

**Back to the Future:
Rethinking the Product of Nature Doctrine as a Barrier
to Biotechnology Patents**

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I. Introduction

U.S. Patent 5,397,696, issued on March 14, 1995, claims “[a] cell line, designated Papua New Guinea-1(pNG-1) ATCC CRL 10528.”¹ In simplest terms, a cell line is the perpetuation, in an artificial medium, of an original sample of cells from a host.² This patent claimed a cell line derived from the white blood cells of a single resident of Papua New Guinea. His tribe, the Hagahai, is an isolated group of fewer than 300 hunter-horticulturalists. The tribe interested medical science because a number of its members carry the human T-cell leukemia virus (HTLV-1) but do not have the disease. It was thought that a Hagahai cell line might prove useful in developing diagnostic tests for and vaccines against HTLV-1. Consequently, a group of researchers from the U.S. National Institutes of Health applied for and received a patent on the cell line itself, “a viral preparation comprising the HTLV-1 variant in the cell line,” and several bioassays, or diagnostic tests.

Shortly thereafter, an international controversy exploded.³ The government of Papua

¹U.S. Patent No. 5,397,696 (issued March 14, 1995), available at www.uspto.gov. For a fuller discussion of this patent, see *infra* notes 130-32 and accompanying text.

²See *infra* notes 116-32 and accompanying text.

³Gary Taubes, *Scientists Attacked for “Patenting” Pacific Tribe*, 270 SCIENCE 1112 (Nov. 17, 1995); Kara K. Ching, Note, *Indigenous Self-Determination in an Age of Genetic Patenting: Recognizing an Emerging Human Rights Norm*, 66 FORDHAM L. REV. 687, 701-02 (1997).

New Guinea objected to the encroachment on its sovereignty.⁴ Human rights groups challenged the concept of ownership of a person's cells, particularly when that person comes from the post-colonial developing world.⁵ Others argued over who should get the patent royalties.⁶ In the face of this pressure, and in the absence of any commercial takers for the patent, the NIH renounced it, formally forfeiting its rights on October 24, 1996.⁷

What was missing from this debate was *any* discussion of whether a cell line or a virus found in the cell line constitutes patentable subject matter under section 101 of the Patent Act of 1952.⁸ That is, no one asked whether these are even the kinds of things on which patents can be granted. Although the provisions of the Patent Act will be well known to readers of this journal, it is important to our argument to recall its basic tenets. According to section 101, a patent application must claim “a new and useful process, machine, manufacture, or composition of matter.”⁹ As traditionally parsed, section 101 imposes three distinct and demanding requirements.¹⁰ First, the invention must indeed be a “process, machine, manufacture, or

⁴ Ching, *supra* note 3, at 701; *see* Sally Lehrman, *Anthropologist Cleared in Patent Dispute*, 380 NATURE 374 (Apr. 4, 1996)(describing dispute between PNG government and anthropologist Carol Jenkins, one of the co-owners of the patent).

⁵Ching, *supra* note 3, at 701; Taubes, *supra* note 3 (both discussing opposition to patent by Rural Advancement Foundation International and other “non-governmental organizations”).

⁶Lehrman, *supra* note 4; Ching, *supra* note 3, at 701-02.

⁷Ching, *supra* note 3, at 701-02.

⁸35 U.S.C. § 101. The claim on the virus has engendered no commentary at all.

⁹*Id.*

¹⁰*In re Bergy*, 596 F. 2d 952, 960-62 (C.C.P.A. 1979). For an explanation of the convoluted history of this case, *see infra* notes 230-53 and accompanying text.

composition of matter.” In other words, it must comprise patentable subject matter.¹¹ Second, the invention must be “new,” a determination performed under section 102's detailed definitions of novelty.¹² In particular, the claimed invention must be distinguishable from (and thus not “anticipated” by) what others knew and were doing, what had been patented in this country and abroad, and what had been disclosed in print at the time of invention.¹³ Third, it must be “useful,” a concept mentioned only in section 101 that is defined by case law.¹⁴ The utility requirement has proved to be a significant obstacle for some classes of biotechnology inventions.¹⁵ In addition, the invention must meet section 103's standard of non-obviousness¹⁶ and must be the subject of a suitably enabling written description.¹⁷

¹¹See 1 DONALD S. CHISUM, CHISUM ON PATENTS (hereinafter CHISUM) at 1-6 (2001 & Supps.) (“An invention may be patented only if it falls within one of the statutory classes of subject matter”).

¹²35 U.S.C. § 102.

¹³*Id.* § 102(a). Section 102(b)'s statutory bars forbid the granting of a patent if anyone, including the inventor, has patented the same invention, described it in print, used it publicly, or offered it for sale, in this or a foreign country, more than one year prior to the filing of the application. Sections 102(c-f) describe other conditions under which the right to patent may be lost and section 102(g) establishes the rules for resolving conflicts about who invented first.

¹⁴See, e.g., *Brenner v. Manson*, 383 U.S. 519 (1966) (applying the utility requirement to chemical patents).

¹⁵John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 112, 128-29 (2001) (reviewing utility as a barrier to biotechnology patents). See *infra notes* 297-300 and accompanying text.

¹⁶*Id.* § 103(a) precludes a patent “if the differences between the subject matter 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.”

¹⁷*Id.* § 112. In the case of biotechnology inventions, the deposit of a specimen may sometimes compensate for deficiencies in the written description. 37 C.F.R. § 1.802 (2001). *Cf.*

As we shall see, some courts and authorities have taken the position that patentable subject matter status is not an independent requirement, but merely a label to be applied when a claimed invention is found to be new and useful.¹⁸ We shall argue, however, that this view has been squarely repudiated by the Supreme Court, most importantly in *Diamond v. Chakrabarty*,¹⁹ the Court's only biotechnology decision. There, the Court held that a biotechnology product will comprise patentable subject matter only if it amounts to "a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity."²⁰ By contrast, "a hitherto unknown natural phenomenon" is ineligible for patent protection.²¹ This aspect of the patentable subject matter requirement has come to be called the product of nature doctrine.²² Its operating principle, which is traceable back to the nineteenth century,²³ is entirely straightforward: one cannot patent a product that occurs in nature in essentially the same form. In the cell line controversy as in numerous related instances, it has been readily assumed by patent lawyers, courts, and commentators that the product of nature doctrine has no relevance to contemporary biotechnology patents. We shall challenge that assumption.

Enzo Biochem, Inc. v. Gen-Probe Inc., 285 F. 3d 1013 (Fed. Cir. 2002)(finding that written description of biotechnology invention was inadequate, and that deposit failed to cure inadequacy).

¹⁸See *infra* notes 193-98 and accompanying text.

¹⁹447 U.S. 303 (1980).

²⁰*Id.* at 309.

²¹*Id.*

²²1 CHISUM, *supra* note 11, at 1-39.

²³See *infra* part III.A.

To cite a second example, isolated and/or purified DNA has been routinely given subject matter status since the 1980s. U.S. Patent 5,747,282, issued May 5, 1998, the so-called breast cancer gene patent,²⁴ has been at least as controversial as the New Guinea cell line patent.²⁵ It claims, in “isolated” form, the DNA sequence of a gene that can cause susceptibility to breast cancer—not just methods or processes for producing or using the DNA sequence, but the actual sequence of chemical bases by which the breast cancer gene does its work in human cells.²⁶ According to the patent, “isolated” is synonymous with “substantially pure,” and means “removed from its naturally occurring environment.” Here again, although there has been a furor over the policy implications of granting such patents, the more fundamental question of why gene sequences are inventions goes largely unasked.²⁷

The explanation for this inattention to the subject matter issue lies in a consensus that has emerged among patent lawyers, has been accepted by the patent office, and has been ratified by

²⁴U.S. Patent No.5,747,282 (issued May 5, 1998)(entitled “17Q-linked Breast and Ovarian Cancer Susceptibility Gene”).

²⁵*E.g.*, Leon R. Kass, *Triumph or Tragedy? The Moral Meaning of Genetic Technology*, 45 AM. J. JURIS. 1, 5 (2000); Amy Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555, 591 (1998); Alistair D. Stewart, *Patenting of Human Genes*, 373 NATURE 185 (Jan. 19, 1995); George Poste, *The Case for Genomic Patenting*, 378 NATURE 534, 535 (Dec. 7, 1995); *cf.* USPTO, Utility Examination Guidelines, 66 FED. REG. 1092 (Jan. 5, 2001)(in announcing new Guidelines, PTO addresses and rejects several comments raising concerns about patenting genes with therapeutic significance).

²⁶The material in this paragraph is derived from the text of the patent, *supra* note 26.

²⁷*See supra* note 25; Daniel J. Kelves & Ari Berkowitz, *The Gene Patenting Controversy: A Convergence of Law, Economic Interests, and Ethics*, 67 BROOKLYN LAW REV. 233, 242-43 (2001); *Symposium on Bioinformatics and Intellectual Property Law*, April 27, 2001, 8 B.U.J. SCI. & TECH. 190 (2002). The participants in the latter symposium did raise the subject matter question, but disposed of it in short order.

the United States Court of Appeals for the Federal Circuit.²⁸ In its short form, the point of the consensus is that modern claim-drafting practices have taken the subject matter requirement out of play in most biotechnology fields.²⁹ With specific reference to the product of nature doctrine, John S. Golden has concluded that the doctrine, “although still extant, is effectively toothless, because biotechnology by nature involves isolating and replicating biological materials to produce ‘unnatural’ levels of purity.”³⁰

Two of the country’s most eminent patent authorities have spelled out the consensus in more detail as it relates to gene patents. Q. Todd Dickinson, formerly commissioner of patents and now in practice with Howrey & Simon, put it this way at a recent conference:

Even though it [DNA] is found in nature, as is said, what the patent is granted on is not the form that’s found in nature, but rather, for the isolated and purified form of that gene. The chemical composition of that gene or that gene fragment has never been known before, and the scientist who made that discovery, has made that invention, and is entitled to it because they have isolated and purified it.³¹

²⁸Golden, *supra* note 15, at 126 (describing role of Federal Circuit in supporting “zeitgeist that led to fivefold increase in worldwide biotechnology patenting from 1980 to 1990”); Nancy T. Gallini, *The Economics of Patents: Lessons from Recent U.S. Patent Reform*, 16 J. ECON. PERSPECTIVES 131, 134 (2002).

²⁹“The question that remains is how much traction traditional requirements for patentability retain. . . . [T]he answer is, practically speaking, ‘not much.’” Golden, *supra* note 15, at 127.

³⁰*Id.*

³¹*The Human Genome Project: DNA Science and the Law: The American Legal System’s Response to Breakthroughs in Genetic Science, Panel One: Intellectual Property and Genetic Science: The Legal Dilemmas* (Washington, D.C. Oct. 19, 2001), 51 AM. UNIV. L. REV. 371, 377 (2002)(remarks of Todd Dickinson). The point that it is merely a claim-drafting problem comes through clearly in a short piece written by a patent practitioner for a scientific audience. Cheryl H. Agris, *Patenting DNA Sequences*, 16 NATURE BIOTECH. 877 (Sep. 1998).

And Rebecca Eisenberg, one of the most-quoted academic patent commentators, has described the consensus in these terms:

The standard patent lawyer's response to the "products of nature" limitation is to treat it as a technical, claim-drafting problem. From this perspective, the prohibition against patenting products of nature only prevents the patenting of DNA sequences in a naturally occurring form that requires no human intervention. . . . Patents have thus issued on "isolated and purified" DNA sequences, separate from the chromosomes in which they occur in nature, or on DNA sequences that have been spliced into recombinant vectors or introduced into recombinant cells of a sort that do not exist in nature. . . . This is not simply a lawyer's trick, but a persuasive response to the intuition that patents should issue only for human inventions.³²

In starkest terms, the purpose of this article is to ask, Are we *sure* it isn't a lawyer's trick? We seek to probe the assumptions that underlie the current consensus, and to ask whether the product of nature doctrine is in fact as irrelevant as it has been assumed to be. In particular, we ask whether that doctrine, as originally propounded and as recently restated by the Supreme Court, has been properly understood by those who have treated it so dismissively. To use Golden's terminology, are biotechnology inventions inevitably "unnatural" enough to surmount the subject matter hurdle?³³ In some instances, the current consensus may be correct. In others, however, we shall argue that, at a minimum, the product of nature doctrine deserves much closer scrutiny.

The argument has both theoretical and practical significance. On the theoretical side,

³²Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences*, 49 EMORY L.J. 783, 786 (2000). Cf. Arti K. Rai, *Intellectual Property Rights in Biotechnology: Addressing New Technology*, 34 WAKE FOREST L. REV. 827, 835 (attacking Federal Circuit's "categorization of DNA-based technology as just another species of chemistry").

³³See *supra* note 30 and accompanying text.

renewed attention to the product of nature doctrine could reinvigorate a significant theoretical debate. Theorists have long argued for the existence of a robust entity known as “the public domain,”³⁴ and many now argue for including within it much of the genetic realm.³⁵ From their perspective, something that has the attributes of public domain material—a product of nature, for example—has a claim to inviolability. Those who would capture it as private property must meet a substantial burden.³⁶ But over the last twenty years of biotechnology patent law development the public domain has rarely risen to the level of an afterthought.³⁷ It has certainly not been treated as a well-defined realm that can be invaded only for good cause. At most, it has been a label affixed to things that fall short of patentability for some reason or other.³⁸ That is, whereas

³⁴The seminal article in the development of the theory of the public domain as an “affirmative” entity may be David Lange, *Recognizing the Public Domain*, 44 L. & CONTEMP. PROBS. 147 (1981).

³⁵*E.g.*, Utility Examination Guidelines, *supra* note 27, at I(2) (noting and rejecting comments stating that “a gene is not a new composition of matter because it exists in nature”); Arti K. Rai & Rebecca S. Eisenberg, *The Public and the Private in Biopharmaceutical Research*, Duke Conference on the Public Domain, November 9-11, 2001 (collected discussion drafts at 157, 160)(hereinafter Duke Conference Papers).

³⁶*E.g.*, James Boyle, *The Second Enclosure Movement and the Construction of the Public Domain*, Duke Conference Papers, *supra* note 35, at 1, 25-30, 38-43. Boyle cited one of the most famous Supreme Court patent cases for the propositions that there is “an existent public domain,” and that it is “unconstitutional under the patent clause for Congress to privatize any portion of that domain.” *Id.* at 26 (*citing* *Graham v. John Deere Co.*, 383 U.S. 1, 5-6 (1966)).

³⁷*See* Rai & Eisenberg, *supra* note 35, at 157 (arguing that public domain tradition “has eroded considerably over the past quarter century as patent claims have reached further upstream from end products to cover fundamental discoveries”); *cf.* Lange, *supra* note 34, at 150 n. 20 (noting how little attention had been paid to the public domain in the years preceding his 1981 article).

³⁸This “negative” view of the public domain has found one of its strongest articulations in the copyright context. Edward Samuels, *The Public Domain in Copyright Law*, 41 J. COPYR. Soc’y U.S.A. 137 (1993). Samuels argued against a “magical” public domain,” and in favor of

many public domain theorists would say that certain things cannot be owned because they are in the public domain, the law has increasingly acted as if things are in the public domain simply because there is no legal basis for owning them.³⁹

Public domain theorists have noted the potential role of the product of nature doctrine in the defense of the realm. At a conference of most of the country's principal public domain scholars last fall, two of the most prominent, Arti Rai and Rebecca Eisenberg (whom we relied on earlier for a statement of the current consensus), suggested that "[o]ne might, for example, reinvigorate the 'products of nature' limitation on patent eligibility so as to exclude discoveries of DNA sequences, proteins, and biochemical mechanisms from patent protection."⁴⁰ This article will offer a plan for just such a reinvigoration.

On a practical level, we propose a legal hook on which to hang the varied, often inchoate concerns about the rapid monopolization of the biological public domain. The patentable subject matter approach could give those who want to go slow on biotechnology patents a workable tool. With obviousness being an issue only in occasional contexts,⁴¹ and with patent lawyers having

a cumulative notion of "what remains after one examines all possible sources of legal protection." *Id.* at 150.

³⁹For a discussion of these contrasting "positive" and "negative" views of the public domain, see William van Caenegem, *The Public Domain: Scientia Nullius?*, 24 EUR. INT. PROP. REV. 324 (2002).

⁴⁰Rai & Eisenberg, *supra* note 35, at 160.

⁴¹Golden, *supra* note 15, at 129-130 ("judicial formulations of the requirement have made it hard to make arguments of non-obviousness stick with regard to biotechnological inventions"). Arti Rai has also concluded that "the CAFC has employed non-obviousness in a way that dramatically lowers the bar for patentability," and has criticized the court's approach. Rai, *supra* note 32, at 833-35. For a detailed analysis of the role of obviousness in biotechnology cases, see

adroitly solved problems of utility⁴² and the written description requirement,⁴³ there is little basis in the text of the statute other than subject matter for denying patents to cell lines, gene sequences, and the like. More than twenty years of pure policy arguments—*we just shouldn't be doing this*⁴⁴—have gotten nowhere in the courts,⁴⁵ and Congress has shown no inclination to put the lucrative biotechnology genie back into the bottle.⁴⁶ Rethinking the subject matter issue could thus provide a framework (or, more cynically, a pretext) for a much broader debate.

Our argument admittedly has a closing-the-barn-door-after-the-horse-has-left quality.

PHILIPPE G. DUCOR, PATENTING THE RECOMBINANT PRODUCTS OF BIOTECHNOLOGY AND OTHER MOLECULES (1998). For an example of a complex biotechnology non-obviousness case, see *In re Deuel*, 51 F.3d 1552 (Fed. Cir.1995).

⁴²See *infra* notes 296-300 and accompanying text.

⁴³Golden, *supra* note 15, at 128.

⁴⁴See, e.g., JEREMY RIFKIN, THE BIOTECH CENTURY: HARNESSING THE GENE AND REMAKING THE WORLD 37-66 (Supp. No. 11 1998).

⁴⁵The best example is *Chakrabarty*, in which the Supreme Court responded to arguments about “high policy” with the comment that “[w]hatever their validity, the contentions now pressed on us should be addressed to the political branches of the Government.” 447 U.S. at 317. See Kelves & Berkowitz, *supra* note 27, at 240-43 (discussing reception of ethical policy arguments in *Chakrabarty*).

⁴⁶For examples of recent demands for Congressional action, see Donna M. Gitter, *International Conflicts Over Patenting DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair-Use Exemption*, 76 N.Y.U.L. REV. 1623 (2001)(advocating Congressional enactment of compulsory licensing scheme to reconcile differences in U.S. and EU law); S. Benjamin Pleune, *Trouble with the Guidelines: On Urging the PTO to Properly Evolve with Novel Technologies*, 2001 U. ILL. J.L. TECH. & POL'Y 365 (2001)(arguing for specialized biotechnology legislation); Mary Breen Smith, *An End to Gene Patents? The Human Genome Project Versus the United States Patent and Trademark Office's 1999 Utility Guidelines*, 73 U. COLO. L. REV. 747 (2002)(arguing for amendment of section 102 to limit human gene sequence patents). Despite such proposals, the patentability sections of the Patent Act have remained materially unchanged since 1952.

But revisiting fundamental questions is a critical function of the legal academy. And such efforts have sometimes had dramatic success in intellectual property law: witness the Second Circuit's 1992 *Computer Associates*⁴⁷ decision, which came out of left field and radically reduced the copyright protection given to computer programs. In patent law itself, the Supreme Court and the Federal Circuit have revised the doctrine of equivalents in ways that few would have predicted just a few years ago.⁴⁸ Consequently, even though we are challenging a conventional wisdom that is deeply ingrained, history inclines us to persist.

The ultimate argument of this article is that while much biotechnology has been properly held to be patentable subject matter, some categories of patents have been wrongly granted. Tellingly, whenever we recount these patent stories to non-patent colleagues, we get the same reaction: That's crazy! You can't patent *that!*⁴⁹ The purpose of the article, in one sense, is to explore the basis for this reaction, and to see if it can be restated in legally salient terms.

In part II of the article, we review the scientific issues that underlie our legal critique. In part III we explore the legal history of the product of nature doctrine, beginning in the nineteenth century and moving forward through the Supreme Court's most recent term. We present substantial legal evidence that the doctrine is alive and well, even if often ignored. Then, in part IV, we discuss the status of the product of nature doctrine in current biotechnology law and practice. In part V, we argue for a renewed application of the doctrine to several specific types of

⁴⁷*Computer Assoc. Intern., Inc. v. Altai, Inc.* 982 F. 2d 693 (2d Cir. 1992).

⁴⁸*Festo Corp. v. Shoketsu Kinzoku Kogyokabushiki Co.*, 234 F. 3d 558 (Fed. Cir. 2001), *vacated and remanded*, 122 S. Ct. 1831 (2002).

⁴⁹Rebecca Eisenberg reports the same reaction, but from her parents' friends rather than her colleagues. *Symposium, supra* note 27, at 194 (remarks of Rebecca S. Eisenberg).

biotechnology patents. In part VI, we conclude that, properly understood, the product of nature doctrine still has a meaningful role to play in the protection of the biological public domain.

II. The Scientific Background

As background for our legal analysis, in this part we review the basic science underlying each of three significant categories of biotechnology patents: claims on genes and DNA sequences, claims on cell lines, and claims on viruses. These basics may be familiar to most readers. We have included them for the benefit of other readers as well as to emphasize the specific principles that will be critical to our legal argument.

A. The Biology of Gene and DNA Sequence Claims

1. DNA and Protein Synthesis

DNA (deoxyribonucleic acid) is a very long molecule that is found in every single cell of every living organism.⁵⁰ In all organisms other than bacteria, most of the cell's DNA is found in the nucleus (bacteria do not have a nucleus).⁵¹ DNA dictates the functioning of the individual cell by directing the making of proteins at the right time and in the appropriate amount.⁵² By cumulative effect, DNA thus controls the growth, development, maintenance, and reproduction of the organism.

DNA is made up of subunits or building blocks called nucleotides. Each nucleotide consists of a sugar (deoxyribose, the D in DNA), a phosphate group, and one of four bases: adenine (A),

⁵⁰GEORGE B. JOHNSON, THE LIVING WORLD 137-38 (1997).

⁵¹*Id.* at 51, 57.

⁵²*Id.* at 143.

guanine (G), cytosine (C), and thymine (T), commonly abbreviated by their first letter.⁵³ A DNA molecule resembles a ladder. The sugar and phosphate groups form the two sides and the bases form the rungs, with one base extending out from each side to join in the middle.⁵⁴ The bases always join in the same way: A with T and C with G.⁵⁵ A-T and C-G are called complementary base pairs.⁵⁶ The complementary bases are joined by weak hydrogen bonds; the bonding process is known as hybridization.⁵⁷ The relative weakness of the bonds means that they can be easily broken and reformed, allowing portions of DNA to be readily unzipped and zipped back together.

The DNA ladder is in fact a flexible rope ladder, which is usually twisted into a shape resembling a winding staircase—Crick and Watson’s famous “double helix.”⁵⁸ The helical structure permits the very large DNA molecule to be compacted into the nucleus. The total length of DNA in the nucleus of a human cell can be thousands of times longer than the cell diameter.⁵⁹ The DNA in the nucleus is organized into units called chromosomes. The number and length of chromosomes are specific for each species of organism. Human beings have 46 chromosomes grouped into 23 pairs in the nucleus of every cell in the body (with the exception of sperm and egg cells, which have 23 unpaired

⁵³*Id.* at 141.

⁵⁴*Id.*

⁵⁵*Id.*

⁵⁶HARVEY LODISH ET AL., *MOLECULAR CELL BIOLOGY* 103 (4th ed. 2000).

⁵⁷*Id.* at G-9; JOHNSON, *supra* note 50, at 142.

⁵⁸JAMES WATSON, *THE DOUBLE HELIX* (1968); JOHNSON, *supra* note 50, at 141.

⁵⁹LODISH ET AL., *supra* note 56, at 295.

individual chromosomes).⁶⁰ These chromosomes contain the human genetic code, or genome. The human genome consists of about 3 billion base pairs;⁶¹ simpler organisms usually have shorter genomes.⁶²

The genome consists of the sequence of the four bases—A, T, C, and G. The sequencing of bases is the medium through which DNA stores and ultimately transmits information. The arrangement of these four bases, over a vast number of iterations, thus determines the nature, functionality, and, often, the health of an organism. In this respect the genome resembles a computer. Both can store enormous amounts of information by the almost endless repetition of very simple operations.⁶³ In the case of the computer, the operation is binary: a memory location is coded as either 0 or 1. In the case of the genome, it is a four-way choice—A, T, C, or G--repeated over and over, 3 billion times in the human genome. Only some regions (usually a small portion) of an organism's genome have functional significance. These functional regions are called genes.⁶⁴

The main function of genes is to make proteins.⁶⁵ Consequently, the process of making proteins

⁶⁰JOHNSON, *supra* note 50, at 121.

⁶¹NEIL A. CAMPBELL ET AL., *BIOLOGY* 249 (1994).

⁶²JOHNSON, *supra* note 50, at 166.

⁶³As Rebecca Eisenberg has put it, “DNA sequences are both molecules and information.” *Symposium, supra* note 27, at 196. *See also* Rai, *supra* note 35, at 836 (“although DNA is, obviously enough, a chemical compound, it is more fundamentally a carrier of information.”); JAMES BOYLE, *SHAMANS, SOFTWARE, AND SPLEENS: LAW AND THE CONSTRUCTION OF THE INFORMATION SOCIETY* 4-5 (1996)(comparing computers and genes).

⁶⁴LODISH ET AL., *supra* note 56, at 114.

⁶⁵*Id.*

is called gene expression.⁶⁶ DNA provides the template and the control mechanisms for making proteins.⁶⁷ Only certain genes are expressed in certain cell types. For example, genes for the functioning of muscles will be expressed in muscle tissue cells, liver genes will be expressed in liver cells, and so on. When they are needed, genes are turned on by DNA regions called promoters.⁶⁸

Proteins are large molecules made up of chains of smaller molecules called amino acids.⁶⁹ Proteins are the working molecules of the cell, and all cell activities involve proteins. There are many different kinds of proteins that perform a wide range of functions. Some provide the structure of cells, giving substance to hair fibers and tendons and ligaments; others fight infections as antibodies; others, such as hemoglobin, transport vital substances around the body; others, called hormones, send signals from cell to cell; while others, called enzymes, facilitate biochemical reactions.⁷⁰

The building, or synthesis, of proteins involves two steps: transcription and translation.⁷¹ If one thinks of the nucleus of a cell as a library, then the DNA is its reference collection: although it contains vital information, it cannot physically leave the library. However, copies can be made and those copies can be taken to where the information is needed.⁷² During the first stage of protein

⁶⁶JOHNSON, *supra* note 50, at 143.

⁶⁷ LODISH ET AL., *supra* note 56, at 111.

⁶⁸BENJAMIN LEWIN, GENES VII 233, 966 (2000).

⁶⁹*Id.* at 138.

⁷⁰CAMPBELL ET AL., *supra* note 61, at 42.

⁷¹JOHNSON, *supra* note 50, at 143-46.

⁷²*Id.* at 143.

synthesis, the sequence of bases in the DNA is copied, or transcribed, by a related molecule called RNA (ribonucleic acid).⁷³ Like DNA, RNA is also made up of nucleotides. It differs from DNA in three principal respects: its sugar group consists of ribose rather than deoxyribose, it has only a single strand, and the DNA base thymine (T) is replaced by a base called uracil (U).⁷⁴

During transcription, DNA unzips (separates into two single strands) in the specific region that contains the code for the protein to be synthesized (*i.e.*, the gene for that protein).⁷⁵ Nucleotides of RNA then match up with one side of the DNA (called the template strand) according to the principles of complementarity: an RNA C binds to a G on the DNA strand, an RNA G binds to a DNA C, an RNA U (the RNA version of T) binds to a DNA A, and an RNA A to a DNA T.⁷⁶ This process yields a strand of RNA called messenger RNA or mRNA.⁷⁷ Its code is the complement of that on the template strand of DNA.

Not all of the DNA in the relevant region actually codes for proteins. Packets of non-coding regions called introns lie between the coding regions, which are called exons.⁷⁸ Because the initial, or primary, mRNA transcript is an exact complement of the template DNA, it contains both the introns and the exons. The non-coding regions, or introns, are then excised in a process called

⁷³*Id.*

⁷⁴LODISH ET AL., *supra* note 56, at G-15, 109.

⁷⁵*Id.* at 116; CAMPBELL ET AL., *supra* note 61, at 181.

⁷⁶JOHNSON, *supra* note 50, at 143.

⁷⁷*Id.*

⁷⁸LODISH ET AL., *supra* note 56, at 115.

splicing.⁷⁹ The result is mature mRNA, which contains only the coding region, or exons, and it is this RNA transcript that leaves the nucleus and enters the cytoplasm of the cell.⁸⁰

Once outside the nucleus, the mature mRNA attaches itself to a structure called a ribosome and the second step in protein synthesis, translation, begins.⁸¹ The code transcribed on the mRNA is translated into a protein with the help of another type of RNA, transfer RNA or tRNA.⁸² The critical functional element in translation is the codon, a sequence of three nucleotides on the mRNA that specifies, or codes for, a particular amino acid.⁸³ Several different codons can code for each of the twenty amino acids, a property that biologists call “degeneracy.”⁸⁴ Each unit of tRNA carries one of the twenty amino acids that are the building blocks of proteins.⁸⁵ Each tRNA unit also carries a three-nucleotide sequence (an anticodon) that is the complement of the mRNA codon for its amino acid.⁸⁶

On the ribosome, the tRNA unit carrying a given anticodon matches up and binds to its complementary mRNA codon, thereby bringing the specified amino acid into place.⁸⁷ The process

⁷⁹*Id.* at 116.

⁸⁰*Id.* at 115.

⁸¹JOHNSON, *supra* note 50, at 145.

⁸²*Id.*

⁸³*Id.* at 145-46.

⁸⁴LODISH ET AL., *supra* note 56, at 117.

⁸⁵JOHNSON, *supra* note 50, at 145-46.

⁸⁶*Id.*

⁸⁷*Id.*

continues, with another complementary tRNA binding to the next codon on the mRNA and bringing another amino acid. Adjacent amino acids are joined by chemical links called peptide bonds.⁸⁸ The chain of linked amino acids continues to grow on the ribosome as the mRNA is read and complementary tRNAs bring appropriate amino acids. The chain of amino acids in a specific sequence ultimately forms a protein, or polypeptide.⁸⁹

2. Genes and Sequences

Prior to Crick and Watson's elucidation of the structure of DNA, genes were described as discrete hereditary entities that controlled an organism's traits.⁹⁰ In current terms, a gene is defined as "the entire nucleic acid sequence that is necessary for the synthesis of a functional polypeptide or RNA molecule."⁹¹ In addition to the coding regions for the specific amino acid sequence of a protein, this definition encompasses the regions that code for tRNA and the rRNA that makes up the ribosome; the regions that control the initiation of transcription, which often lie at a distance from the coding regions; and the regions that regulate the splicing of the primary mRNA transcripts.⁹²

Over 90% of an organism's DNA is not involved in protein synthesis.⁹³ In other words, less than 10% of an organism's DNA consists of genes. The function, if any, of the vast majority of this extra

⁸⁸CAMPBELL ET AL., *supra* note 61, at 184-85.

⁸⁹*Id.*

⁹⁰JOHNSON, *supra* note 50, at 137.

⁹¹LODISH ET AL., *supra* note 56, at 295.

⁹²*Id.* at 295, 297.

⁹³*Id.* at 294.

DNA is not yet known.⁹⁴ It comes in various forms, including non-coding regions, or introns, non-functional gene duplicates called pseudogenes, highly repetitious sequences known as short tandem repeats, and unclassified spacer DNA.⁹⁵ The coding regions, or exons, tend to be highly similar across species and between individuals of a given species. However, the non-coding regions, especially the repetitious stretches of DNA, vary greatly, and it is this variability that permits DNA fingerprinting of individual human beings.⁹⁶

With the advent of automated sequencing technologies that permit the rapid identification of nucleotide sequences, there has been significant progress in identifying the coding regions of the human and other genomes.⁹⁷ The artificial production, or synthesis, of DNA has also become routine. One important method for discovering coding regions involves the synthesis of what is known as cDNA (the c stands for copy or complementary DNA). cDNA differs from naturally occurring genomic DNA in that the non-coding introns are absent.⁹⁸ Synthesis of cDNA is made possible by the enzyme⁹⁹ reverse transcriptase.¹⁰⁰ As its name suggests, it allows for transcription

⁹⁴*Id.* at 298.

⁹⁵*Id.* at 298-99.

⁹⁶*Id.* at 298-99, 302; LEWIN, *supra* note 68, at 48.

⁹⁷LEWIN, *supra* note 68, at 75-76. A complete draft of the human genome was announced in June 2000. Elizabeth Pennisi, *Human Genome: Finally, the Book of Life and Instructions for Navigating It*, 288 *SCIENCE* 2304 (2000).

⁹⁸LODISH ET AL., *supra* note 56, at 219.

⁹⁹Enzymes are proteins whose function is to facilitate chemical reactions. CAMPBELL ET AL., *supra* note 61, at 801.

¹⁰⁰LODISH ET AL., *supra* note 56, at 220. Reverse transcriptase was first isolated from a group of viruses called retroviruses. They propagate by converting their RNA to DNA. The Human T-Lymphotropic Virus (HTLV-I) claimed in the Papua New Guinea patent, *supra* notes

to occur in reverse: instead of DNA specifying mRNA as in the nucleus of the cell, isolated mature mRNA is transcribed into DNA.¹⁰¹ As in the cell, this is accomplished through the complementary binding of bases: C to G, G to C, A in RNA to T in DNA, and U in RNA to A in DNA. The result is a single strand of cDNA; because mRNA contains no introns, this cDNA necessarily includes only coding regions. Further synthesis yields the DNA complement to the first cDNA strand, producing a cDNA “clone,” a double-stranded DNA with only the coding regions present.¹⁰² Importantly, because cDNA always contains the coding regions of a gene that is being expressed, it can be very useful in identifying genes and locating them on chromosomes.¹⁰³ cDNA copies of genes have been compiled into vast cDNA “libraries.”¹⁰⁴

Recently, a large number of highly controversial patent applications have claimed segments of cDNA called expressed sequence tags, or ESTs.¹⁰⁵ An EST is “a length of cDNA that is generally

1-8 and accompanying text, is a retrovirus, the first human retrovirus ever discovered and isolated. (HIV is also a retrovirus.) Robert C. Gallo & Marvin S. Reitz, *Retroviruses and Human Disease*, in *RETROVIRUS BIOLOGY AND HUMAN DISEASE 1-8* (Robert C. Gallo & Flossie Wong-Staal eds., 1990). See *infra* notes 135-36 and accompanying text.

¹⁰¹DNA is a more stable molecule than RNA and is thus easier to work with in a laboratory. Molly A. Holman & Stephen R. Munzer, *Intellectual Property Rights in Genes and Gene Fragments: A Registration Solution for Expressed Sequence Tags*, 85 Iowa L. Rev. 735, 745 (2000).

¹⁰² LEWIN, *supra* note 68, at 955; LODISH ET AL., *supra* note 56, at 219-20.

¹⁰³ LODISH ET AL., *supra* note 56, at 223-35. cDNA can also be used in a number of other applications, including insertion into bacteria or other microorganisms for protein production. JOHNSON, *supra* note 50, at 160.

¹⁰⁴LODISH ET AL., *supra* note 56, at 223.

¹⁰⁵Holman & Munzer, *supra* note 101, at 753-54.

only a partial sequence of a gene being expressed at the time a specific tissue is sampled.”¹⁰⁶ ESTs are usually derived by random sampling of cDNA libraries.¹⁰⁷ ESTs typically contain 400-500 base pairs, versus 2,000-25,000 in full length genes.¹⁰⁸ Quick and inexpensive by the standards of genetics, ESTs are useful as a preliminary step in isolating genes, identifying coding regions of genomic DNA, and analyzing patterns of gene expression in living tissue.¹⁰⁹ In each instance, these sequenced bits of cDNA are used as tags “to fish a gene out of a portion of chromosomal DNA” or from a cDNA library by matching up complementary base pairs.¹¹⁰

The patentability of ESTs remains uncertain. In the early 1990s, the National Institutes of Health filed patent applications on about 2,700 ESTs, but ultimately abandoned them.¹¹¹ Utility has been a particular problem, since ESTs are useful primarily as an intermediate research tool in the search for full-length genes.¹¹² Nonetheless, in a comprehensive recent analysis, Molly A. Holman and Stephen R. Munzer have concluded that “[i]t is difficult to identify an absolute bar to the

¹⁰⁶*Id.* at 748.

¹⁰⁷Holman and Munzer provide an excellent summary of the EST science background and a cogent analysis of the legal controversy over EST patents. *Id.* For further scientific background, see National Center for Biotechnology Information (NCBI), *A Science Primer, ESTs: Gene Discovery Made Easier*, <http://www.ncbi.nlm.nih.gov/About/primer/est.html> (visited Aug. 9, 2002). The NCBI site has an EST database as well as useful tutorials on a range of biotechnology topics. For a detailed technical treatment, see Tyra G. Wolfsberg & David Landsman, *A Comparison of Expressed Sequence Tags (ESTs) to Human Genomic Sequences*, 25 NUCLEIC ACIDS RES. 1626 (1997).

¹⁰⁸Holman & Munzer, *supra* note 101, at 749.

¹⁰⁹*Id.*

¹¹⁰NCBI, *A Science Primer*, *supra* note 110.

¹¹¹Holman & Munzer, *supra* note 101, at 750-51.

¹¹²*Id.* at 749, 758-60.

patentability of ESTs.”¹¹³ The product of nature doctrine appears not to have figured in the debate.

For purposes of our argument, it is important to recognize the similarities and differences between naturally occurring genomic DNA and its synthetic counterpart, cDNA (including ESTs, which are fragments of cDNA). The latter is, of course, synthesized outside the body. Moreover, the precise nucleotide sequence of cDNA does not exist in the body, since natural DNA includes both coding and non-coding sequences. However, the sequence of the initial single strand of cDNA does represent the complement of a naturally-occurring mRNA sequence (save for the U-T substitution), and the second, complementary cDNA strand carries the exact mRNA sequence (again with the U-T substitution). As we shall see, patent claims to genes and DNA sequences can take a variety of forms. All successful patents claim the gene or sequence in isolated (removed from its natural environment) and/or purified (non-coding regions removed) form; some are also limited to synthetic products. The claimed DNA can be defined by its nucleotide sequence or (as in the case of the breast cancer gene patent) by the function it performs.¹¹⁴ In the latter category, a patent might claim the sequence that codes for a particular protein or chain of amino acids. Patents are also now granted on isolated proteins themselves.¹¹⁵ The question to which we shall return is whether these claiming practices serve adequately to distinguish the claimed sequences from their natural counterparts.

¹¹³*Id.* at 761.

¹¹⁴*See infra* notes 346-47 and accompanying text.

¹¹⁵*E.g.*, U.S. Patent No. 6,429,291 (issued Aug. 6, 2002)(claiming “an isolated protein comprising” a specified amino acid sequence). This patent can be contrasted with U.S. Patent No. 6,437,218 (issued Aug. 20, 2002), which claims “an isolated and purified DNA fragment encoding a protein comprising” a specified amino acid sequence, but not the protein itself.

B. The Biology of Cell Line Claims

The purpose of a cell line is to extend the natural life of a living cell for research purpose—as biologists sometimes describe it, to “immortalize” the cell.¹¹⁶ To establish a cell line, cells must first be taken directly from an organism and grown in an artificial medium. This is called a primary culture.¹¹⁷ A series of sub-cultures can be taken from the primary culture and in turn grown in artificial media, producing a lineage called a cell strain.¹¹⁸ When these cell cultures can be induced to grow for substantially longer than normal, they are referred to as cell lines.¹¹⁹

The problem to be overcome is that normal cells can only be cultured for a limited period of time before they senesce and die.¹²⁰ The life span of a particular cell is dependent on its age and the species and tissue from which it originated.¹²¹ A cell has strict control mechanisms that determine the number of times it can divide in its life span.¹²² Human embryonic cells can only divide about 50 times before they cease growth.¹²³ Following its final division, a cell may function for a time but

¹¹⁶LEWIN, *supra* note 68, at 875; LODISH ET AL., *supra* note 56, at 186.

¹¹⁷LODISH ET AL., *supra* note 56, at 185.

¹¹⁸*Id.* at 186.

¹¹⁹MICHAEL BUTLER, ANIMAL CELL CULTURE AND TECHNOLOGY: THE BASICS 7-8 (1996).

¹²⁰*Id.* at 10; LODISH ET AL., *supra* note 56, at 186.

¹²¹BUTLER, *supra* note 119, at 10.

¹²²*Id.* at 10-11.

¹²³*Id.* at 10.

will eventually die.¹²⁴ Cancer cells, which grow uncontrollably, are the exception to these rules.¹²⁵

For normal cells to grow indefinitely, or at least for an extended period, they must undergo a process called transformation.¹²⁶ The process involves the disabling or alteration of one or more of the cell's growth control mechanisms.¹²⁷ Transformation can be brought about in a variety of ways, including treatment with mutagens, viruses, or oncogenes.¹²⁸ It is also possible to break down the cell division control mechanisms and promote extended growth by mixing, or coculturing, the cells of interest with cells of another type in a single medium.

When claiming a cell line in a patent, the inventor usually refers to a cell culture that has been transformed and has the capacity for long-term or indefinite growth. The cell line, with the exception of its growth potential, may or may not be substantially different from the primary culture from which it was derived.¹²⁹ As an example, claim 1 of the Papua New Guinea Human T-Lymphotropic Virus (HTLV-I) patent refers to “a human T-cell line persistently infected with a Papua New Guinea Human T-Lymphotropic Virus, designated PNG-1.”¹³⁰ T-cells are a type of

¹²⁴*Id.*; LODISH ET AL., *supra* note 56, at 186.

¹²⁵LEWIN, *supra* note 68, at 875-78.

¹²⁶BUTLER, *supra* note 119, at 13; LODISH ET AL., *supra* note 56, at 186.

¹²⁷BUTLER, *supra* note 119, at 13; LEWIN, *supra* note 68, at 875-76.

¹²⁸BUTLER, *supra* note 119, at 14; LEWIN, *supra* note 68, at 877-78.

¹²⁹BUTLER, *supra* note 119, at 13.

¹³⁰The discussion and analysis of the Papua New Guinea patent is based on the “Description” section of the patent itself, *supra* note 1, and two articles by the principal inventor: Richard Yanagihara et al. *Isolation of Htlv-i from Members of a Remote Tribe in New Guinea*, 323 NEW ENG. J. MED. 993-994 (1990); Richard Yanagihara et al., *Characterization of a Variant of Human T-lymphotropic Virus Type I Isolated from a Healthy Member of a Remote, Recently Contacted Group in Papua New Guinea*, 88 PROC. NATL. ACAD. SCI. USA 1446 (1991).

white blood cell responsible for creating immunity.¹³¹ The establishment of the PNG-1 cell line involved obtaining original cells from blood samples from 24 Hagahai men and women from Papua New Guinea. This 260-member group has a high incidence of the HTLV-I virus, which is thought to cause leukemia, but individuals do not exhibit disease symptoms. The components of the blood samples were separated. One group of white blood cells, or lymphocytes, was cocultured with umbilical cord blood lymphocytes obtained from healthy Caucasian newborns with no evidence of infection by the virus. One of these cocultures, derived from the blood of a healthy 20-year-old Hagahai man, showed signs of the virus. This coculture grew very slowly, however, and had only a few cells containing the virus. Therefore, a third type of blood cells from an unrelated human source was added. This new coculture resulted in the establishment of the PNG-1 cell line, a long-term T-cell line persistently infected with HTLV-1.

The PNG-1 cell line required the addition of two cell types before a long-term cell line became established. It was also dependent on chemical additives to sustain optimal growth. To assess changes in the transformed cell line, comparisons were made between cell-surface proteins from the PNG-1 cells and from the two cell types that were used in coculturing. There were no cell-surface protein markers in common between PNG-1 cells and the two additional cell types.¹³² This is evidence that the PNG-1 cell line retained its genetic identity. The addition of the two cell types appears only to have facilitated the long-term growth of the culture.

For purposes of our analysis, the PNG-1 example can be summarized as follows: (1) The claimed

¹³¹CAMPBELL ET AL., *supra* note 61, at 822.

¹³²See JOHNSON, *supra* note 50, at 160; LODISH ET AL., *supra* note 56, at 7, 850-62 (discussing identification or “marker” function of cell-surface proteins).

cell line existed outside of its natural environment (the body), and in fact could only exist in isolation from its natural environment. (2) In order to sustain their long-term growth, the cells of interest had to be cocultured with other kinds of cells from other organisms. (3) Nonetheless, the cells of interest—which interest was the sole reason for creating the cell line—appeared to be genetically indistinguishable from their naturally-occurring precursors.

C. The Biology of Claims to Viruses

In the same Papua New Guinea patent, claim 2 is directed to “a viral preparation comprising” the actual virus found in the PNG-1 cell line.¹³³ Viruses are parasitic chemicals that exist on the boundary between life and non-life. They typically consist of a single DNA (or, in the case of retroviruses, RNA) molecule within a protein sheath.¹³⁴ Despite containing genetic material, they cannot reproduce on their own. Instead, they must enter, or infect, the cells of another organism and take advantage of the host’s molecular machinery to reproduce, sometimes with disastrous results for the host.¹³⁵ The HTLV-1 virus is a retrovirus, meaning that it reverses the usual DNA-to-RNA flow of information. It propagates by converting its RNA to DNA, which is inserted into a host cell and then reproduced.¹³⁶ The claimed virus was observed, using electron microscopy, either directly from the PNG-1 cell line or after cells had been lysed (broken apart) to release viral particles. As the patent points out, “[a] substantially pure preparation of the PNG-1 variant [the virus] can easily be

¹³³The discussion and analysis of the Papua New Guinea patent in this section is also based on the “Description” section of the patent itself, *supra* note 1, and the two articles by the principal inventor cited in note 130 *supra*.

¹³⁴JOHNSON, *supra* note 50, at 222-24.

¹³⁵*Id.* at 171, 190.

¹³⁶*Id.* at 91; LEWIN, *supra* note 68, at 968.

isolated from the cell line or a lysate thereof by one skilled in the art without undue experimentation.”

The inventors did substantial genetic research to identify the virus isolated from the cell line. They found that it differed slightly from standard HTLV-I viruses previously isolated from patients in Japan and elsewhere, and they therefore termed it a variant. All of the genetic sequencing and experimentation with respect to the virus were simply for taxonomic identification and differentiation. The virus itself was not altered in any way. Consequently, the virus claimed in the patent is genetically indistinguishable from the naturally occurring variant. The distinction is that it is claimed in the form of a “preparation,” meaning that it has been isolated from its human host and maintained in a purified condition within the cells of the cell line culture.

III. The Legal History of the Product of Nature Doctrine

A. The Product of Nature Doctrine in the Pre-Biotechnology Era

For more than a hundred years, the Patent Office and the courts have denied patentability to claims on what have been regarded as true products of nature. The phrase has actually been used in two different but related ways. In the first sense, product of nature refers to a composition of matter that does not comprise patentable subject matter because it is indistinguishable from something that occurs in nature. To illustrate this meaning, the PTO’s *Manual of Patent Examining Procedures* gives the example of “[a] shrimp with the head and digestive tract removed.”¹³⁷ In its other sense, the phrase refers to claims that fail the novelty and/or non-obviousness tests because they are drawn

¹³⁷U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURES § 706.03(a) (8th ed. Aug. 2001).

to known natural products that have been derived from a new source or process,¹³⁸ or are in only a marginally purer form than is found in nature.¹³⁹ We shall focus primarily on the first sense–subject matter–but, as we shall see, the two meanings have sometimes become intertwined.¹⁴⁰

The product of nature doctrine appears as early as 1889, when, in *Ex parte Latimer*, the Commissioner of Patents rejected a claim on “a new article of manufacture . . . consisting of the cellular tissues of the *Pinus australis* [southern pine] eliminated in full lengths from the silicious, resinous, and pulpy parts of the pine needles and subdivided into long, pliant filaments adapted to be spun and woven.”¹⁴¹ In the initial rejection of the claim, the examiner emphasized the identity of

¹³⁸1 CHISUM , *supra* note 11, at 1-39--40, 1-72–73.

¹³⁹*Id.* at 1-39–40, 1-74–77.

¹⁴⁰*See infra* notes 190-200 and accompanying text.

¹⁴¹*Ex parte Latimer*, 1889 Comm’r Dec. 123 (1889). A claim for the process of producing the claimed fiber had been allowed and was not at issue in the appeal to the Commissioner. *Id.* at 125. The patent examiner treated the subject matter question raised by Latimer’s product claim as one of first impression. *Id.* at 124. The examiner cited as collaterally relevant the Supreme Court’s earlier decision in *American Wood Paper Co. v. Fibre Distintegrating Co.*, 90 U.S. 566 (1874). 1889 Comm’r Dec. at 124. Although the *American Wood Paper* case is sometimes treated as part of the lineage of the product of nature doctrine, the examiner was correct: it was in fact a novelty case, in which the Supreme Court held that cellulose derived from wood pulp by a new process was not novel because it was indistinguishable from cellulose previously obtained from other sources via existing processes. 90 U.S. at 593-94.

A second early Supreme Court case had come closer to stating the product of nature doctrine, though it did not use the phrase. In *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884), the Court stated that “artificial alizarine” (a dye) derived from a new process was unpatentable because the claimed product was chemically indistinguishable from that obtained naturally from madder root. *Id.* at 311. However, the holding of the case was that the defendants could not be held liable for infringement because there was no way to construe the plaintiffs’ claim so as to cover the defendants’ product. *Id.* at 313. *See generally* M. Jacob, *Patentability of Natural Products*, 52 J. PAT. OFF. SOC’Y 473, 474-75 (1970)(reviewing old cases). Perhaps tellingly, Jacob, a patent lawyer, acknowledged that his purpose was to criticize the rejection of natural products on subject matter grounds. *Id.* at 474.

the claimed substance and its natural counterpart: “The claim and description do not set forth any physical characteristics by which the fiber can be distinguished from other vegetable fibers. . . . Hence, since the fiber claimed is not, and cannot be, distinguished from other fibers by any physical characteristic, the claim therefor must be refused.”¹⁴²

In affirming the rejection, the Commissioner elaborated on the theme of indistinguishability: “What is this product which applicant claims? It is not asserted or pretended in the present application that the product, which is the result of applicant’s process, is in any manner affected or produced by the process, or that its natural condition as a fiber has in any wise been affected, changed, or altered.”¹⁴³ In addition to—or perhaps because of—being a naturally occurring product, the fiber was not novel, but was instead “a well known material, the knowledge of which is almost co-extensive with the human family.”¹⁴⁴ The allowance of such a patent, he wrote, would make it “possible for an element or principle to be secured by patent,” with the ultimate consequence that, “successively, patents might be obtained upon the trees of the forest and the plants of the earth.”¹⁴⁵ Continuing to press the point, the Commissioner contrasted Latimer’s disallowed claim with one drawn to a constituent or portion of the plant that had been “treated so as to form a new material.” While that surely would have comprised patentable subject matter, Latimer’s “invention” was more nearly analogous to a middle ear bone removed “in its natural condition,” or “wheat which has been

¹⁴²1889 Comm’r Dec. at 124.

¹⁴³*Id.* at 125.

¹⁴⁴*Id.*

¹⁴⁵*Id.* at 125-26.

cut by a reaper or by some new method of reaping,” each of which is a mere “natural product.”¹⁴⁶

Finally, adumbrating the economic arguments of many contemporary defenders of biotechnology patents,¹⁴⁷ the Commissioner commented on the pressures he felt to allow the patent:

I have given this application no little consideration, and have experienced an anxiety, if possible, to secure the applicant a patent. The alleged invention is unquestionably very valuable, and one, according to the statements presented to me, of immense value to the people of the country. . . . [B]ut while the production may be thus regarded as a very valuable one, the invention resides, I am compelled to say, exclusively in the process and not at all in the product. . . .
. . . I am aware not aware of any instance in which it has been held that a natural product is the subject of a patent, although it may have existed from creation without being discovered.¹⁴⁸

Thus, in 1889, we find the product of nature doctrine laid out in all of its essential elements:

1. A product whose physical characteristics are indistinguishable from those of its naturally-occurring counterpart does not constitute patentable subject matter.
2. Alternatively, it may be said that such a product is unpatentable because it lacks novelty.
3. Neither the novelty of a process used to produce a product of nature, nor the unprecedented status of its discovery, can cure the inherent unpatentability of the product.
4. The utility and consequent value of the product are irrelevant to its status as patentable subject matter.

¹⁴⁶*Id.* at 126-27.

¹⁴⁷Gallini, *supra* note 28, at 131-32; *Symposium, supra* note 27, at 192-93 (remarks of Rebecca S. Eisenberg).

¹⁴⁸1889 Comm’r Dec. at 127.

The earlier post-*Latimer* cases stick closely to these basic propositions.¹⁴⁹ To take a striking example, the Third Circuit’s 1928 decision in *General Electric Co. v. De Forest Radio Co.*¹⁵⁰ is a direct application of the reasoning of *Latimer*, even though it does not cite it.¹⁵¹ The case involved the development of tungsten wire, a major advance in the history of the electric light bulb.¹⁵² GE, as assignee of an inventor named Coolidge, sued De Forest and others for infringement of a patent claiming “[s]ubstantially pure tungsten having ductility and high tensile strength,”¹⁵³ tungsten wire, and the processes for making the claimed products.¹⁵⁴ The district court had found all of the relevant claims invalid and dismissed the complaint.¹⁵⁵

With respect to pure tungsten itself, the court of appeals stated the critical question pertaining to “the subject matter of the patent” as follows: “Whether the tungsten of which the patent speaks is the tungsten of nature with its inherent quality of ductility or is a new metal produced by Coolidge

¹⁴⁹ The above-quoted reference in the *Manual of Patent Examining Procedures* to the unpatentability of a decapitated and gutted shrimp, for example, is taken from a 1941 administrative decision, *Ex parte Grayson*, 51 U.S.P.Q. 413 (1941). See *supra* note 137 and accompanying text.

¹⁵⁰28 F.2d 641 (3d Cir. 1928).

¹⁵¹Remarkably, according to LEXIS, *Latimer* has actually been cited only twice in the patent case law: in *Chakrabarty* and its predecessor/companion case, *In re Bergy*, 563 F. 2d 1031 (C.C.P.A. 1977). For the complex procedural history of these cases, see *infra* notes 230-53 and accompanying text.

¹⁵²*Id.* at 649-50 (Buffington, J., concurring and dissenting).

¹⁵³*Id.* at 642.

¹⁵⁴*Id.* at 643-45. There were also claims on “wrought tungsten” with particular properties, but GE presented no evidence of their infringement, so the court did not decide their validity. *Id.* at 644.

¹⁵⁵*General Electric Co. v. De Forest Radio Co.*, 17 F.2d 90 (D. Del. 1927); see 28 F. 2d at 641, 648.

which is wholly different from anything that nature provides.” If the former, it would be unpatentable as a product of nature “even if Coolidge was the first to uncover it and bring it into view,” and regardless of the contribution made by the purification process.¹⁵⁶

This is precisely what the Third Circuit concluded:

Coolidge took tungsten as it “existed” (WO₃) or as it is found in the earth, its native abode, and by his process converted it into pure tungsten or tungsten that is substantially pure, and, doubtless, was first to discover that when pure it has characteristics, notably those of ductility and high tensile strength, which are wholly different from the characteristics of the impure oxid [*sic*] of tungsten, notable among which is extreme brittleness. What he produced by his process was natural tungsten in substantially pure form. What he discovered were natural qualities of tungsten. Manifestly he did not create pure tungsten, nor did he create its characteristics. These were created by nature¹⁵⁷

The court apparently found that the product claims on tungsten wire were directed to patentable subject matter, but rejected them as obvious.¹⁵⁸ The process claims were upheld and the case was remanded for trial on the issue of infringement.¹⁵⁹

The court’s statement of the product of nature doctrine follows directly from the principles set out in *Latimer*, but its application of the doctrine seems considerably more aggressive. Consistent with *Latimer*, where the claim is on the product itself, the dispositive question is whether it differs materially from what is found in nature. The novelty of the discovery is irrelevant to the product’s

¹⁵⁶28 F.2d at 642.

¹⁵⁷*Id.* at 642-43.

¹⁵⁸*Id.* at 643-44. The court did not state explicitly that the wire was patentable subject matter, but its ensuing discussion of utility and obviousness would have been moot if it were not.

¹⁵⁹*Id.* at 644-48.

subject matter status, as is the inventive nature of the process used in the discovery. As long as its properties are discovered rather than created by the applicant, he is not a statutory inventor.

The most controversial aspect of the *General Electric* decision arises from the fact that the pure tungsten claimed by Coolidge had not been found in nature. The district court observed that “[i]n nature tungsten is found only in combination with other elements”;¹⁶⁰ the court of appeals described tungsten as “usually” existing in nature in oxide form, but cited no evidence that it ever occurred in a pure state.¹⁶¹ Significantly, both courts also noted that naturally occurring tungsten is brittle, with the useful property of ductility only found in the purified form produced by Coolidge’s process.¹⁶² Thus, it could be plausibly argued that Coolidge’s purified tungsten did differ substantially from what was found in nature. But both courts were unreceptive. Their view was that since tungsten is an element, all of its properties are natural by definition.¹⁶³ So the subject matter test that emerged from the case seemed to be a theoretical rather than empirical one: not whether the product is actually known to occur in nature in its claimed form, but whether it can occur in nature.

Three years later, the Court of Customs and Patent Appeals followed and cited *General Electric* in a pair of companion cases captioned *In re Marden*.¹⁶⁴ The inventor appealed from the rejection

¹⁶⁰17 F.2d at 92.

¹⁶¹28 F.2d at 642.

¹⁶²*Id.*; 17 F. 2d at 92, 96.

¹⁶³*See* 28 F. 2d at 643 (“What he discovered were natural qualities of pure tungsten. Manifestly he did not create pure tungsten, nor did he create its characteristics.”); 17 F. 2d at 96 (ductility is “a discovered, inherent property”).

¹⁶⁴47 F.2d 957 and 958 (C.C.P.A. 1931).

of two patent applications. One claimed “ductile uranium” and several uranium wire products;¹⁶⁵ the other involved nearly identical claims relating to vanadium.¹⁶⁶ The court rejected all of them on the same reasoning employed in *General Electric*. With respect to uranium, the court found that it “is a product of nature, and the appellant is not entitled to a patent on the same, or upon any of the inherent natural qualities of that metal.”¹⁶⁷ The case was in fact easier than *General Electric*: there, the court allowed that the applicant might have been the first to discover the ductility of pure tungsten, whereas here, the ductility of uranium had long been known. Thus, the *Marden* court was able to follow up on its product of nature rationale with language about lack of novelty.¹⁶⁸

The vanadium product claims were similarly disposed of. “[P]ure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same.”¹⁶⁹ So also for the properties Marden claimed to have discovered: “The quality of purity of vanadium or its ductility is a quality of a natural product and as such is not patentable.”¹⁷⁰ As in the case of the uranium claims, the court treated this as empirically known rather than axiomatic, Marden’s counsel

¹⁶⁵*Id.* at 957.

¹⁶⁶*Id.* at 958.

¹⁶⁷*Id.* at 957.

¹⁶⁸*Id.* (“There is, therefore, nothing new and no invention in the product of ductile uranium.”). This mixing of subject matter (current section 101) and novelty (current section 102) language is an instance of the two-faced quality of the product of nature doctrine. Courts may say simultaneously (and consistently) that an article is absolutely unpatentable as a product of nature, and that the same article lacks novelty because all products of nature are known or presumed to be. *See supra* notes 137-40 and accompanying text.

¹⁶⁹*Id.* at 959. As is evident, the rejection of the vanadium claims also involved a mixture of subject matter and novelty language.

¹⁷⁰*Id.*

having admitted in his brief that “all metals are ductile to a greater or lesser degree.”¹⁷¹

Some of the later cases, especially those involving chemical patents, reflect a blurring of the *Latimer* definitional boundaries and, consequently, an effective relaxation of the product of nature barrier. In its 1948 decision in *In re Williams*,¹⁷² the CCPA reversed the Patent Office’s rejection of an application for a patent on a chemical compound called a lactone. Lactones come in three forms: “laevo rotary,” “dextro rotary,” and “racemic.” The laevo rotary form has the property of deflecting polarized light to the left, the dextro deflects it to the right, while the mixed, or racemic, form produces no deflection at all.¹⁷³ Williams claimed only the laevo rotary form, “substantially free from the dextro rotary form.”¹⁷⁴ The examiner’s rejection was based on lack of novelty and lack of invention (what now would be called obviousness).¹⁷⁵ The racemic form of the lactone had been disclosed in earlier publications. Since the racemic mixture necessarily contained both the laevo and dextro forms, the examiner reasoned, the laevo form could not have been novel.¹⁷⁶

The Fourth Circuit reversed the novelty rejection on the grounds that “[t]he existence of a compound as an ingredient of another substance does not negative novelty in a claim to the pure

¹⁷¹*Id.*

¹⁷²80 U.S.P.Q. 150 (C.C.P.A. 1948).

¹⁷³*Id.* See Karl Bozicevic, *Distinguishing “Products of Nature” from Products Derived from Nature*, 69 J. PAT. & TRADEMARK OFF. SOC’Y 415, 419-20 (1987).

¹⁷⁴80 U.S.P.Q. at 151.

¹⁷⁵See *infra* notes 217-19 and accompanying text (discussing substitution of obviousness for lack of invention in 1952 Patent Act).

¹⁷⁶80 U.S.P.Q. at 151.

compound.”¹⁷⁷ The court drew on a proposition asserted in the 1910 “aspirin case”¹⁷⁸: “that a pure compound may, under certain conditions, be patentable over the same compound in an impure form.”¹⁷⁹ If purification of a substance previously known only in an impure form could be a basis for novelty, it reasoned, then so could separation of an ingredient from an existing compound, since the two processes are logically indistinguishable.

On its face, *Williams* is a novelty decision that has nothing to do with the subject matter status of products of nature. But, as we shall see, the idea that purification alone can distinguish a claimed product from a natural occurring counterpart eventually took hold in the subject matter case law as well.¹⁸⁰ One patent lawyer, laying out “guideposts” for colleagues seeking to avoid the product of nature barrier, has cited *Williams* for the general proposition “that it is, under certain circumstances, possible to obtain patent protection on a chemical compound that exists in nature.”¹⁸¹ While there is no evidence in its text that *Williams* intended to articulate so broad a rule, this is certainly a fair characterization of its effect.

Aspects of the same theme resurfaced ten years later in *Merck & Co. v. Olin Mathieson Chemical Corp.*¹⁸² The case involved a suit for infringement of Merck’s patent on “[a] vitamin B₁₂-active

¹⁷⁷*Id.*

¹⁷⁸*Farbenfabriken of Elberfeld Co. v. Kuehmsted*, 171 F. 887 (7th Cir. 1910).

¹⁷⁹80 U.S.P.Q. at 151.

¹⁸⁰*See* Bozicevic, *supra* note 173, at 419-420; *infra* notes 202-03 and accompanying text.

¹⁸¹*Id.* at 420.

¹⁸²116 U.S.P.Q. 484 (4th Cir. 1958).

composition” derived from the fermentation¹⁸³ of any of several strains of fungi.¹⁸⁴ The defendants argued that the patent was invalid and thus unenforceable. The district court had agreed, finding the patent invalid under the product of nature doctrine, principally because of evidence that the identical B₁₂ compound existed naturally in cattle livers.¹⁸⁵

The history of the Merck discovery is complex, but its details are all relevant to our story.¹⁸⁶ As early as 1926, medical researchers discovered that “pernicious anemia” patients benefitted from having cattle liver added to their diets. Over the next twenty years, several research groups searched for what they called “the anti-pernicious anemia principle.” Some theorized that it was a hormone, whereas others believed that it was a combination of several ingredients. No one, however, succeeded in isolating or identifying the substance that produced the anti-anemia effect. Then, in 1947, Merck researchers isolated an identical pure crystalline substance from both the fermentation products of several species of microorganisms and the livers of cattle. Clinical tests proved that this substance was the anti-pernicious anemia principle. After further analysis, the Merck researchers decided to classify it as a vitamin. It was put in the B group because it was water-soluble, and it was the twelfth member to be added to the group. Significantly, the patent claims were directed not to the pure crystalline substance that had originally been isolated, but only to compositions having a

¹⁸³Fermentation is an anaerobic organism’s analog to respiration.

¹⁸⁴*Id.* At 485. There were actually three product claims that differed only with respect to the concentration of active ingredients.

¹⁸⁵152 F. Supp.690 (W.D. Va. 1957).

¹⁸⁶116 U.S.P.Q. at 485-88.

level of vitamin activity actually lower than that of the pure substance.¹⁸⁷

Olin Mathieson's defense followed the syllogistic lines laid out in such cases as *General Electric* and *Marden*. Merck's own research had proved that its fermentation derivative was identical to the anti-pernicious anemia principle found in cattle liver. Since the cattle liver ingredient was pre-existing and naturally occurring, the Merck product must be characterized as an unpatentable product of nature. The Fourth Circuit, however, found the facts to be "far from the premise of the [product of nature] principle."¹⁸⁸

First, the court reviewed the legal substance of the product of nature doctrine. While it acknowledged the continuing vitality of the doctrine, it did so in a backhanded way. Taking a reductionist approach, the court observed that "[a]ll of the tangible things with which man deals and for which patent protection is granted are products of nature in the sense that nature provides the basic source materials."¹⁸⁹ Consequently, rather than being a freestanding bar to patentability, the doctrine is better thought of as a label, a way in which "unpatentable products have frequently been characterized."¹⁹⁰ In this case, it stated, the product of nature defense was actually "a contention that the patented compositions are not 'new and useful . . . compositions of matter' within the meaning of § 101."¹⁹¹ In fact, it went on, the defense is really an amalgam of two separate arguments about novelty:

¹⁸⁷*Id.* at 487.

¹⁸⁸*Id.* at 489.

¹⁸⁹*Id.* at 488.

¹⁹⁰*Id.*

¹⁹¹*Id.* at 488-89.

(1) that a patent may not be granted upon an old product though it be derived from a new source by a new and patentable process, and (2) that every step in the purification of a product is not a patentable advance, except, perhaps, as to the process, if the new product differs from the old “merely in degree and not in kind.”¹⁹²

The Fourth Circuit found both branches of the product of nature rule to be inapplicable to Merck’s fermentation-derived B-12 compound. With respect to the first, the court emphasized that “[u]ntil the patentees produced them there were no such B₁₂ active compositions. No one had produced even a comparable product. The active substance was unidentified and unknown.”¹⁹³ With respect to the second branch, the court found that the Merck compound was far more than an advance in purification “merely in degree.” On the contrary, the advance here was a quantum leap from the “complete uselessness” of the naturally occurring compound to the “great and perfected utility” of the patented version.¹⁹⁴

From one perspective, *Merck* is simply a straightforward application of the product of nature doctrine as set out in such cases as *Latimer*, *General Electric*, and *Marden*. It reached a different result on materially different facts. Critically, the Merck patent limited its claims to a substance that not only was derived from a different source than its pure, naturally occurring counterpart, but had different properties—lower levels of activity. A comparison to *General Electric* (the tungsten case) makes the point: whereas GE’s Coolidge had claimed the pure, naturally occurring tungsten he had

¹⁹²*Id.* at 489.

¹⁹³*Id.* Interestingly, in this portion of its analysis the court cited two nineteenth-century Supreme Court cases—*American Wood Products* and *Cochrane*—that were not really product of nature cases. The former involved the novelty of a substance previously derived from other commercial processes, whereas in the latter the treatment of the doctrine was effectively dictum. *See supra* note 141.

¹⁹⁴*Id.* at 490.

discovered, with all of its “natural qualities,” Merck had identified and isolated naturally occurring vitamin B-12, but then claimed a substance with different qualities.

But from another perspective *Merck* represents a subtle yet significant departure from the prior law. In the earlier cases, the crucial issue—indeed, the only issue--was whether the claimed substance was in fact distinguishable from the natural counterpart. If not, then it was unpatentable, regardless of how unanticipated or useful its discovery might be. Novelty was relevant almost as an afterthought: the inherent unpatentability of a product of nature could be restated in terms of the impossibility of anything found in nature being new. Importantly, some of those cases also clearly implied that something was natural if it had the potential to occur in nature, regardless of whether it had actually been observed to do so.

Here, by contrast, in the statement of the doctrine, if not its application, the emphasis seems to be on the novelty of the discovery rather than the product itself. Recall the court’s rhetoric about “[n]o one [having] produced even a comparable product,” and the active substance being “unidentified and unknown.”¹⁹⁵ Under the traditional formulation of the doctrine, why should this have mattered? The claimed substance either was or was not distinguishable from the natural counterpart, regardless of the circumstances of its discovery. But in these comments and in its introductory remarks about “product of nature” being merely a label put on something that is otherwise unpatentable, the Fourth Circuit can be plausibly read as implying that the novelty of a product’s discovery can somehow overcome the lack of novelty inherent in a natural product itself.

Also enigmatic is the court’s repeated emphasis on the utility of the Merck compound. If enhanced utility is merely a factual difference between the claimed and natural products (recall

¹⁹⁵116 U.S.P.Q. at 489.

“complete uselessness” versus “great and perfected utility”¹⁹⁶), then the reference is consistent with the earlier cases. Once again, however, when these remarks are taken in the context of the court’s introductory comments, one wonders whether it is being suggested that great utility, standing alone, can trump product of nature status.

From a broader perspective, the *Merck* court’s remarks can be viewed as a commentary on the concept of patentable subject matter. The conventional view, embodied in the older formulations of the product of nature doctrine, is that patentable subject matter status is an independent and initial hurdle that must be cleared before novelty, utility, and non-obviousness can even be considered.¹⁹⁷ In this view, the subject matter requirement derives from section 101’s authorization of a patent to the inventor or discoverer of “any new and useful process, machine, manufacture, or composition of matter.”¹⁹⁸ Things like plant fiber and tungsten are simply not characterizable as “new . . . compositions of matter” because they exist in nature. “New” as it appears in section 101 is not a term of art, but is to be taken in its ordinary sense.

Merck and some of the other purity cases, however, seem to treat the patentable subject matter standard as nothing more than a summary of the novelty, utility, and non-obviousness requirements.¹⁹⁹ By treating the product of nature doctrine as merely a subset of the novelty test (and

¹⁹⁶*Id.* at 490.

¹⁹⁷This view is also embodied in the leading contemporary patent treatise, the title of whose very first chapter is “Eligible Subject Matter.” 1 CHISUM, supra note 11, ch.1. For a discussion of how the Supreme Court views this question, see *infra* notes 253-58 and accompanying text.

¹⁹⁸35 U.S.C. § 101. This language dates back to the nineteenth century.

¹⁹⁹This outlook becomes quite explicit in some of the post-*Merck* purity cases. In *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970), for example, the Court of Customs and Patent

by finding utility somehow relevant to whether something is a product of nature), those cases effectively hold that if a claimed invention is novel (in section 102 terms), useful, and non-obvious, then it automatically comprises patentable subject matter. We shall argue below that current biotechnology patent practice has put aside the traditional understanding of patentable subject matter and has instead resurrected the logic of the purification cases.²⁰⁰ First, however, it is necessary to return to 1948 and review the Supreme Court's pivotal decision in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*²⁰¹

B. *Funk*

The *Funk* case involved a patent issued to an inventor named Bond, who had remedied a longstanding inefficiency in agriculture.²⁰² Leguminous plants such as beans, peas, and alfalfa are

Appeals held that

the criteria for determining whether given subject matter is “new” within the meaning of § 101 are no different than the criteria for determining whether that subject matter possesses the “novelty” expressed in the title of § 102. The word “new” in § 101 is defined and is to be construed in accordance with the provisions of § 102. Thus, that which possesses statutory novelty under the provisions of § 102 is also new within the intendment of § 101.

Id. At 1402. *See also* Application of Cofer, 354 F. 2d 664, 666-67 (C.C.P.A. 1966)(merging utility and non-obviousness in deciding that crystalline form of chemical is patentable over previously known liquid form).

The CHISUM treatise characterizes CCPA cases like these as taking “a fundamentally different approach” from *Merck*. 1 CHISUM, *supra* note 11, at 1-74. We disagree. We see these cases as acknowledging explicitly what was implicit but nonetheless clear in the *Merck* analysis.

²⁰⁰*See infra* part IV.A and accompanying text.

²⁰¹333 U.S. 127 (1948).

²⁰²*Id.* at 128-30.

able to produce natural fertilizers by “fixing” nitrogen from the air. The plants’ ability to fix nitrogen depends on the presence in their roots of bacteria from several species of the genus *Rhizobium*. The bacteria infect the roots and form nodules on them. Farmers have long purchased laboratory-cultured root-nodule bacteria to “inoculate” their legume crops and enhance their nitrogen-fixing capacity. No single species of *Rhizobium* will infect the roots of all types of legumes; rather, each species will infect only a particular legume group. Moreover, prior to the Bond patent, the different bacterial species exhibited a mutually inhibiting effect when applied to legume roots in combination. Therefore, suppliers of laboratory-produced root-nodule bacteria sold “inoculants” which contained only a single species. Farmers who grew several types of legumes were forced to buy a separate inoculant for each crop.

Bond’s contribution was to discover, “by certain methods of selection and testing,”²⁰³ that particular strains of each of the root-nodule species did not exert the mutually inhibitive effect. “Thus he provided a mixed culture of Rhizobia capable of inoculating the seeds of plants belonging to several cross-inoculation groups.”²⁰⁴ He obtained product patents on the multi-species inoculants.²⁰⁵ In a patent infringement action brought by Bond’s assignee, the district court held the patent invalid “for want of invention.”²⁰⁶ The Seventh Circuit reversed, holding that whereas the district court “thought that [Bond] had merely discovered a law of nature,” his contribution had in

²⁰³*Id.* at 130.

²⁰⁴*Id.*

²⁰⁵He also obtained process patents on the methods of selection and testing. These claims were not at issue in the case. *Id.*

²⁰⁶*Id.* at 127.

fact been the “application of scientific knowledge to things existing in nature and the utilization of them in a desirable composite product which had not been previously achieved.”²⁰⁷ The court of appeals’ analysis paralleled that in such cases as *Williams* and *Merck*, using the novelty of the discovery and the utility of the product to beat back the product of nature argument.²⁰⁸

The Supreme Court reversed, invalidating Bond’s product claims for failure to “disclose an invention or discovery within the meaning of the patent statutes.”²⁰⁹ In four and one-half succinct pages, the Court laid out the product of nature doctrine in language reminiscent of *Latimer*.²¹⁰ It is worth quoting at length:

Bond does not create a state of inhibition or of non-inhibition in the bacteria. Their qualities are the work of nature. Those qualities are of course not patentable. For patents cannot issue for the discovery of the phenomena of nature. . . . The qualities of these bacteria, like the heat of the sun, electricity, and or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none. He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.²¹¹

At first glance, the opinion seems to reflect a robust, affirmative conception of the public domain, even though that phrase is not used. It is the realm of “phenomena” that, because they are

²⁰⁷*Kalo Inoculant Co. v. Funk. Bros. Seed Co.*, 161 F. 2d 981, 986 (7th Cir. 1947).

²⁰⁸*Id.* at 982-86. *See supra* notes 172-200 and accompanying text.

²⁰⁹333 U.S. at 132.

²¹⁰*See supra* notes 141-48 and accompanying text.

²¹¹333 U.S. at 130.

“manifestations of laws of nature,” indeed, “the work of nature,” are “free to all men and reserved exclusively to none.”²¹² Moreover, it appears that when the claimed subject matter lies within this natural realm, no amount of novelty or utility in its discovery can render it patentable. As the Court observed, the “[d]iscovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect” was “no more than the discovery of some of the handiwork of nature and hence is not patentable.”²¹³ This was so “however ingenious the discovery of that natural principle may have been,” and regardless of the fact that it “contributed utility and economy to the manufacture and distribution of commercial inoculants.”²¹⁴ The impression clearly conveyed is that products of nature are unpatentable because they can never comprise statutory subject matter, regardless of any other attributes a claimed invention may possess.

This straightforward reading is undercut, however, by other language toward the end of the majority opinion. Two statements are of particular significance: that the “aggregation of species fell short of invention within the meaning of the patent statute”;²¹⁵ and that “a product must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery.”²¹⁶ In support of the latter remark, the Court cited the then-applicable patentability

²¹²*Id.*

²¹³*Id.* at 131.

²¹⁴*Id.*

²¹⁵*Id.*

²¹⁶*Id.* at 131-32.

statute, 35 U.S.C. 31.²¹⁷ That section combined most of the requirements of present sections 101 (subject matter), 102 (novelty), and 103 (non-obviousness). However, it used the word “invention” to do the work of the current “non-obvious.”²¹⁸ Thus, the case can be plausibly read as turning not so much on the involvement of a product of nature as on the inventor’s failure to apply the “work of nature” in a non-obvious way.²¹⁹

In fact, both readings seem correct, and the two can coexist. The Court did reaffirm the unpatentability of products of nature in clear and unambiguous terms. What Bond discovered through his experiments—that particular strains of bacteria, when combined, did not have the usual mutually inhibiting effect—was nothing more than the work of nature. The subject matter of his discovery was therefore inherently unpatentable. What Bond claimed, however, was, nominally at least, not the discovery but its application: “[a]n inoculant comprising” the non-mutually-inhibiting strains he had discovered.²²⁰ In theory, the Court acknowledged, the application of the work of nature can be patentable. Here, however, the application was but “a simple step” which added nothing of an inventive nature to the underlying discovery.²²¹

²¹⁷At the time of the *Funk* decision, the United States Code had most recently been recodified in 1946. The 1952 Patent Act, most of which remains in effect, made major changes in both form and substance, including breaking down former section 31 into three separate sections and substituting non-obviousness for invention.

²¹⁸*See* 1 CHISUM, *supra* note 11, at 1-43.

²¹⁹*See id.*

²²⁰333 U.S. at 128 n. 1 (quoting from Bond’s patent claims).

²²¹*Id.* at 132. Our colleague Andrew Chin has also argued to us that *Funk* can be read as a utility case, citing the statement that “[t]he combination of species produces . . . no enlargement of the range of their utility.” *Id.* at 131. (Professor Andrew Chin, University of North Carolina School of Law, pers. comm.) However, the ellipsis is material: the omitted portion of the quoted

Accordingly, the minimalist way to phrase the holding is that Bond failed because he did not take an inventive (or non-obvious) step beyond the prior art. It is highly relevant, however, that the prior art was not the usual mix of patents and publications,²²² but rather the work of nature. An equally correct, but, we believe, fairer characterization of the holding is that Bond failed because his real and only discovery was the product of nature, which he applied in the most obvious way possible: exactly as he found it. In other words, his patent was denied because his purported “application” was not materially distinguishable from the work of nature. By clear implication, Bond might have achieved invention only by claiming something quite different from the work of nature itself. From this perspective, *Funk* is a lineal descendant of *Latimer*, with the invention/non-obviousness analysis adding little or nothing to the traditional product of nature doctrine. As we shall suggest in the next section, the Court itself seemed to take this view when it next visited the issue.

C. *Chakrabarty*

*Diamond v. Chakrabarty*²²³ represents the Supreme Court’s only foray into biotechnology, and it remains the most significant case in the field. In a 5-4 decision, the Court held that “a live, human-

sentence reads “no new bacteria, no change in the six species of bacteria, and” We interpret these three observations—about the lack of new bacteria, new species, or new utility—as simply another way of saying that the combination is unpatentable because it is a product of nature. A new and distinct utility would be significant as *evidence* that the invention was substantially different from the predecessor natural product. Therefore, we reject the proposition that *Funk* is really a utility case. *Cf.* note 256 *infra* (addressing same point in *Chakrabarty*).

²²²*See supra* notes 12-13 and accompanying text.

²²³447 U.S. 303 (1980).

made micro-organism is patentable subject matter under 35 U.S.C. § 101.”²²⁴ Chakrabarty claimed a bacterium of the genus *Pseudomonas* that had been genetically engineered to give it enhanced “hydrocarbon degradative” (oil-eating) properties. He had previously discovered that the hydrocarbon-degrading capabilities of bacteria depended on the presence within the bacterial cell of certain plasmids. Plasmids, according to the Court, “are hereditary units physically separate from the chromosomes of the cell”²²⁵—free-floating rings of DNA. Each single plasmid “provid[es] a separate hydrocarbon degenerative pathway”;²²⁶ that is, it enables the bacteria in which it resides to break down one of the many hydrocarbon compounds that comprise crude oil. Because naturally occurring individual bacteria contain only single plasmids, prior to Chakrabarty’s work, biological control of oil spills required “the use of a mixture of naturally occurring bacteria, each capable of degrading one component of the oil complex.”²²⁷ This practice was inefficient because only some of the bacteria in the mixture survived long enough to do their work; multiple applications of the mixture were therefore required. Consequently, “the bulk of the oil often remain[ed] unattacked for a long period of time (weeks) and [was] free to spread or sink.”²²⁸

Chakrabarty’s contribution was to create a new strain of *Pseudomonas* that contained “at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon

²²⁴*Id.* at 305.

²²⁵*Id.* at 305 n. 1. Bacterial cells do not have nuclei. *See supra* note 51 and accompanying text.

²²⁶*Id.* at 305.

²²⁷*Id.* at 305 n. 2.

²²⁸*In re Bergy*, 596 F. 2d 952, 969 (C.C.P.A. 1979)(lower court decision in *Chakrabarty*). *See infra* note 230.

degradative pathway.”²²⁹ He accomplished this by recombinant DNA methods: transferring multiple plasmids (which consist of DNA) into a *Pseudomonas* cell and then replicating it. Since naturally-occurring *Pseudomonas* cells contain only a single plasmid, Chakrabarty’s new strain was something that did not and, as far as was known, could not occur in nature.

Chakrabarty’s convoluted history in the patent office and the Court of Customs and Patent Appeals is itself a significant part of the product of nature story. Chakrabarty’s case was for a time paired with an application filed by an inventor named Bergy on June 10, 1974.²³⁰ Bergy claimed “a biologically pure version of the microorganism *Streptomyces vellosus*.”²³¹ The examiner rejected this claim as drawn to a product of nature and thus not comprising patentable subject matter under section 101. The PTO Board of Appeals affirmed, on the broader grounds that section 101 precluded the patenting of living organisms.²³² In its first opinion in the case, the CCPA reversed the board. Since the board had based its decision on a much broader proposition than the product of nature doctrine, the court deemed “the product-of-nature issue to have been abandoned and no longer in the case.”²³³ However, because the government had raised the issue at oral argument, the court went on

²²⁹447 U.S. at 305. In fact, Chakrabarty’s application described a strain containing four stable plasmids, and he noted that he had not yet found the upper limit to how many plasmids could be maintained within a single bacterial cell. *In re Chakrabarty*, 571 F. 2d 40, 42 (C.C.P.A. 1978)(earlier lower court decision).

²³⁰*In re Bergy*, 563 F. 2d 1031, 1032 (C.C.P.A. 1977), *remanded sub nom.* Parker v. Bergy, 438 U.S. 902 (1978), *on remand*, 596 F. 2d 952 (C.C.P.A. 1979), *aff’d sub nom.* Diamond v. Chakrabarty, 447 U.S. 303 (1980).

²³¹563 F. 2d at 1032.

²³²*Id.* at 1033-34.

²³³*Id.* at 1035.

to observe that it was, in any event, “wholly lacking in merit.”²³⁴ The reason was that “[t]he biologically pure culture [that Bergy claimed] does not exist in, is not found in, and is not a product of, ‘nature’. It is man-made and can be produced only under carefully controlled laboratory conditions.”²³⁵ The court then rejected the Board’s conclusion that living things are inherently unpatentable.²³⁶

The CCPA’s comment on the product of nature doctrine was, ostensibly, a straightforward extension of *Merck* and other earlier purity cases.²³⁷ The court simply recognized that under some circumstances a purified version of a naturally-occurring substance may be sufficiently distinguishable from the natural precursor to constitute an invention. Because its remarks were so brief, it is not possible to discern the court’s view on the relationship between the product of nature doctrine and the requirements of sections 102 (novelty) and 103 (non-obviousness). That uncertainty was resolved in a later opinion.²³⁸

Meanwhile, Chakrabarty’s application was proceeding on a parallel track. The examiner rejected it on two grounds: (1) that it claimed a product of nature and (2) that it claimed an inherently unpatentable living organism.²³⁹ The PTO Board of Appeals reversed the examiner on the first point,

²³⁴*Id.*

²³⁵*Id.* The court also repudiated some confusing but often cited dicta about the product of nature doctrine from the earlier case of *In re Mancy*, 499 F. 2d 1289, 1294 (C.C.P.A. 1974). 563 F. 2d at 1035-36; *see generally* 1 CHISUM, *supra* note 11, at 1-41 (discussing *Mancy*).

²³⁶563 F. 2d at 1035-39.

²³⁷*See supra* notes 172-99 and accompanying text.

²³⁸*See infra* notes 246-51 and accompanying text.

²³⁹*In re Chakrabarty*, 571 F. 2d 40, 42 (C.C.P.A. 1978).

concluding that the claimed microorganism was not naturally occurring, but affirmed on the second.²⁴⁰ The Court of Customs and Patent Appeals then reversed the Board, relying on its recently rendered *Bergy* decision to hold that Chakrabarty's invention comprised statutory subject matter under section 101.²⁴¹

Next, in response to the government's petition for certiorari in *Bergy*, the Supreme Court vacated the judgment of the CCPA and remanded the *Bergy* case for further proceedings²⁴² in light of its decision in *Parker v. Flook*,²⁴³ a case that involved the unpatentability of mathematical formulas and other laws of nature. The CCPA then vacated its decision in *Chakrabarty* and scheduled the two cases together for reargument.²⁴⁴ In a single opinion, the CCPA reiterated its earlier judgments that both inventions comprised statutory subject matter.²⁴⁵ But it added one significant element to the earlier opinions: an unequivocal statement of its belief that whether an invention comprises statutory subject matter is a freestanding inquiry under section 101, to be decided without reference to novelty, utility, or non-obviousness.²⁴⁶

The court spoke of three "doors" that the inventor must open "on the difficult path to patentability": section 101, section 102 (novelty), and section 103 (non-obviousness, which was

²⁴⁰*Id.*

²⁴¹*Id.* at 43.

²⁴²*Parker v. Bergy*, 438 U.S. 902 (1978).

²⁴³437 U.S. 584 (1978).

²⁴⁴*In re Bergy*, 596 F. 2d 952, 956-57 (C.C.P.A. 1979).

²⁴⁵*Id.* at 987.

²⁴⁶*Id.* at 960-61.

termed “invention” in pre-1952 patent statutes).²⁴⁷ Section 101 mentions three requirements—novelty, utility, and statutory subject matter. By longstanding and universal consensus, according to the court, “these three requirements are *separate and distinct*.”²⁴⁸ The next point is that “of the three requirements *stated* in § 101, only two, utility and statutory subject matter, are *applied* under § 101”; novelty is decided under section 102.²⁴⁹ The only relevant subject matter question is “whether the invention falls into a named category.”²⁵⁰ Consequently, “[a]n invention can be statutory subject matter and be 100% old, devoid of any utility, or entirely obvious.”²⁵¹ Thus, the subject matter inquiry is whether the claimed invention is or is not a statutory machine, manufacture, or composition of matter, and the answer should not be influenced by the presence or absence of novelty or utility.

The government then appealed the now-consolidated cases to the Supreme Court. After certiorari was granted, Bergy withdrew his patent application, mooting the appeal in his case.²⁵² In reviewing *Chakrabarty*, the Supreme Court addressed a single question: “whether a live, human-made micro-organism is patentable subject matter under 35 U.S.C. § 101.”²⁵³ The first substantive issue the Court took up was whether the bacterium was, on the one hand, a patentable manufacture

²⁴⁷*Id.* at 960-61.

²⁴⁸*Id.* at 960 (emphasis in original).

²⁴⁹*Id.* at 961 (emphasis in original).

²⁵⁰*Id.* at 962.

²⁵¹*Id.* at 963.

²⁵²447 U.S. at 307.

²⁵³*Id.* at 305.

or composition of matter, or, on the other, something within the unpatentable categories of “laws of nature, physical phenomena, and abstract ideas.”²⁵⁴ Significantly, the Court cited *Funk* for the proposition that one cannot patent “manifestations of . . . nature, free to all men and reserved exclusively to none.”²⁵⁵

The Court then devoted a full page to distinguishing the earlier case. In *Funk*, the patentee had simply discovered a natural possibility: the combination of certain root-nodule bacteria that did not exert a mutually inhibiting effect on each other. Chakrabarty, by contrast, had “produced a new bacterium with markedly different characteristics from any found in nature.”²⁵⁶ He had, in other words, intervened at the genetic level to make something that nature had not and, apparently, could not. The Court’s conclusion was straightforward: “His discovery is not nature’s handiwork, but his own; accordingly it is patentable subject matter under § 101.”²⁵⁷

²⁵⁴*Id.* at 309.

²⁵⁵*Id.* (citing *Funk*, 333 U.S. at 130).

²⁵⁶*Id.* at 310. As Andrew Chin has reminded us, this sentence concludes with the clause “and one having the potential for substantial utility.” He connects this observation to his comments about the role of utility in *Funk*. See *supra* note 221. However, the just-quoted clause is the only reference to utility in *Chakrabarty*’s entire product of nature discussion. It is all but buried in the rhetoric about nature’s handiwork, hitherto unknown natural phenomenon versus nonnaturally occurring manufactures, and the like. Moreover, the Court did not repudiate the CCPA’s conclusion that statutory subject matter status is unaffected by either novelty or utility. See *supra* notes 246-51 and accompanying text. We find it difficult to ascribe any significance at all to this clause; we certainly see no basis for treating *Chakrabarty* as primarily or even importantly a utility case. On the contrary, the Court elsewhere suggests that distinct utility is intended to be taken, as in *Funk*, as *evidence* of the materiality of the differences between the claimed invention and the predecessor products of nature: “a product of human ingenuity ‘having a distinctive name, character [and] use.’” *Id.* at 309-10 (quoting *Hartranft v. Wiegmann*, 102 U.S. 609, 615 (1887)).

²⁵⁷*Id.* The Court went on to reject two other objections to patentability: that the enactment of the 1930 Plant Patent Act and the 1970 Plant Variety Protection Act evidenced a congressional

Several aspects of *Chakrabarty* are relevant to our argument. First, it is clear that the Supreme Court, like the CCPA, viewed the product of nature question purely as an issue of section 101 patentable subject matter. The entire discussion dealt with whether Chakrabarty's bacterium was the kind of thing that could be patented—that is, whether it was something he had made or a sample of “nature's handiwork” that he had discovered. The references to novelty and non-obviousness that had cropped up in some of the lower court cases²⁵⁸ are absent here. The unambiguous implication is that arguments about novelty and non-obviousness are unresponsive to an objection that something is unpatentable because it is a product of nature.

Second, it is equally clear that the *Chakrabarty* Court viewed *Funk* as good law, in fact as the definitive statement of the product of nature doctrine. Without a hint of aspersion, the Court recited *Funk*'s statement of the law, and then took great care to distinguish its facts. One cannot read *Chakrabarty* and find any evidence that the product of nature doctrine had changed since 1948.

It is irrelevant to our argument whether *Chakrabarty* and *Funk* were rightly or wrongly decided. In fact, we find the *Chakrabarty* Court's effort to distinguish *Funk* not entirely persuasive. It can be argued that in each case the inventor simply produced an aggregation that did not appear to exist naturally: in *Funk*, of bacterial species within an inoculant,²⁵⁹ and in *Chakrabarty*, of plasmids within

understanding that living things did not comprise patentable subject matter; and that living things should remain unpatentable pending an affirmative congressional authorization. *Id.* at 310-18.

²⁵⁸See *supra* note 199 and accompanying text.

²⁵⁹This is an inference drawn from the facts that (1) in nature, each species was observed to infect only particular groups of plants and (2) despite long use of the bacteria, they had always been sold and applied one species at a time because of the problem of mutual inhibition. *Funk*, 333 U.S. at 128-30. Presumably, had non-mutually-inhibiting combinations been apparent in nature, they would have been exploited commercially.

a bacterial cell. Neither aggregation was known to occur in nature. Yet, once produced, each performed its multiple tasks without further intervention. The principal distinction appears to be that the *Funk* inventor did his work by mixing cells, whereas Chakrabarty had to introduce new genetic material within a cell. Where the question is the patentability of the resulting product, it is not clear why this distinction should be dispositive. Again, however, the resolution of this question is immaterial to our point, which is simply that the product of nature doctrine emerged from *Chakrabarty* alive, well, and essentially in its original form.

D. Supreme Court Postscript: *J.E.M. Ag Supply*

On December 10, 2001, the Supreme Court decided *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.*²⁶⁰ The holding of the case, which is not directly relevant to our argument, was that the enactment of the Plant Patent Act of 1930 (“PPA”)²⁶¹ and the later Plant Variety Protection Act (“PVPA”)²⁶² should not be read as evidence of congressional intent to deny conventional utility patent protection to plants. What is relevant, however, is that the Court briefly revisited *Chakrabarty*’s product of nature discussion. In analyzing the PPA legislation, the *J.E.M.* Court cited *Chakrabarty* for the proposition that before 1930, there was a “‘belief that plants, even those artificially bred, were products of nature for purposes of the patent law.’”²⁶³ It relied further on

²⁶⁰122 S. Ct. 593 (2001).

²⁶¹The PPA, presently codified at 35 U.S.C. §§ 161-64, confers a form of patent protection (usually called a “plant patent”) on asexually reproduced plants.

²⁶²The PVPA, enacted in 1970 and codified at 7 U.S.C. § 2402(a), provides patent-like protection for certain sexually reproduced plants.

²⁶³122 S. Ct. at 600 (*quoting Chakrabarty*, 447 U.S. at 311-12).

Chakrabarty to demonstrate that this belief was mistaken: “As this Court held in *Chakrabarty*, ‘the relevant distinction’ for purposes of § 101 is not ‘between living and inanimate things, but between products of nature, whether living or not, and human-made inventions.’”²⁶⁴

The point we extract from *J.E.M.* is a limited one. *Chakrabarty*’s product of nature analysis is, from a doctrinal perspective, identical to that in *Funk*. In *J.E.M.*, the Court cited that analysis without reservation or any suggestion that it is outmoded. Significantly, it chose to reemphasize that the product of nature doctrine is a section 101 problem—that is, a question of patentable subject matter, as distinct from novelty, utility, or non-obviousness. Thus, every indication is that the Supreme Court continues to believe in the product of nature doctrine as originally conceived.

E. Summary: The Product of Nature Doctrine at the Beginning of the Biotechnology Age

What do we know about the status of the product of nature doctrine as *Chakrabarty* heralded the dawn of the biotechnology age? The following points seem well established:

1. The Supreme Court and the Court of Customs and Patent Appeals (whose precedent was adopted by its successor, the Federal Circuit, in 1982²⁶⁵) have viewed the subject matter status of an invention as a separate and distinct question to be decided without reference to novelty, utility, or non-obviousness. Properly framed, the subject matter question is whether the claimed invention is the kind of thing on which a patent can be granted: that is, whether it is an invented machine, manufacture, or composition of matter. Something which is old, useless, and/or obvious can still comprise statutory

²⁶⁴*Id.* (quoting *Chakrabarty*, 447 U.S. at 313).

²⁶⁵*South Corp. v. United States*, 690 F. 2d 1368, 1369 (Fed. Cir. 1982)..

subject matter. Conversely, something can be nonstatutory in its subject matter even though it is new, useful, and non-obvious.

2. According to these same courts, the product of nature question is properly addressed as part of the section 101 subject matter inquiry. Specifically, if something is a product of nature, it cannot properly be characterized as a manmade machine, manufacture, or composition of matter. Consequently, if something is a product of nature, it should be held to be unpatentable, without ever reaching the questions of its novelty, utility, or non-obviousness.
3. Notwithstanding points 1 and 2, a number of courts over the years have introduced considerations of novelty and utility when discussing the product of nature doctrine. Some such cases have treated “product of nature” not as a separate and distinct barrier to patentability under section 101 but simply as a label to be applied when a claimed invention is found to lack novelty. Other courts seem to have been dissuaded from labeling something an unpatentable product of nature by the striking utility of a product itself or the novelty of the circumstances of its discovery.
4. The approaches described in point 3 seem to have been definitively repudiated by the opinion of the Court of Customs and Patent Appeals in *Chakrabarty*, as reinforced by the Supreme Court’s own *Chakrabarty* opinion.
5. The line between a product of nature, which does not constitute statutory subject matter, and a manmade machine, manufacture, or composition of matter, which does, has not been well defined. In *Funk* and *Chakrabarty*, the Supreme Court identified inventions that fall on the two sides of the line. In *Funk*, the Court held that the

creation of a mixture of bacteria species that might occur in nature, but had not been observed to do so, is the mere discovery of a product of nature. In *Chakrabarty*, by contrast, the Court held that the insertion of new DNA into a bacterial species to create an organism that had not occurred and presumably could not occur in nature was the invention of a composition of matter. So, in the biological context, it is clearly insufficient to bring about, without more, an unprecedented combination of existing species. Conversely, it is clearly sufficient to alter the genetic composition of an existing species.

6. The lower courts have been even less helpful in delineating the boundary between products of nature and patentable inventions. In the first place, courts have been inconsistent in deciding whether the product of nature problem is a section 101 subject matter issue, a section 102 novelty issue, a section 103 non-obviousness issue, or some combination of the three. Nonetheless, there has been a fairly consistent requirement that, regardless of the legal framework being used, a claimed invention with a natural precursor or variant must differ in some substantial and material way from the natural version. In making this judgment, courts have focused on both the structure and the properties of the substance in question. Finally, a number of courts have focused on the purity of the claimed substance as a sufficiently material distinction. No guidelines can be drawn from these cases other than the general proposition that purification can, in principle, serve to distinguish a claimed substance from a natural counterpart.

IV. The Product of Nature Doctrine and Current Biotechnology Practice

A. The PTO's Approach

Since *Chakrabarty*, the product of nature doctrine has become a virtual nullity in both the Patent Office and the courts. With little discussion, a consensus has emerged that modern claim-drafting practices have extinguished the doctrine as a plausible objection to almost any kind of biotechnology claim. Based on the evidence of Patent Office materials, case law, and the academic literature, the entire patent law community seems satisfied with this resolution. Whether this resolution is, in all contexts, consistent with the doctrine's hundred-plus-year history is another question, and one to which we shall ultimately turn.²⁶⁶

In *Bergy* and *Chakrabarty*, the PTO made aggressive use of section 101 in an effort to deny patents on living organisms. When its position was repudiated, first by the Court of Customs and Patent Appeals and then by the Supreme Court, the Office retreated almost entirely. In *In re Allen*, the Board of Patent Appeals and Interferences reviewed an examiner's rejection under section 101 of a product-by-process claim to polyploid oysters.²⁶⁷ A polyploid cell or organism has more than the customary one pair of each chromosome.²⁶⁸ The Board of Appeals reversed the examiner's position that "living entities" are unpatentable under section 101, deeming that question irrelevant under *Chakrabarty*.²⁶⁹ It did, however, acknowledge the proposition that "if the claimed subject matter occurs naturally, it is not patentable subject matter under section 101."²⁷⁰ However, the Board found that the examiner had "presented no evidence that the claimed polyploid oysters occur naturally

²⁶⁶ See *infra* part V.B.

²⁶⁷ 1987 Pat. App. LEXIS 21 (April 3, 1987).

²⁶⁸ CAMPBELL ET AL., *supra* note 61, at 815.

²⁶⁹ 1987 Pat. App. LEXIS 21 at *5.

²⁷⁰ *Id.*

without the intervention of man, nor has the examiner urged that polyploid oysters occur naturally.”²⁷¹ On the contrary, the record led “to no conclusion other than that the claimed polyploid oysters are non-naturally occurring manufactures or compositions of matter.”²⁷² The Board ultimately affirmed the examiner’s rejection on obviousness grounds.²⁷³

Allen is thus entirely consistent with *Chakrabarty*, and indeed with *Latimer*, in its statement and application of the product of nature doctrine. Thereafter, however, the doctrine all but disappears as a serious concern. The PTO handles patents claiming DNA sequences by analogy to prebiotechnology chemical patents, and those cases are read with a liberality that belies their complexity.²⁷⁴ One sees glimpses in the case law of “purification” becoming a magic word whose mere recital meets any product of nature objection.²⁷⁵

The emergence of the consensus about the patentability of claims drawn to “isolated and purified” DNA sequences is reflected in what is perhaps the most significant Federal Circuit biotechnology case. The Federal Circuit’s 1991 decision in *Amgen, Inc. v. Chugai Pharmaceutical Co.*,²⁷⁶ which involved DNA sequence patents, dealt with many issues that can be particularly difficult in the biotechnology context, including priority of conception, obviousness, the enabling description requirement, and the doctrine of inequitable conduct before the patent office. Although

²⁷¹ *Id.*

²⁷² *Id.* at *5-6.

²⁷³ *Id.* at *7-14.

²⁷⁴ Rai, *supra* note 35, at 835-38.

²⁷⁵ See, e.g., *Jewish Hospital of St. Louis v. IDEXX Laboratories*, 951 F. Supp. 2, 5 (D. Maine 1996) (patent claimed newly-defined antigens in dog blood; amendment to patent “added language that the antigens were ‘essentially purified and isolated’” in order “to meet the examiner’s objection that without such limiting language the patents would be claiming a product of nature, an unpatentable subject”).

²⁷⁶ 927 F. 2d 1200 (Fed. Cir. 1991).

none of the *Amgen* opinions mentioned the product of nature doctrine by name, the case is reflective of the post-*Chakrabarty* consensus about the minimal role the doctrine should play. A specialized interpretation of the purification rule has all but mooted the product of nature doctrine.

In *Amgen*, three companies fought over the patent rights to the DNA sequences that encode the protein human erythropoietin, which stimulates the production of red blood cells.²⁷⁷ It will be recalled from part II that DNA codes for the production of proteins by the arrangement, or sequence, of the bases adenine, thymine, guanine, and cytosine.²⁷⁸ Particular three-base combinations, called codons, specify the production of particular amino acids, which then link to form proteins. Thus, the DNA sequence of the gene of interest will determine which amino acids and, ultimately, which proteins its host cell produces.

The broadest of the product claims in Amgen’s U.S. Patent No. 4,703,008 (the “‘008 patent”), entitled “DNA Sequences Encoding Erythropoietin,” reads as follows: “2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.”²⁷⁹ Amgen, in other words, claimed a purified and isolated form of any gene that codes for erythropoietin. In this context, “purified and isolated” means that the coding region of the relevant DNA has been identified and has been reproduced outside of its natural environment.²⁸⁰ The district court held that claim 2 was valid and infringed, and the Federal Circuit affirmed.²⁸¹ Neither opinion suggested that patentable subject matter was an issue in the case. However, the district court did touch on the significance of

²⁷⁷*Id.* at 1203-05.

²⁷⁸*See supra* part II.A.1. The underlying biology is discussed in the Federal Circuit’s *Amgen* opinion, 927 F.2d at 1207-08 n. 4, and at greater length in the district court opinion. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 13 U.S.P.Q. 2d 1737, 1741-45 (D. Mass. 1989).

²⁷⁹927 F. 2d at 1202, 1204.

²⁸⁰13 U.S.P.Q. 2d at 1742-43.

²⁸¹927 F. 2d at 1219.

the phrase “purified and isolated” in another context.

The defendants argued that the ‘008 patent was invalid for lack of novelty, its contribution having been fully anticipated by the previous work of another scientist.²⁸² Before ruling on anticipation, the court observed, it was first necessary to “determine what the ‘invention’ is.”²⁸³ Remarkably (for reasons to be developed momentarily), Amgen took the position that “the claimed invention is the DNA sequence encoding human EPO.”²⁸⁴ Unremarkably, the defendants argued that “the claimed invention is a ‘purified and isolated’ DNA sequence encoding EPO, or in other words, the cloned EPO gene, not the listing of 4000 bases.”²⁸⁵ The court forcefully rejected Amgen’s position: “The invention as claimed in the ‘008 patent is not as plaintiff argues the DNA sequence encoding human EPO since that is a nonpatentable natural phenomenon ‘free to all men and reserved to none’. . . . Rather, the invention . . . is the ‘purified and isolated’ DNA sequence encoding erythropoietin.”²⁸⁶ In affirming the district court’s finding of no anticipation, the Federal Circuit made the same point: “The subject matter of claim 2 was the novel purified and isolated sequence which codes for EPO.”²⁸⁷

Amgen’s position is remarkable because it is contrary to the consensus that underlies all DNA patents. As discussed in part I,²⁸⁸ patent lawyers, patent examiners, and the courts have assumed that DNA comprises patentable subject matter because what is claimed is not raw DNA sequences, but rather DNA in an isolated and purified—and thus non-natural—form. Indeed, Amgen’s claims in the

²⁸²13 U.S.P.Q. 2d at 1759. The novelty question arose under 35 U.S.C. § 102(g).

²⁸³13 U.S.P.Q. 2d at 1759.

²⁸⁴*Id.* (citing Amgen’s post-trial brief).

²⁸⁵*Id.*

²⁸⁶*Id.* (quoting *Charkrabarty*).

²⁸⁷927 F. 2d at 1206.

²⁸⁸*See supra* notes 28-32 and accompanying text.

'008 patent tracked this consensus. That both courts rejected Amgen's broader claim interpretation argument is reassuring. Yet it is disappointing that two courts thought it sufficient to recite the consensus conclusion without any critical analysis. This conclusory approach may have dissuaded others from asserting the doctrine in contexts where it might have considerable bite.²⁸⁹

The PTO's view emerges even more vividly in the breast cancer gene patent.²⁹⁰ The invention "relates to methods and material also used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles [alternative forms of the gene] of which cause susceptibility to cancer, in particular, breast and ovarian cancer."²⁹¹ Making ingenious application of a variety of known techniques, the inventors were able to identify the sequence of base pairs that performs the work of coding for the protein for which the human BRCA1 gene codes. This discovery led to the first and broadest of the allowed claims: "an isolated DNA coding for a BRCA-1 polypeptide [protein], said polypeptide having the amino acid sequence set forth in SEQ ID NO: 2."²⁹² In other words, a patent was granted on an isolated DNA sequence that codes for a protein made up of the specified sequence of amino acids.

The only thing that distinguishes the claimed sequence from sequences in living human cells that code for the same protein is the word "isolated." According to the definition provided in the patent, "isolated" is a synonym for "substantially pure." These equivalent terms denote "nucleic acid . . . which is substantially separated from other cellular components which naturally accompany a native human sequence"; in other words, "isolated" "embraces a nucleic acid sequence . . . which has

²⁸⁹ See *infra* part V.B.

²⁹⁰ United States Patent 5,747,282 (issued May 5, 1998). See *supra* notes 24-27 and accompanying text.

²⁹¹ *Id.*

²⁹² *Id.*

been removed from its naturally occurring environment.”²⁹³ The chemical difference between the claimed sequence and the comparable sequence that actually occurs in the human body is that the “isolated” sequence does not include any noncoding DNA. Nonetheless, what emerges is a patent on a DNA sequence that is defined by the fact that it does exactly the same coding work as the human BRCA1 gene. This claim perhaps represents the gene patent in its most sweeping and abstract form.

The current versions of the PTO’s regulations and examination manual embody the Office’s practical retreat from the product of nature doctrine. The current regulations contain an entire subpart dealing with biotechnology inventions.²⁹⁴ These provisions deal in considerable detail with the deposit and written description requirements for such inventions, but make no reference to patentable subject matter. The current edition of the *Manual of Patent Examining Procedures* also has a lengthy section entitled “Patentable subject matter—living subject matter,” but it amounts to little more than a series of quotations from Chakrabarty.²⁹⁵ As is the case with the regulations, the manual’s biotechnology section deals only with the deposit and written description requirements.²⁹⁶

Much more revealing is the lengthy process that the PTO recently went through in revising its utility examination procedures. The patent community has long believed that the utility requirement presents the most formidable obstacle to biotechnology patents.²⁹⁷ Somewhat oversimplified, the reason is that it is relatively easy to identify base pair sequences, but often

²⁹³ *Id.* Earlier in the patent, under the heading “Gene Isolation,” the impression conveyed is that “isolate” means nothing more than “identify.”

²⁹⁴ 37 C.F.R. ch.1, Subpart G, §§ 1.801-1.825 (2001).

²⁹⁵ MANUAL OF PATENT EXAMINING PROCEDURES, *supra* note 137, at § 2105.

²⁹⁶ *Id.* § 2400.

²⁹⁷ Golden, *supra* note 15, at 128-29; M. Scott McBride, *Patentability of Human Genes: Our Patent System Can Address the Issues Without Modification*, 85 MARQU. L. REV. 511, 530-32 (2001).

difficult to figure out what those sequences do.²⁹⁸ The PTO, too, saw the utility requirement as a way to control the flood of gene and gene-related patents, and set out to tighten its utility standards.

On December 21, 1999, the PTO published new Interim Utility Guidelines and invited comments.²⁹⁹ In early 2001, the PTO published the final guidelines, together with the comments and its responses.³⁰⁰ Many of the comments went beyond the narrow topic of utility and addressed other patentability issues, and some went directly to the product of nature question. For example, “several comments” argued that “genes are discoveries rather than inventions” and are thus unpatentable.³⁰¹ Other comments (again, “several”) took the position that “a gene is not a new composition of matter because it exists in nature.”³⁰²

The PTO rejected all of these comments summarily, in language that is aggressively dismissive of the product of nature objection. It summarized its reasoning as follows:

A patent claim directed to an isolated and purified DNA molecule could cover, *e.g.*, a gene excised from a natural chromosome or a synthesized DNA molecule. An isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.³⁰³

²⁹⁸McBride, *supra* note 297, at 531-32; Holman & Munzer, *supra* note 101, at 758-60.

²⁹⁹Revised Utility Examination Guidelines, Requests for Comments, 64 FED. REG. 71440 (Dec. 21, 1999).

³⁰⁰Utility Examination Guidelines, 66 FED. REG.1092 (Jan. 5, 2001). The guidelines now require a “specific and substantial utility” which “would be considered credible by a person of ordinary skill in the art.” *Id.* at II.B.2(a).

³⁰¹*Id.* at I.(1).

³⁰²*Id.* at I(2).

³⁰³*Id.*

The PTO's logic is difficult to follow. According to the first sentence, an isolated *and* purified DNA molecule is, apparently, distinguishable from a DNA molecule that occurs naturally in an organism, whether that isolated and purified molecule is created by excision from a natural chromosome or by synthesis. In the second sentence, however, excision from the organism is equated with isolation, and synthesis with purification. In the same sentence, either isolation *or* synthesis is treated as a sufficient basis for distinguishing a DNA sequence from its naturally occurring counterpart. Thus, it appears at the end that the PTO really meant that a product of nature objection can be overcome by claiming either an isolated gene or a purified gene. If "purified" is meant to imply the deletion of noncoding regions, as is usually assumed, it is striking that this limitation, while sufficient, is not necessary for patentability.

In the next paragraph, the PTO muddied the waters even further with two peculiar citations concerning the significance of purification. The first citation is to Learned Hand's 1911 opinion in *Parke-Davis & Co. v. H.K. Mulford & Co.*,³⁰⁴ a case upholding a patent on an adrenaline compound derived from animal glands. The PTO quoted Hand for the proposition "even if it [the adrenaline] were merely an extracted product without change, there is no rule that such products are not patentable."³⁰⁵ But the quotation is misleading. In the first place it is dictum; the patent was not granted "only for a degree of purity," but for an unprecedented adrenaline compound that was not in the salt form in which other known compounds occurred.³⁰⁶ Moreover, the rest of the paragraph from which the PTO extracted the quote went on to state the product of nature doctrine in its traditional form: "Everyone, not already saturated with scholastic distinctions, would recognize that

³⁰⁴ 189 F. 95 (S.D.N.Y. 1911), *aff'd*, 196 F. 496 (2d Cir. 1912).

³⁰⁵ 66 FED. REG. 1092 at I(2) (*quoting* 189 F. at 103).

³⁰⁶ 189 F. at 103.

[the patentee's] crystals were not merely the old dried glands in a purer state. . . ." There remains a "line between different substances and degrees of the same substance," a line which "is to be drawn rather from the common usages of men than from nice considerations of dialectic."³⁰⁷ Purity, in other words, is a basis for patentability only if it creates a material difference between the claimed product and its natural precursor. The unmistakable import of Hand's *Parke-Davis* language is that a claim to purity invites an inquiry into the materiality of the difference; it does not provide a blanket exemption from product of nature scrutiny.³⁰⁸

The second cited case is *In re Bergstrom*,³⁰⁹ decided by the Court of Customs and Patent Appeals in 1970. The court reversed the PTO's denial of a patent claiming a purified version of a naturally occurring chemical. The examiner had rejected the application because the claimed compounds, since they "are naturally occurring" . . . therefore "are not "new" within the connotation of the patent statute."³¹⁰ In the portion of the reversal quoted by the PTO, the CCPA held that the examiner's findings were unsupported by the record; in fact, the claimed compounds, "as far as the record establishes, do not exist in nature in pure form."³¹¹ The PTO deduced from this language the conclusion that "[l]ike other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or when synthesized in a laboratory from the chemical

³⁰⁷*Id.*

³⁰⁸*See* 1 CHISUM, *supra* note 11, at 1-75 (under *Parke-Davis*, purity distinguishes a claimed product from a natural precursor "only if the new pure compound differs 'in kind' rather than merely 'in degree' from the old compound"). The PTO's citation of a 1911 case is also a bit ironic, since the current consensus implies that old cases are irrelevant because modern claim drafting techniques have mooted the product of nature problem. *See supra* notes 29-30 and accompanying text.

³⁰⁹427 F. 2d 1394 (C.C.P.A. 1970).

³¹⁰*Id.* at 1397 (*quoting* patent examiner).

³¹¹66 FED. REG.1092 at I(2)(*quoting* 427 F. 2d at 261).

starting points.”³¹²

This proposition is troubling in several respects. First, it rests on the assumption that DNA molecules really are “like other chemical compounds.” Arti Rai has convincingly attacked this assumption as “fundamentally misconceived.”³¹³ She reasoned that “[a]lthough DNA is, obviously, enough, a chemical compound, it is more fundamentally a carrier of information.”³¹⁴ Consequently, its value is as much as an aid to further discovery as a finished product.

Second, the PTO’s language further confuses the relationship among isolation, purification, and synthesis. It now appears that isolation plus purification is one ground for patentability, while synthesis is another distinct ground; just above, purification seemed to be equated with synthesis.³¹⁵ Third, the implication is that a claim to isolation and purification automatically avoids a product of nature objection. Yet *Bergstrom*, like the other purity cases, says only that purification may provide a sufficient distinction from a natural counterpart.

The fourth and perhaps most important problem relates to the portion of the *Bergstrom* opinion that the PTO did not quote. Immediately following the excerpt that the PTO selected, the CCPA made clear that *Bergstrom* was a section 102 novelty case, not a section 101 patentable subject matter case. The patentability of the compound turned on whether the subject matter could be termed “new.”³¹⁶ Although the PTO had focused on the word “new” as used in section 101, this was error; according to the CCPA, that term only takes on meaning under the novelty provisions of

³¹²*Id.*

³¹³Rai, *supra* note 32, at 836.

³¹⁴*Id.*

³¹⁵*See supra* note 303 and accompanying text.

³¹⁶427 F. 2d at 1402.

section 102.³¹⁷ Thus, the PTO responded to a comment directed at a section 101 problem with a reference to a section 102 case.

The PTO's current view of the product of nature doctrine can be stated succinctly: it is a dead letter. While utility and enabling disclosure remain serious issues, there is no evidence that the PTO scrutinizes biotechnology applications for violation of the doctrine, as long as claims contain such words as "isolated and purified." When finally forced to confront the product of nature doctrine in the utility comment process, the PTO's response was conclusory and in many respects incoherent. It quoted a couple of old cases that it appeared to misread. Perhaps most tellingly, it responded to what the Supreme Court has defined as a section 101 problem with a section 102 case.

B. The Lower Courts Since *Chakrabarty*

This is a short section. On July 5, 2002, we did a LEXIS search of all decisions of the Federal Circuit, which came into existence in 1982. We used a variety of terms to search for all possible references to the product of nature doctrine. We found only a single case in which the doctrine received any substantive mention: the Federal Circuit's decision in the *J.E.M.* case, which was affirmed by the Supreme Court.³¹⁸

The post-*Chakrabarty* story from the district courts is essentially the same. A similar search

³¹⁷*Id.*

³¹⁸The doctrine was also mentioned in passing in a plant patent case, *Imazio Nursery, Inc. v. Dianagreenhouses*, 69 F. 3d 1560, 1563 (Fed. Cir. 1995). The court observed that before the passage of the Plant Patent Act, plants were not thought to be patentable subject matter, in part because of "the belief that plants, even those bred by man, were products of nature and therefore not subject to patent protection." The enactment of the Plant Patent Act, the court explained, was a statement of Congress' belief that the work of the plant breeder was sufficient human intervention. In addition, the doctrine played an important role in the *Amgen* case, but by virtue of its absence from the analysis. *See supra* notes 276-89 and accompanying text.

of district court opinions yielded only a few references, most of them spurious,³¹⁹ and none of them dealing squarely with the product of nature doctrine. One complex biotechnology case did, however, deal with the concept of “purity” in an unusual way. Purification, it will be recalled from part III.A, has long played a role in rendering some naturally-occurring products patentable over their natural precursors. As is apparent from the *Amgen* consensus, the isolation and purification of DNA sequences is what is assumed to transform naturally-occurring DNA into a patentable invention. The case in question also involved Amgen, this time as a defendant.

In *Schering Corporation v. Amgen, Inc.*,³²⁰ the plaintiffs alleged that Amgen had infringed a patent covering the synthesis of human interferon, a naturally occurring protein that functions as an anti-viral and anti-tumor agent in the body.³²¹ Charles Weisserman, the inventor named in the patent, was the first to identify and isolate the DNA sequence that codes for interferon. Weisserman induced human white blood cells to produce interferon by exposing them to a virus. He then collected RNA from the induced cells. Since this RNA had transcribed the interferon sequence from the induced cells’ DNA and then translated that sequence into the protein interferon, it contained the complement of the critical DNA sequence. Weisserman then made cDNA fragments from the RNA and spliced the fragments together into plasmids.³²² By inserting these plasmids into bacterial cells,

³¹⁹The search turned up several trademark cases containing the phrase “nature of the product,” for example.

³²⁰18 F. Supp. 2d 372 (D.Del. 1998). The case has an unusual history. The opinion under discussion was interlocutory, dealing only with claim construction. Realizing that it could not prevail under the district court’s construction and seeking an appealable final judgment, Schering moved for summary judgment of non-infringement on behalf of the defendant, Amgen. The district court granted this motion. 35 Fed. Supp. 2d 375 (D.Del. 1999). Schering then appealed from this judgment, raising only the issue of claim construction. The Federal Circuit affirmed. 222 F. 3d 1347 (Fed. Cir. 2000).

³²¹18 F. Supp. 2d. at 377.

³²²See *supra* note 225 and accompanying text.

Weisserman was able to turn the easily-replicated bacteria into interferon factories.

One of Schering's claims, claim 8, covered a "substantially pure DNA sequence selected from the group consisting of [the DNA sequences found to code for interferon], said DNA sequences coding on expression for only a single polypeptide chain."³²³ The meaning of "substantially pure" came up not in connection with patentability, but rather in interpreting the scope of the claim in order to assess possible infringement.³²⁴ Schering, the plaintiff, argued that "substantially pure" referred to any DNA sequences, naturally occurring or synthetically produced, that had been identified as coding for interferon and were available for that use. Amgen's position was that "substantially pure" referred only to naturally-occurring DNA that been isolated from its host genome. In its view, synthetic versions of the pertinent DNA sequences could not infringe.³²⁵

The court concluded that "'substantially pure DNA sequences' can be both naturally occurring and non-naturally occurring [synthesized] DNA sequences. . . . The purity in question only refers to the alpha interferon DNA being separated, isolated and identified apart from the human genome and any other relevant bacterial genome."³²⁶ "Pure," in other words, simply meant "isolated." Consequently, claim 8 covered any DNA, natural or synthetic, that was known to code for interferon and that had been isolated from its original source and not yet inserted into a new bacterial host. Note the irony: biotechnology plaintiffs--including Amgen itself, at least in the claim-drafting stage--have usually avoided products-of-nature objections by emphasizing that they are not

³²³*Id.* at 397 n. 35.

³²⁴The opinion produced an interlocutory order that dealt only with claims interpretation. *Id.* at 400. *See supra* note 320.

³²⁵*Id.* at 397.

³²⁶*Id.* at 399. The reference to a "bacterial genome" resolved a second dispute in the case. The plaintiffs argued that claim 8 covered DNA that had been spliced into plasmids and then inserted into bacteria; Amgen said that it did not. Amgen prevailed on this point.

claiming naturally occurring DNA. Here, however, the plaintiffs, in order to enhance their prospective infringement case, insisted that they were making such a claim. In that context, the court's conclusion is unexceptionable. However, the court did inject into the reported case law the potentially mischievous statement that “naturally occurring” DNA sequences can be the subject of a patent.

V. Applying the Product of Nature Doctrine to Contemporary Biotechnology

With the underlying science and legal history of the product of nature as background, we turn now to our ultimate question: whether the doctrine, properly understood and rigorously applied, can and should play a role in determining the patentability of biotechnology inventions. We conclude that it can and should, but if, and only if, it is properly understood. By “proper” understanding, we mean the understanding expressed by the Supreme Court in *Funk* in 1948³²⁷ and *Chakrabarty* in 1980³²⁸ and endorsed in *J.E.M.* just last year.³²⁹ It is an understanding that is consistent with the original statement of the doctrine in *Latimer* and the early-twentieth-century federal cases,³³⁰ as well as with the Court of Customs and Patent Appeals' analysis in *Chakrabarty* and its companion case.³³¹ It is, however, an understanding that was not always adhered to in the chemical purity cases. Consequently, it is an understanding that the contemporary patent community—practitioners, the Patent Office, commentators, and the Federal Circuit—has chosen to ignore.

A. The Relevant Aspects of the Doctrine

³²⁷ See *supra* part III.B.

³²⁸ See *supra* part III.C.

³²⁹ See *supra* part III.D.

³³⁰ See *supra* part III.A.

³³¹ See *supra* notes 246-51 and accompanying text.

Several elements of the doctrine that we developed in part III of the article are especially relevant to current biotechnology practice:

First, patents claiming products of nature violate section 101. As both the Court of Customs and Patent Appeals and the Supreme Court emphasized in *Chakrabarty*, the first question to be asked in assessing any patent claim is whether it is drawn to statutory subject matter.³³² In other words, does the patent claim the invention of a machine, manufacture, or composition of matter? The question is to be answered by examining the nature of the thing that is claimed. If the thing claimed is nonstatutory, then its novelty, utility, and non-obviousness are irrelevant.

Products of nature are nonstatutory subject matter. This defect cannot be remedied by a showing of novelty, utility, or non-obviousness. Nonetheless, in some cases, the latter three elements may have collateral relevance. If a claimed invention is a product of nature, then it is also likely to be known by others and thus to lack novelty.³³³ (Note, however, that the converse proposition is not true: the fact that an invention possesses novelty does not prove that it is not a product of nature, since new products of nature are discovered every day.) In addition, the presence of novelty or a new form of utility may provide *evidence* that the claimed invention is materially distinguishable from a naturally-occurring counterpart, and is thus not itself a product of nature.³³⁴

Second, the case law reveals no bright line between statutory inventions and nonstatutory product of nature claims. The test to be applied is an open-ended one: does the claimed invention differ in substance, and not merely degree, from any wholly natural counterparts? There is no warrant in the case law for deeming any particular distinction to be either uniformly sufficient or uniformly insufficient. As Learned Hand put it in 1911, there is a “line between different substances

³³²See *supra* notes 246-58 and accompanying text.

³³³See *supra* notes 144-46, 168 and accompanying text.

³³⁴See *supra* note 221 and accompanying text.

and degrees of the same substance,” which “is to be drawn rather from the common usages of men than from nice considerations of dialectic.”³³⁵ Even the so-called purity cases (such as *Parke-Davis*, from which the Hand quotation is drawn) when closely read, do nothing more than hold, in their respective contexts, that purity supports the conclusion that the claimed invention differs in substance rather than merely degree from its natural counterpart.³³⁶

Third, if a claimed invention is nothing more than a product of nature, its source is irrelevant.³³⁷ If the product itself is substantially the same as its natural counterpart, it fails the statutory subject matter test, regardless of how it is produced.

Fourth, words such as “isolated,” “purified,” and “synthesized,” should not be accorded talismanic status. This point follows directly from the preceding two. Because the distinction between a statutory invention and a nonstatutory product of nature is one of substance rather than form, cases should not be resolved on the basis of incantations. Rather, there should be a fact-specific inquiry into the materiality of the differences that are created by the processes such as isolation, purification, and synthesis. The case law simply does not support the existence of linguistic safe harbors.

Fifth, despite the absence of bright-line tests, the clear import of more than a hundred years of precedent is that, where a claimed invention has a natural precursor or variant, the differences must be quite robust. Among the inventions that came up short were those in *Funk*, which combined species in a novel and non-obvious way³³⁸; *General Electric*, which claimed a pure form of tungsten that had *not* been found in nature³³⁹; and *Marden*, which made similar claims to pure forms of

³³⁵*Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95, 103, (S.D.N.Y. 1911), *aff'd*, 196 F. 496 (2d Cir. 1912).

³³⁶*See supra* notes 183-89, 304-11 and accompanying text.

³³⁷*See supra* notes 146-48, 156 and accompanying text.

³³⁸*See supra* part III.B.

³³⁹*See supra* notes 160-63 and accompanying text.

vanadium and uranium.³⁴⁰ The successful claim in *Chakrabarty*, by contrast, rested on the alteration of the genetic makeup of a living organism.³⁴¹ Even the chemical cases that underlie the current biotechnology consensus—assuming that they are correctly analyzed statutory subject matter cases—all reflect a fact-specific analysis of the purification involved, rather than unthinking reliance on the presence of a magic word. The claimed vitamin compound in *Merck*, for example, had lower levels of vitamin activity than naturally occurring B₁₂,³⁴² whereas in *Parke-Davis*, the claimed adrenalin compound was “not merely the [natural version] in a purer state,” but adrenalin in an unprecedented non-salt form.³⁴³ In sum, under any view of the case law, a party challenging a patent in court should be able to insist that the court determine precisely what words “purify” and “isolate” mean.

B. Do Biotechnology Inventions Stand Up to Product of Nature Scrutiny?

If, as we have argued, the product of nature doctrine is not dead but merely forgotten, and if it imposes meaningful standards that cannot be overcome by semantic sleight-of-hand, the final question is whether its revival would have any effect on the granting of biotechnology patents. We conclude that it could, in at least some significant contexts. To illustrate why, we revisit several types of biotechnology patents.

1. Genes and Gene Sequences

The words “isolated” and/or “purified,” sometimes in combination with “synthesized,” have mooted all debate about the subject-matter status of genes and gene sequences. This consensus operating assumption is valid, at least in a literal sense: *DNA* with its non-coding regions (introns) excised does not exist in a naturally occurring cell. Whether a claim is drawn to synthesized cDNA

³⁴⁰See *supra* notes 164-71 and accompanying text.

³⁴¹See *supra* part III.C.

³⁴²See *supra* note 187 and accompanying text.

³⁴³189 F. at 103.

or to naturally occurring but isolated and purified DNA, an inventor can justifiably say that the invention is not, and cannot be, a product of nature. The reason is that, in a cell, the chemical that undergoes splicing (excision of introns) and translates the coding information is RNA, not DNA.³⁴⁴ Thus, whereas one of the strands of cDNA will contain precisely the same genetic information as the mature RNA from which it was derived, it is a different chemical; and whereas cDNA is chemically identical to naturally occurring DNA, it lacks the non-coding regions found in the latter.

This argument holds regardless of the length of the DNA sequence that is being claimed. Even ESTs, which may be only a couple of hundred base pairs long, are made of cDNA,³⁴⁵ and are therefore equally distinguishable from naturally occurring DNA and RNA.

This is the context in which the anti-product of nature consensus seems strongest. But even here, there is a counterargument to be made. If, as we argue, there are no magic words, then patent examiners, litigants and courts should at least *ask* the question: how material are the differences between naturally occurring DNA and RNA and isolated, purified, and/or synthesized DNA? We believe the answer to be less obvious than the current consensus assumes.

Preliminarily, recall that the words *isolated*, *purified*, and *synthesized* have been used in all possible combinations in patents that have been allowed. The only distinctions that have been uniformly insisted on as a requirement to patentability are that the DNA be removed from its natural environment and have its non-coding regions excised. As a result, despite its nominal chemical distinctiveness, what is patented is functionally indistinguishable from natural DNA and RNA. It contains exactly the same genetic information as its natural counterpart. It can do precisely the same work as a naturally occurring gene—protein synthesis—and it employs precisely the same processes to do it, whether in the body or in the laboratory. Indeed, as we pointed out earlier, the breast cancer

³⁴⁴See *supra* notes 78-79 and accompanying text.

³⁴⁵See *supra* note 106 and accompanying text.

gene patent uses this functional indistinguishability as the means of identifying the claimed gene: “An isolated DNA coding for a BRCA-1 polypeptide [with a specified amino acid sequence].”³⁴⁶ In other words, what is claimed is whatever it is that does the work of the naturally occurring breast cancer gene. “Isolated” is almost redundant: on the one hand, it means that the non-coding regions have been excised, but on the other, the non-coding regions do not participate in doing the work.

In evaluating the materiality of the differences between claimed DNA sequences and their natural counterparts, we are left with chemical distinctions versus informational and functional identity. Critically, it is these informational and functional properties that are the whole reason for seeking DNA patents. Researchers isolate, purify, and synthesize DNA both as an intermediate step in the process of gene identification and as a tool for building proteins.³⁴⁷ Thus, patentable DNA is identical to its natural counterpart with respect to the qualities that researchers deem most significant, and distinct in ways that can be fairly characterized as incidental.

We believe it is at least worth asking where such distinctions lie on the traditional products of nature continuum. Are they more substantial than the differences between naturally occurring tungsten oxide and the pure form claimed—unsuccessfully—in the *General Electric* case? Are they more nearly analogous to the differences between naturally occurring, mutually inhibiting root-nodule bacteria and the *Funk* combination, or to the differences between naturally occurring, single-plasmid bacteria and *Chakrabarty*’s genetically engineered strain? We suggest that when the product of nature doctrine is viewed in its full historical context, from *Latimer* through *Chakrabarty*, the answers to such questions are not nearly so self-evident as the current consensus would imply. Above all, we conclude, given the Supreme Court’s consistent restatement of the doctrine from 1948

³⁴⁶ See *supra* notes 291-93 and accompanying text.

³⁴⁷ See Rai, *supra* note 35, at 835-37.

through October of last year, these are questions that an aggressive litigant should attempt to put before the Supreme Court. The answers seem far from preordained.

2. Cell Lines

The arguments against cell line claims of the sort allowed in the Papua New Guinea patent³⁴⁸ seem even stronger. In that patent, it will be recalled, tests showed that the cells of interest retained their genetic identity through the co-culturing process. They differed from their natural occurring counterparts only in that they had been induced to grow in an artificial medium, a medium that could not be replicated in nature. The sole reason for producing this medium, however, was to perpetuate the cells of interest for research and therapy purposes, and such purposes could be achieved only if the cells retained their genetic identity.

The comparison between *Funk* and *Chakrabarty* seems especially pertinent here. The *Funk* inventor took several naturally occurring bacteria and induced them to live in a new medium, a multi-species inoculant. The invention failed the product of nature test, however, because the constituent organisms did not differ from their natural counterparts. *Chakrabarty*, on the other hand, passed the test because he altered the genetic nature of a natural organism. The Papua New Guinea cell line seems closer to the invention in *Funk* than that in *Chakrabarty*. As in *Funk*, the inventors caused a naturally-occurring cell to live in a new and nonnatural medium for longer than normal without altering the genetic characteristics of that cell. Absent repudiation of the product of nature doctrine—and there is no evidence to suggest that such a result would be forthcoming—is it not at least plausible to believe that, if the Supreme Court were confronted with a cell line case, it would analogize to *Funk* rather than to *Chakrabarty*?

3. Viruses

³⁴⁸See *supra* notes 130-32 and accompanying text.

Our analysis of the Papua New Guinea patent claim to a “viral preparation comprising the HTLV-1 variant in the cell line”³⁴⁹ is very similar. The phrase “viral preparation” implies isolation from the natural environment and preservation in an artificial medium. The virus in question is the retrovirus thought to cause a form of leukemia. The members of the Hagahai tribe, who were the original cell line donors, carry the virus but do not exhibit symptoms of the disease. The virus in the claimed preparation was identified and isolated from the Hagahai cell line. To be of research value, it had to be identical to the virus found in the cell line and carried by the Hagahai—and it was. Therefore, as in *Funk*, the claim was drawn to a naturally occurring organism induced to exist in an artificial medium. Again, unless the product of nature doctrine were to be repudiated, it is not evident why the result should be different from that reached in *Funk*.

4. Proteins

We made brief reference above to a very new patent claiming “an isolated protein comprising the [specified] amino acid sequence.”³⁵⁰ The protein in question, according to the patent, has been implicated in the malignant transformation of breast cancer cells. The patent discloses a vast body of research revealing the amino acid sequences that comprise the protein and the DNA sequences that code for it. However, nowhere in the patent is the protein—the thing that is claimed—distinguished from its natural counterpart other than through the single word “isolated.”

There are only a couple of ways to justify the grant of such a patent. One is to conclude, as at least one court has,³⁵¹ that the mere invocation of the word “isolated” immunizes any chemical against a product of nature objection, absolutely and incontestably. Another is to assume that such

³⁴⁹See *supra* notes 133-36 and accompanying text.

³⁵⁰U.S. Patent No. 6,429,291 (issued Aug. 6, 2002). See *supra* note 115 and accompanying text.

³⁵¹*Jewish Hospital of St. Louis v. IDEXX Laboratories*, 951 F. Supp. 2d 2, 5 (D. Maine 1996). See *supra* note 275.

immunity is unnecessary because the product of nature doctrine is dead. As we have attempted to demonstrate throughout this article, neither of these assumptions is valid. If our legal argument is correct, then the subject matter status of isolated proteins is, at a minimum, worthy of close scrutiny. Such scrutiny should proceed along the traditional common law track of analogy to precedent. If this process is carried to its logical conclusion, we believe, the more compelling analogies will prove to be those to southern pine filaments, pure tungsten, and mixed root-nodule bacteria. Despite the shared genetic engineering background, the analogy between this isolated protein and *Chakrabarty's* recombinant organism seems attenuated at best.

VI. Conclusion

Since the beginning of the biotechnology era, the patent office and the lower courts, including the Federal Circuit, have treated the product of nature doctrine as if it were dead. We believe, however, with apologies to Mark Twain, that the reports of its demise are greatly exaggerated. On the contrary, having traced its history from 1889 through the Supreme Court's most recent term, we discern a consistent and resilient thread. Where a claimed invention has a natural counterpart, it must be shown to differ from that counterpart in substance, not merely in degree. This is a question of patentable subject matter that must be decided without reference to novelty, utility, and non-obviousness.

The essence of the product of nature doctrine has sometimes been confused by lower court cases involving purified variants of natural chemicals. However, such cases are either distinguishable from true product of nature cases or, if not, are inconsistent with the analysis to which the Supreme Court has consistently adhered. Moreover, making a direct leap from ordinary chemicals to DNA and its products is, we and others have argued, a dubious proposition, both factually and logically.

Accordingly, there is no warrant in the history of the product of nature doctrine for allowing it to be circumvented by the mere incantation of some combination of the words “isolated,” “purified,” and “synthesized.” Instead, what is required is a detailed factual assessment of the specific ways in which the claimed invention differs from its natural counterpart. When that analysis is performed against the background of the case law, substantial questions arise about the patentability of a good deal of subject matter whose statutory status is now taken for granted. All of the inventions we discuss may well survive, but they should survive after a process of rigorous scrutiny, not blithe assumption. At a minimum, it is time for litigants and courts to revisit the product of nature doctrine as it has actually been handed down. The results could prove surprising.