industry's research funding is increasing and because universities are assuming a more active and sophisticated role in establishing industry-university relations (*64*).

In addition, businesses of all nations operate in an increasingly competitive worldwide market. Some nations favor cooperation between native businesses; however, potential risks of antitrust liabilities for joint venture research and development programs may have impeded cooperative research efforts of domestic industries. This is partly due to vast potential civil liabilities and to doubts about the validity of patents obtained as a result of such efforts or certain licensing practices that may later be held to be illegal (*65*). Because patents provide a crucial incentive for research and innovation (*66*), as foreign competition increases, strong domestic and international protection of worthwhile research and licensing programs and of patents and trademarks will be important to the success of U.S. business in world markets (*67*).

The Reagan Administration responded to some of these issues in its bill, the National Productivity and Innovation Act (NPIA) of 1983 (*68*), which is designed to "create a legal environment that does not unreasonably discourage investment in new technologies and does not deter the efficient exploitation of these technologies" (*69*). This goal would be achieved in part by eliminating costly punitive damages for antitrust violations for research and development joint ventures. The NPIA addresses another problem by making products of patented processes no longer importable into the United States without infringing the U.S. process patent. This would be a significant gain for the biotechnology industry. Several other bills affecting intellectual property laws also have been introduced.

Other factors will affect biotechnology as an intellectual property. For example, the creation of a new federal court of appeals on 1 October 1982—the Court of Appeals for the Federal Circuit (CAFC)—should bring a needed uniformity to patent infringement decisions (*70*). As part of its jurisdiction, this court now hears all patent infringement appeals from the nation's district courts, rather than the other courts of appeal, some of which had been notoriously antipatent in philosophy. The CAFC will influence the proper scope and range of equivalents to be accorded claims for biotechnological inventions as well as the statutory subject matter and other infringement issues peculiar to this technology. Related bills are also appearing; the proposed patent term restoration acts would extend the term of chemical or pharmaceutical patents beyond their present 17 years to compensate for delays in obtaining EPA or FDA product approvals. The necessity of such an act is debatable (*71*); however, its proposal exemplifies a renewed interest in strengthening intellectual properties.

In addition to concerns over competitiveness and protectability, a recent lawsuit has sharply focused attention on another legal uncertainty, the ownership of cell lines and cellular components such as genes or plasmids. Hoffmann–La Roche and the University of California disputed the ownership of a bacterial strain that incorporated a human interferon gene copied from a human cell cultured by a University of California scientist (*72*). The real concern, of course, was that only the owner would earn royalties from the sale of interferon: does the cell donor, the culturing researcher, host institution, or commercializing business have a superior proprietary interest?

The case was settled for an undisclosed amount, leaving no judicial resolution as a precedent. It highlights the increasing complexity of cooperative research efforts. Unfortunately, the lesson learned by many from this dispute is that scientific material should not be shared without prior license agreements. This may have a chilling effect on the more collegial practice of informal sharing that has been the norm for biomedical researchers. The new protocol may in time become routine but should not unduly hamper technological development.

Conclusions

Intellectual property protection will play a major role in the rate at which biotechnology develops in the United States. Legal uncertainties, such as the standard for enabling disclosures in patent applications claiming multicellular organisms, may ultimately require congressional intervention. The courts will probably resolve many of the remaining patent, trade secret, copyright, and

trademark issues. Proposed federal legislation in the funding, patent, antitrust, and technology transfer areas will enhance the development and competitiveness of the domestic industry. Finally, a better understanding of intellectual property by research scientists, businesspeople, and university administrators will increase the pace of technological development in biotechnology and other fields.

References and Notes

1. A. L. Demain, *Science* **214**, 987 (1981).
2. H. Miller, *Biotechnology* **1**, 382 (1983).
3. F. McChesney and R. Adler, *Environ. Law Rep.* **13**, 10,366 (1983).
4. For instance, the Greek historian Phylarchus (third century B.C.) recorded a law of the Sybarites giving confectioners or cooks who invented "any peculiar and excellent dish" exclusive rights to make it for 1 year "in order that others might be induced to labour at excelling in such pursuits" [C. D. Yonge, Transl., *The Deipnosophists of Athenaeus* (Bohn, London, 1854), vol. 3, p. 835].
5. G. Ramsey, *J. Pat. Off. Soc.* **18**, 6 (1936).
6. Simplistically, the later practice involved a "bad" monopoly, whereas the patents granted to inventors were "good" monopolies. Because of these historical usages, today " 'monopoly' is a word as filled with ambiguity as the word 'love,' and, nearly as full of emotional implications" [G. Rich, *ibid.* **24**, 103 (1942)].
7. 21 *Statutes of James I*, chap. 3 (1624).
8. 35 *U.S. Code*, sect. 154.
9. *Ibid.*, sects. 283 and 284.
10. The patentee has long been recognized to have a personal common law (or natural) right to make, use, and sell an item in the absence of legal proscription. Thus a patent grant does not create any affirmative rights in the patentee. See, for example, *Fuller* v. *Berger*, 120 *Fed. Rep.* 274 (Seventh Circuit Court, 1903).
11. 7 *U.S. Code*, sects. 135–135k and 136–136y; see implementing regulations at 40 *Code Fed. Regul.* sect. 162.5.
12. U.S. Constitution, Article I, Section 8, Clause 8. The present-day equivalent of "useful arts" is "technological arts" [*In re Musgrave*, 431 *Fed. Rep.* 2nd ser. 882 (Court of Customs and Patent Appeals, 1970)]. The "sciences" were the philosophical or liberal arts for which writings are encouraged through copyright protection. The American colonies granted numerous patents for new inventions, in addition to awarding monopolies to encourage the establishment of new industries and foreign industries new to America. These constitutional provisions were noncontroversial and were adopted partly to encourage industrial development to replace the machinery of England on which the states had been dependent. Rapid approval of the first patent statute was supported by George Washington, and it was enacted by the first Congress in 1790.
13. For example, "as means of transportation suited to the times, were the first automobiles actually better than the horse?" [G. Rich, *J. Pat. Off. Soc.* **42**, 82 (1960)]. Cars were sold long before adequate roads were built and before gas stations arrived in most towns.
14. G. Rich, *J. Pat. Off. Soc.* **24**, 177 (1942).
15. Over 4 million inventions have been patented; most have probably never been marketed.
16. 35 *U.S. Code*, sect. 112, 1st paragraph (Table 1).
17. *Ibid.*, sect. 112, 2nd paragraph (Table 1).
18. Patents typically present a series of claims (each affording a separate property grant) having progressively more limited scope—thus, should a broad claim be invalidated, the patentee may be able to rely on a more narrow property grant.
19. 35 *U.S. Code*, sect. 282.
20. An invention can be appropriate statutory subject matter and yet be unpatentable because it is a reinvention of something previously known, even when the *n*th inventor had no knowledge of it; also, a novel invention may be devoid of any patentable utility.
21. *Lowell* v. *Lewis*, 1 Mason 182, 15 *Fed. Cases* 1018, No. 8568 (Circuit Court of the District of Massachusetts, 1817). Unfortunately, the Supreme Court has overly narrowed the utility requirement to things of known, practical commercial utility [*Brenner* v. *Manson*, 383 *U.S. Rep.* 519 (1966)].
22. 447 *U.S. Rep.* 303 (1980). See also the lower court opinion in *Chakrabarty* by Judge G. Rich for a clear and thorough introduction to the basic provisions of the patent statute [*Application of Bergy*, 599 *Fed. Rep.* 2nd ser. 952 (Court of Customs and Patent Appeals, 1979)].
23. Brief for the Petitioner, Summary of Argument. PTO placed reliance on the enactment of the Plant Patent Act of 1930 and the Plant Variety Protection Act of 1970 as implicit evidence that Congress had not intended section 101 to encompass living organisms. In response, the Supreme Court found "no basis" for reading into these two congressional actions "an intent to modify the plain meaning of the words found in §101" (*Chakrabarty*, 447 *U.S. Rep.*, at 314).
24. Citing congressional committee reports accompanying the Patent Act of 1952, the Supreme Court noted that Congress intended statutory subject matter to "include anything under the sun that is made by man" (*Chakrabarty*, *ibid.*, at 309). PTO's test for patentability is applied on a case-by-case basis to determine whether a claimed invention is the product of human ingenuity.
25. *Application of Merat*, 519 *Fed. Rep.* 2nd ser. 1390 (Court of Customs and Patent Appeals, 1975), *affirmed*, on other grounds.
26. R. Palmiter *et al.*, *Nature (London)* **300**, 611 (1982).
27. *Application of Bergy*, 563 *Fed. Rep.* 2nd ser. 1031 (Court of Customs and Patent Appeals, 1977).
28. *Graham* v. *John Deere*, 383 *U.S. Rep.* 1 (1966).
29. G. Rich, *George Wash. Univ. Law Rev.* **28**, 393 (1960). Before the Patent Act of 1952, the predecessor to "unobviousness" was known as the "requirement for invention," and its replacement by the unobviousness standard was a major accomplishment of the act.
30. *Fields* v. *Conover*, 443 *Fed. Rep.* 2nd ser. 1386 (Court of Customs and Patent Appeals, 1971).
31. *Application of Nelson*, 280 *ibid.* 172 (Court of Customs and Patent Appeals, 1960).
32. *Application of Gay*, 309 *ibid.* 769 (Court of Customs and Patent Appeals, 1962).
33. The requirement is subjective, and the applicant is essentially under the honor system to comply, at the penalty of having a patent later invalidated through litigation should information about the concealment be exposed.
34. *Ex Parte Jackson*, 217 *U.S. Pat. Q.* 804 (Patent Office Board of Appeals, 1982).
35. *Application of Argoudelis*, 434 *Fed. Rep.* 2nd ser. 1390 (Court of Customs and Patent Appeals, 1970).
36. 886 *Off. Gaz.* 638 (1971).
37. Plant Patent Act of 1930, 35 *U.S. Code*, sects. 161–164, at sect. 162.
38. J. Schwaber and E. Cohen, *Nature (London)* **244**, 446 (1973); G. Kohler and C. Milstein, *ibid.* **256**, 495 (1975).
39. See, for example, U.S. Patent 4,364,932 (1982).
40. M. Sun, *Science* **218**, 868 (1982).
41. *Machine Co.* v. *Murphy*, 97 *U.S. Rep.* 120 (1877).
42. *Westinghouse* v. *Boyden Power Brake Co.*, 170 *ibid.* 537 (1898).
43. *Nationwide Chemical Corp.* v. *Wright*, 458 *Fed.* Suppl. 828 (Middle District of Florida, 1976), *affirmed*, 584 *Fed Rep.* 2nd ser. 714 (Fifth Circuit Court, 1978).
44. Detecting infringement may also be difficult in microorganism technologies [B. Collins, in *Infringement of Patents*, D. Dunner, Ed. (Practicing Law Institute, New York, 1981), pp. 185–287].
45. "Litigation, like war, is a net social loss because it is both expensive and unproductive" (*6*, p. 86).
46. This is a simple explanation of a term often said to be incapable of exact definition. For a complete analysis, see R. Milgrim, *Trade Secrets* (Bender, New York, 1967, with annual updates).
47. *Restatement of Torts*, sect. 757 (1939).
48. T. Kiley, in *Protecting Trade Secrets*, G. Rose, Ed. (Practicing Law Institute, New York, 1981), pp. 443–456.
49. A. Whale, *ibid.*, pp. 405–442.
50. *Fed. Regist.* **48**, 24,556 (1983).
51. 5 *U.S. Code*, sect. 552.
52. M. Nimmer, *Nimmer on Copyright* (Bender, New York, 1963, and annual updates). The duration of a copyright also differs—copyright protection exists from the time that a work is fixed in a tangible medium of expression to the end of its author's life plus 50 years [17 *U.S. Code*, sect. 302(a)]. The works of an employee endure for 100 years after creation or for 75 years after publication, whichever is shorter [*ibid.*, sect. 302(c)].
53. 17 *U.S. Code*, sect. 102(a). The requirement of "originality" means independently created and is less stringent than that of novelty for patentability. "Works of authorship" were purposely left undefined, but illustrative categories include literary, dramatic, and choreographic works; motion pictures; and sound recordings. The constitutional term "writings" in Article I, Section 8, Clause 8, which provides the congressional authority for the copyright law, has been broadly interpreted to include "any physical rendering of the fruits of creative intellectual or aesthetic labor" [*Goldstein* v. *California*, 412 *U.S. Rep.* 561 (1973)].
54. 17 *U.S. Code*, sect. 106.
55. *Ibid.*, sect. 102(a).
56. *Ibid.*, sect. 117; *Williams Electronics, Inc.* v. *Artic International, Inc.*, 685 *Fed. Rep.* 2nd ser. 870 (Third Circuit Court, 1982).
57. I. Kayton, *George Wash. Law Rev.* **550**, 191 (1982).
58. *Morrissey* v. *Procter & Gamble*, 379 *Fed. Rep.* 2nd ser. 675 (First Circuit Court, 1967).
59. 17 *U.S. Code*, sect. 101; see also M. Nimmer (*52*, sect. 2.18).
60. 17 *U.S. Code*, sect. 102(b).
61. 15 *U.S. Code*, sect. 1127; see also J. McCarthy, *Trademarks and Unfair Competition* (Lawyers Co-operative, Rochester, N.Y., 1973, plus updates).
62. *Commercial Biotechnology: An International Analysis* (Office of Technology Assessment, Washington, D.C., 1984).
63. F. Press, *Science* **218**, 28 (1982); R. R. Nelson and R. N. Langlois, *ibid.* **219**, 814 (1983); A. B. Giamatti, *ibid.* **218**, 1278 (1982); R. Roy, *ibid.* **178**, 955 (1972).
64. B. J. Culliton, *ibid.* **216**, 155 (1982); G. A. Keyworth, II, *ibid.* **217**, 606 (1982).
65. E. Kessler and R. Adler, *Am. Pat. Law Assoc. Q. J.* **9**, 318 (1981).
66. *Ibid.* **10** (1982), entire issue.
67. G. J. Mossinghoff, *Pat. Trademark Copyright J.* **26**, 546 (1983); E. G. Jefferson, *Science* **222**, 243 (1983).
68. U.S. Congress, S. 1841 and H.R. 3878 (98th Congress, First Session, 1983).
69. R. B. Andewelt, *Pat. Trademark Copyright J.* **27**, 73 (1983).
70. L. Shapiro, *Dist. Lawyer* **7**, 29 (1983).
71. M. Sun, *Science* **222**, 593 (1983). "The term is now an historical accident. . . . If changed it would be just as arbitrary. [The term of 17 years was] a period arrived at by compromise between a former term of fourteen years, supposed to be the time required to train two apprentices in succession, and twenty-one years which was once allowed by a statute permitting a further extension of seven years" (*14*, p. 162).
72. B. J. Culliton, *Science* **219**, 372 (1983); M. Sun, *ibid.* **220**, 393 (1983).

73. The assistance of the following in reviewing the manuscript is gratefully acknowledged: Carolyn R. Adler, Esq.; Robert L. Price, Esq., Judge Giles S. Rich; Steven A. Soffen, Esq.; and John E. Tarcza.