

Molecular Subject Matter

TOWARDS A MOLECULARISED SUBJECT MATTER

The early twentieth century saw a number of changes in the way natural phenomena were investigated that had important ramifications for plant-based subject matter. Of particular importance was the emerging field of transmission studies, labelled genetics by Bateson in 1906,¹ which was concerned with the study of the ‘units that were assumed to be strung together along the length of the chromosomes and that had the capacity to guide the formation of individual traits’.² At the heart of the new discipline was a new entity: the *gene* (a term first coined by Wilhelm Johannsen in 1909).³ Over time the gene came to operate, like atoms in physics and molecules in chemistry, as the fundamental unit of biological explanation. As Rheinberger and Müller-Wille said, from the early twentieth century onwards the gene ‘became central to all main branches of the life sciences and promoted unprecedented visions of controlling and directing life’.⁴

Despite the prominent role that the gene played in classical genetics, because the experimental systems were ‘ill-suited for providing insights into the material molecular basis of genetic phenomena’,⁵ scientists had no real idea of what genes were nor what they did. As a result, the classical gene remained a largely theoretical concept that had to be inferred from external phenotypic variants, which were treated as

¹ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 12.

² Hans-Jörg Rheinberger, ‘Gene Concepts Fragments from the Perspective of Molecular Biology’ in (ed) P. Beurton, R. Falk, and H. Rheinberger, *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press, 2000), 219, 220–21.

³ The new discipline distinguished ‘between genetic units and unit characters, taken in their entirety, between genotype and phenotype, respectively’. In 1909 Wilhelm Johannsen ‘codified this distinction ... by introducing the notions of *genotype* and *phenotype*, respectively, for these two spaces’. *Ibid.*

⁴ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 1.

⁵ *Ibid.*, 59.

indicators or windows into the genotype.⁶ With no consensus as to whether genes were real or fictitious, genes were taken as abstract elements of an equally abstract space; they were hypothetical factors responsible for external phenotypic differences between organisms (such as the gene for white flowers in peas).

While classical genetics made many important discoveries,⁷ it left many things unanswered including questions ‘about the make-up of genes, the mechanism of gene replication, what genes do, and the way that genes bring about phenotypic differences’.⁸ The situation began to change, however, with the molecularisation of genetics that began in the middle of the twentieth century.⁹ A key feature of the new biology that took shape in the 1960s was that it was couched in terms of molecular level phenomena. The resulting molecularisation of biology fundamentally changed the way the gene and, with it, biology were seen. It also had an important impact on the way patent law interacted with biological subject matter.

There were two features of the molecular gene that distinguished it from the gene of classical genetics. The first related to the fact that by the middle of the twentieth century the gene was no longer seen as a quasi-mythical entity.¹⁰ Instead, it had come to be recognised as a material chemical molecule made up of deoxyribonucleic acid (DNA).¹¹ That is, the gene was transformed from an abstract idea inferred from external phenotypic variants into a real physical chemical entity.¹² The second distinguishing feature of the molecular gene relates to its function. Unlike the gene of classical genetics, which was seen as a theoretical abstract entity that controlled an aspect of the phenotype, the molecular gene was reconceptualised as a carrier of

⁶ Given that scientists in the first half of the twentieth century were unable to access the material nature of genes, the nature and existence of the classical gene had to be inferred from external phenotypic variants. Laurence Perbal, ‘The Case of the Gene: Postgenomics between Modernity and Postmodernity’ (2015) 16(7) *EMBO Reports* 777.

⁷ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 7.

⁸ Hans-Jörg Rheinberger, ‘Gene Concepts Fragments from the Perspective of Molecular Biology’ in (ed) P. Beurton, R. Falk, and H. Rheinberger, *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press, 2000), 219; citing Muller who said in 1951: ‘[T]he real core of gene theory still appears to lie in the deep unknown. That is, we have as yet no actual knowledge of the mechanism underlying that unique property which makes a gene a gene – its ability to cause the synthesis of another structure like itself ... in which even the mutations of the original gene are copied ... We do not know of such things yet in chemistry.’

⁹ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 7. See also Michel Morange, *The Black Box of Biology: A History of the Molecular Revolution* (Cambridge, MA: Harvard University Press, 2020).

¹⁰ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 7.

¹¹ Hans-Jörg Rheinberger, ‘Gene Concepts Fragments from the Perspective of Molecular Biology’ in (ed) P. Beurton, R. Falk, and H. Rheinberger, *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press, 2000), 219, 226.

¹² *Ibid.*, 221.

information for the precise specification of the structure of a protein that, in turn, was responsible for the characteristics of organisms.¹³ Specifically, the molecular gene came to be seen as a fundamental entity that provided ‘the information’, ‘the blueprint’, or ‘the program’ for an organism that ‘directed’ the development and functioning of organisms by ‘producing’ the proteins that build and maintain living biological organisms.

For the molecular biologist, the gene was defined *structurally* as sequences of DNA (RNA in some viruses) that specify the amino acid sequences of a protein,¹⁴ and *functionally* as a segment of DNA whose ordered sequence of bases stored the ‘information’ for the synthesis of a protein or other gene product.¹⁵ Importantly the structural and functional dimensions of the gene were united by the notion of genetic information transfer, which explained how molecular order was transferred from one class of molecules to another. In ‘one molecule, the DNA, the order was structurally perpetuated; in the other it was “expressed” ... and became the basis of the biological function of either an RNA or a protein’.¹⁶ With this, the structural (chemical/physical) and functional (biological/informational) conceptions of the gene converged on a single entity – the molecular gene.¹⁷ As we will see, the merging of these approaches had an important impact on the way that patent law interacted with genes.

Based on the central dogma of molecular biology, which taught that a gene is a sequence of DNA that produces RNA, which, in turn, produces the proteins that are responsible for the characteristics of organisms,¹⁸ the molecular gene was understood as a self-replicating molecule of DNA ‘that not only holds the secrets of life but that it also executes its cryptic instructions – it was, in short, the “Master Molecule.”’¹⁹ Within this reductionist vision of life, genes, and genes alone, were thought to be responsible for biological traits and characteristics. The molecular gene was taken to be the guarantor of intergeneration stability, the factor responsible for individual

¹³ Evelyn Fox Keller, ‘The Postgenomic Genome’ in (ed) Sarah S. Richardson and Hallam Stevens, *Postgenomics: Perspectives on Biology after the Genome* (Durham, NC: Duke University Press, 2015), 14.

¹⁴ Karola C. Stoltz, Adam Bostanci, and Paul Griffiths, ‘Tracking the Shift to “Postgenomics”’ (2006) *Community Genetics* 190, 191.

¹⁵ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 64.

¹⁶ *Ibid.*

¹⁷ Hans-Jörg Rheinberger, ‘Gene Concepts Fragments from the Perspective of Molecular Biology’ in (ed) P. Beurton, R. Falk, and H. Rheinberger, *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press, 2000), 219, 228.

¹⁸ Evelyn Fox Keller, ‘The Postgenomic Genome’ in (ed) Sarah S. Richardson and Hallam Stevens, *Postgenomics: Perspectives on Biology after the Genome* (Durham, NC: Duke University Press, 2015), 14.

¹⁹ Evelyn Fox Keller, *The Century of the Gene* (Cambridge, MA: Harvard University Press, 2000), 54. The ‘central dogma’ of molecular biology, namely, the idea that there was a direct correspondence between the sequence of nucleotides in a gene and the sequence of amino acids in a protein provided the slogan: DNA makes RNA, RNA makes protein, makes us’. See also Hans-Jörg Rheinberger, ‘Beyond Nature and Culture: Modes of Reasoning in the Age of Molecular Biology and Medicine’ (2005) *Science in Context* 249, 255.

traits, and, at the same time, the agent for directing an organism's development.²⁰ Genes were seen as inviolable messages passed between generations (save for occasional mutations) and as the ultimate causal factors lying behind development.²¹ As a result, there was no longer any room for Divine providence, mysterious life forces, or external environmental influences.²² Instead, the focus was now on the gene as the master molecule that underpinned all aspects of living matter. Given this vision of life, it is not surprising that the molecular gene came to operate as 'the organizing principle of twentieth-century biology'.²³ As we will see, it also came to play an important role in the way patent law interacted with biological subject matter.

The promise that was held out that molecular biology would eventually come to invent biological reality seemed to come to fruition in the 1970s with the advent of genetic engineering (or recombinant DNA technology).²⁴ As Rheinberger said, genetic engineering was a thoroughly constructive and synthetic process. This was because with 'DNA technology, molecular biology ... turned, in less than twenty years, from a mode of discovery into a praxis of invention. Or, to be more exact, it has turned from the benign illusion of constituting a simple mode of discovery into a deliberate praxis of molecular writing, of bio-construction'.²⁵

While molecular biology had previously approached the 'cell and its molecular elements from the outside in order to learn something about their physical and chemical properties',²⁶ genetic engineering offered a new way of doing biology, the key feature of which was that it made use of the organism's own molecules to copy, cut, and paste other molecules.²⁷ In doing so, gene editing provided researchers with a powerful new set of biological tools that allowed them to manipulate an organism's genome. With the help of these tools, researchers could copy and cut DNA, join different DNA segments together, and transfer DNA between organisms.²⁸ Researchers were now in a position where they could insert alien DNA into the genomes of plants and modify organisms to endow them with new characteristics and traits.

²⁰ Evelyn Fox Keller, *The Century of the Gene* (Cambridge, MA: Harvard University Press, 2000), 140–41.

²¹ 'Introduction' in (ed) P. Beurton, R. Falk, and H. Rheinberger, *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press, 2000), ix.

²² Sakari Tamminen and Eric Deibel, *Recoding Life: Information and the Biopolitical* (London: Routledge, 2019), 1.

²³ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 1. See also Hans-Jörg Rheinberger and Staffan Müller-Wille, 'Gene' in *Stanford Encyclopedia of Philosophy* (Revised 10 March 2009), 1.

²⁴ Hans-Jörg Rheinberger, 'Beyond Nature and Culture: Modes of Reasoning in the Age of Molecular Biology and Medicine' (2005) *Science in Context* 249, 256.

²⁵ *Ibid.*

²⁶ The 'basic genetic communication system of the organism itself ... provided a "soft" technology for effectively interfering with the physiology of plant, animal, and human information processing'. *Ibid.*, 256.

²⁷ Hans-Jörg Rheinberger, 'What Happened to Molecular Biology' (2008) 3 *BioSocieties* 303, 306.

²⁸ Hans-Jörg Rheinberger and Staffan Müller-Wille, *The Gene from Genetics to Postgenomics* (Chicago: University of Chicago Press, 2017), 76.

The results were creations such as insect resistant potatoes, glyphosate resistant soy plants, virus resistant papayas, and tomatoes that ripened slowly.

FROM PLANT TO BIOLOGICAL TO MOLECULAR SUBJECT MATTER

For much of the twentieth century, plant-based subject matter was largely limited to the external surface of individual plants (or parts thereof). Beginning in the 1970s, however, the type of plant-based subject matter that was presented to the law for scrutiny changed. Unsurprisingly, as research in biology progressed, so too did the landscape for biological patents. While this resulted in a diverse and wide-ranging subject matter (that still includes traditionally bred plants), in broad brush terms plant-based subject matter expanded in three new directions.

The first important change occurred when plant subject matter shifted below the surface to include the plant at the molecular and cellular level. As well as protecting the tools of molecular biology²⁹ – such as selectable markers, promoters, cloning vectors, bacteriophage DNA, and methods of gene introduction – patent protection was also gradually extended to include the things uncovered using those new tools. This included DNA sequences (complete or partial genes), promoters, enhancers, individual exons, plasmids, vectors, nucleic acid sequences (proteins), transit peptides, and isolated host cells transformed with expression vectors.³⁰

Facilitated by the shift away from individual plants, patent protection also expanded to include groups or classes of taxonomically different plants. This included patents, for example, over transgenic fruit-bearing plants, glyphosate (round-up) resistant plants, or a patent for genetically modified plants selected from the group consisting of wheat, oat, barley, rice, maize, millet, rye, sorghum, triticale, buckwheat, quinoa, soybeans, beans, peas, alfalfa, potatoes, sweet potatoes, cassava, yam, tomatoes, peppers, tobacco, and cotton.³¹

From the 1970s, the ability for scientists to cut, paste, and edit genes not only underpinned the formation of a new industrial sector (biotechnology)³² it also led to a third type of new subject matter being presented to the law for scrutiny, namely genetically modified plants. While similar to earlier patents in that protection was limited to specific plants, these differed in that they were the product of genetic

²⁹ Notably the Cohen–Boyer patent, ‘Process for producing biologically functional chimeras’, was a novel process to introduce genetic capability into microorganisms for the production of nucleic acids and proteins.

³⁰ For early protection of nucleotides see Charles Heidelberger et al., ‘5-Flourouracil’ US Patent No. 2,802,005 (6 August 1957). See Jacob S. Sherkow and Henry T. Greely, ‘The History of Patenting Genetic Material’ (2015) *Annual Review of Genetics* 161, 164. For history of DNA patents (1971–1980) see Robert Cook-Deegan and Christopher Heaney, ‘Patents in Genomics and Human Genetics’ (2010) 11 *Annual Rev Genomics Human Genetics* 383, 391–92.

³¹ See Carlos Correa, Juan Correa, and Bram De Jonge, ‘The Status of Patenting Plants in the Global South’ (2020) *Journal of World Intellectual Property* 121.

³² N. Rasmussen, *Gene Jockeys: Life Science and the Rise of Biotech Enterprise* (Baltimore: John Hopkins University Press, 2014).

engineering rather than traditional breeding programs. Early examples include patents on tomato plants genetically engineered to produce fruit with an extended shelf-life³³ and patents for groups of plants (such as Patent Number 4,940,835, which covered soybean, cotton, alfalfa, canola, flax, tomato, sugar beet, sunflower, potato, tobacco, corn, wheat, rice, and lettuce that were genetically modified to be resistant to the herbicide glyphosate).³⁴

The splintering of plant-based subject matter that began in the 1970s was also accompanied by subtle but important changes in the way that the subject matter was viewed. The process of change occurred in two stages. The first change that occurred was that plants became biological in the sense that they were grouped with and spoken about alongside other biological organisms as part of a new category of subject matter. While there were exceptions, for most of the twentieth-century plants were treated as a distinct *sui generis* type of subject matter; their unique nature demanded that they be treated as objects in their own right. The situation began to change in the 1970s, however, when plants were grouped with and spoken about alongside other biological organisms. After the asexually reproduced plants of plant patent law were linked to the sexually reproduced plants of plant variety protection, this new grouping was subsequently associated with the plants of utility patent law and eventually to bacteria, microorganisms, fungi, and other biological organisms.

Over time, the focus of attention also gradually shifted from specific individual organisms towards a more abstract legal grouping of living or biological subject matter. The process that began in the discussions surrounding the possible introduction of the *Plant Variety Act* in the 1960s crystallised in 1980 in *Chakrabarty* when the Supreme Court spoke of patents for living matter.³⁵ Adopting a form of ‘organism agnosticism’,³⁶ the law began to treat biological organisms (with the exception of humans) as a single unified category of subject matter. While this new legal category was relatively short-lived, nonetheless it was still important not least because in so far as plants were subsumed within biological (or living) matter, they effectively disappeared or were at least much less prominent than they had been previously.

Ironically, at the same time as plants were being subsumed within a broader class of biological (or living) subject matter, biological subject matter was also stripped of any vital force. As the Supreme Court said in *Chakrabarty*, ‘the relevant distinction for purposes of [patentable subject matter] is not between living and inanimate things, but between products of nature, whether living or not, and human-made

³³ William R. Hiatt, ‘PG Gene and Its Use in Plants’ US Patent No. 4,801,540 (31 January 1989). Marketed as the Flavr Savr tomato.

³⁴ Dilip M. Shah et al., ‘Glyphosate-Resistant Plants’ US Patent No. 4,940,835 (10 July 1990). The patent included a deposit at the ATCC: ‘Claim 59. Plasmid pMON546, ATCC accession number 53213’.

³⁵ This took on a new form in the litigation which questioned the applicability of utility patent protection for plants. *JEM AG Supply v. Pioneer Hi-Bred International* 534 U.S. 124, 150 (2001).

³⁶ Jane Calvert and Erika Szymanks, ‘A Feeling for the (micro)Organism? Yeastiness Organism Agnosticism, and Whole Genome Synthesis’ (2020) *New Genetics and Society* 1, 4.

inventions'.³⁷ While it would take some time for the process to be normalised, the rejection of vitalism marked the beginning of the second stage of the transformation of plant-based subject matter, as plant now biological subject matter was reconfigured as molecular subject matter.

As we have seen, intellectual property law's engagement with plant-based subject matter across much of the twentieth century was concerned with the external surface rather than the internal workings of plants. The situation changed in the 1980s as patents shifted below the surface of organisms to protect molecular-level innovations. Gradually, but with increasing frequency, the molecular gene not only made an appearance in intellectual property law, it also came to be treated as the common denominator that united all biological subject matter. While traditionally bred seeds and plants continued to be protected, they were largely sidelined. Moreover, while there were separate discussions about transgenic plants, these tended to be filtered through a (generic) molecular lens. While the transformation was never complete, biological living subject matter (that had previously subsumed plants) was effectively replaced by a molecularised subject matter. The biological subject matter was 'displaced, with the molecule overtaking or territorializing the organism'.³⁸ This was reflected in the way that the subject matter was spoken about, how it was classified, and consequently how it was dealt with by the law. The upshot of this was that within intellectual property law, to paraphrase Sarah Franklin, plant became biological became molecular subject matter.

The shift to a molecular subject matter and the way that it obfuscated the place of plants within patent law was illustrated by the problems that Rural Advancement Foundation International (RAFI) faced when it set out to review the utility patents that had been granted for plants in the United States between 1985 and 1995. While patents for gene-edited transgenic plants (which claim plants altered with foreign DNA) were readily identifiable, RAFI complained that it was difficult to get a complete picture of the transgenic plants that had been patented. The reason for this was that within the patent classificatory system, DNA sequences and the means of inserting foreign DNA were not considered transgenic plant patents 'even when the patent claims extend to plants that contain the patented gene or exhibit a patented trait'.³⁹ In short, the problem was that patents for plants were presented and classified as molecular inventions rather than as plant-based inventions.

There were a number of characteristics of molecular subject matter that were important for the way it interacted with patent law. Of these three stand out. The first notable characteristic of molecular subject matter related to the way the subject matter was represented. As we have seen, plant-based subject matter changed

³⁷ *Diamond v. Chakrabarty* 447 U.S. 303, 313 (1980).

³⁸ Richard Doyle, *On beyond Living: Rhetorical Transformation of the Life Sciences* (Stanford, CA: Stanford University Press, 1997), 1.

³⁹ RAFI, 'Utility Plant Patents: A Review of US Experience (1985-July 1995)', *RAFI Communique*, (July/August 1995), 3.

considerably since the 1970s. At around the same time as utility patent protection was first allowed for traditionally bred plants, the subject moved inwards to include molecular-level innovations and outwards to include groups or classes of plants. It also expanded to include genetically modified transgenic plants. At the same time, the focus of attention shifted from plants to living (biological) subject matter and then below the surface to molecular subject matter. Within this biological milieu, gene patents were taken as the archetypical subject matter. The molecular gene or usually just simply the gene came to dominate discussions about plant-based subject matter. For all ostensible purposes, gene patents were treated as if they were a shorthand for molecular subject or genetic material matter more broadly.⁴⁰ In this sense, patent law mimicked the reductionist approach that had been adopted within molecular biology (albeit over a different time scale⁴¹) whereby biological systems were studied through their most elementary unit: the gene.

A second notable feature of molecular subject matter was that it saw the scope of the subject matter expand to include human genetic material. While when dealing with biological entities at the level of organism, it had not been possible even to discuss extending patent protection to humans, this changed when patent law shifted below the surface and biological subject matter was molecularised. Reinforced by ongoing efforts to map the genome of different biological organisms, which revealed that biological organisms (including humans) share a high degree of genetic similarity,⁴² there has been a tendency within patent law both doctrinally and in the accompanying commentary to treat all molecular level genetic material the same: questions about human DNA, for example, could be answered by discussions about the plant DNA, and vice versa. Thus, while the formal question the American Civil Liberties Union asked the Supreme Court in *Myriad Genetics* was whether human genes were patentable, the human dimension of the inquiry was quickly lost as the discussions broadened out to include discussions about leaves picked from plants in the Amazon, baseball bats carved from trees, animals, and genes generally.

A third characteristic of molecular subject matter that had an important bearing on how it was treated by patent law was in terms of the way the molecular gene was construed. In its early dealings with gene patents, patent law embraced a particular way of thinking about the molecular gene that continues to dominate today (albeit with some important changes). Building on a reductionist reading of genetic function, patent law presupposed that genes were solely responsible for the biological features of higher-level phenomena. Indeed as the Supreme Court's Justice Thomas

⁴⁰ See Patent & Trademark Office Society, 'Statement of the P.T.O.S. to the U.S.P.T.O. on Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, First Paragraph "Written Description" Requirement' (1999) 81 *Journal of Patent and Trademark Society* 140, 141–42.

⁴¹ While biologists at the beginning of the twentieth century shifted their focus of attention below the surface to explore organisms at the molecular or cellular level, this did not occur in the legal realm until much later.

⁴² Humans reportedly share 85% DNA with mice, 61% percent with the fruit fly, and around 50% with bananas.

said in the *Myriad Genetics* decision, ‘Genes form the basis for hereditary traits in living organisms’.⁴³ Patent law also ‘adopted a simplistic understanding of gene function’,⁴⁴ which parallels the central dogma of molecular biology that DNA produces RNA, which produces the proteins that are responsible for the characteristics of organisms.⁴⁵ As Jane Calvert said, ‘patenting fits nicely into this model because there is the assumption that if the function of the gene is discovered, then there will necessarily be a link to a protein, and that this protein will result in a trait. In this sense there is a parallel between the central dogma and the patenting requirements’.⁴⁶

As many commentators have noted, the decision to extend patent protection to cover genes was a seamless and non-controversial process. Indeed, unlike the controversy that greeted Chakrabarty’s patent over a living organism in the 1980s, the patenting of genes hardly attracted any attention at all.⁴⁷ A key reason for this was that genes were treated both epistemologically and ontologically as chemical compounds.⁴⁸ As the Federal Circuit said in *Amgen*, a ‘gene is a chemical compound, albeit a complex one’.⁴⁹ The longevity of this way of thinking about the gene can be seen from the comment by the editor of the *Journal of Heredity* in 1936 when discussing David Burpee’s attempt to patent the double nasturtium (that I discussed in the previous chapter) that a ‘gene for doubleness might conceivably be granted a “chemical patent” under the old [utility] patent laws (assuming that a gene is a chemical catalyst)’.⁵⁰ Given that by 1970s, patent law had been protecting chemical inventions for over 150 years, it is not surprising that once the decision had been made that genes were chemical compounds that the courts and the USPTO ‘hardly blinked at allowing patents on newly isolated genes’.⁵¹ Indeed it wasn’t until the 1990s, some 20

⁴³ *Assoc. for Molecular Pathology v. Myriad Genetics* 133 S.Ct. 2107, 2111 (2013).

⁴⁴ ‘It assumed in DNA patenting that a gene is analogous to a chemical compound, and has only one function’. Jane Calvert, ‘Patenting Genomic Objects: Genes, Genomes, Function and Information’ (2007) 16(2) *Science as Culture* 207, 208.

⁴⁵ *Ibid.*, 219. As we see below this ‘does not reflect the more sophisticated understandings of gene function provided by developments in genomics’.

⁴⁶ *Ibid.*, 213. It is assumed that if the function of a gene is disclosed in patenting then there is an unproblematic link to a utility.

⁴⁷ Rebecca Eisenberg, ‘Why the Gene Patenting Controversy Persists’ (December 2002) 77(12) *Academic Medicine* 1381. See Rebecca Eisenberg, ‘Patenting the Human Genome’ (1990) 39 *Emory Law Journal* 721; cf., Jeffrey S. Dillen, ‘DNA Patentability: Anything but Obvious’ (1997) *Wisconsin Law Review* 1024.

⁴⁸ Jane Calvert and Pierre-Benoît Joly, ‘How Did the Gene Become a Chemical Compound? The Ontology of the Gene and the Patenting of DNA’ (2011) 50(2) *Social Science Information* 157, 174.

⁴⁹ *Amgen v. Chugai Pharmaceuticals* 927 F.2d 1200, 1206 (Fed Cir 1991).

⁵⁰ Robert Cook, ‘What Is a “Basic Plant Patent?”’ (1936) *The Journal of Heredity* 213, 215.

⁵¹ Rebecca Eisenberg, ‘Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences’ (2000) 49 *Emory Law Journal* 783, 784–85 (The advantage of assuming that a ‘gene is a chemical compound, albeit a complex one’ was that ‘it provided a relatively clear point of departure for analyzing patent law issues presented by the first generation of biotechnology products produced through recombinant DNA technology’). Jane Calvert and Pierre-Benoît Joly, ‘How Did the Gene Become a Chemical Compound? The Ontology of the Gene and the Patenting of DNA’ (2011) 50(2) *Social Science Information* 157, 159. In 1988 the USPTO, the EPO, and the JPO issued a joint communique

or so years after the first gene patents had been granted, that there was anything like a public discussion about the validity and desirability of gene patents.⁵²

The first public discussions about gene patents were triggered in the early 1990s when a team from the National Institutes of Health led by Craig Venter applied for patents that claimed thousands of partial cDNA sequences. The function of these partial sequences, called ‘expressed sequence tags’, was not known at the time, but it was assumed that they had a functional role to play in the organism that would be discovered with further research. Unlike the challenge to Myriad Genetics’ breast cancer gene patents that took place in beginning of the twenty-first century, the debates over patents for expressed sequence tags were much more circumscribed. Indeed, while the debates and their subsequent resolution did see more onerous utility obligations imposed on gene patents,⁵³ they also confirmed that for patent law purposes genes were to be treated as chemical compounds and, as such, that there was nothing out-of-the-ordinary preventing them from being patented. With the utility-related hurdle overcome, patentees were able to return to their previous practice of patenting genes and related molecular material, a practice that remained unchallenged until the early part of the twenty-first century.

While the assimilation of genes within patent law as talisman for molecularised subject matter more generally may have been relatively straightforward, nonetheless the molecularisation of biological subject matter did bring about a number of changes. In particular, it changed the way that the law thought about the nature of the relationship between inventor and subject matter. Molecularisation also changed the way that the subject matter was described, as well as how it was judged and evaluated. I will look at each in turn.

MOLECULARISATION AND THE UNBUNDLING OF PLANT-BASED SUBJECT MATTER

As with other forms of biological subject matter, one of the problems that arose when people first thought about extending patent protection to plants was that it was not possible to reduce botanical innovations to first principles, at least in a form

explaining their position regarding the patentability of *Directive* technologies. The communique provides: ‘Purified natural products are not regarded under any of the three laws as products of nature or discoveries because they do not in fact exist in nature in an isolated form. Rather, they are regarded for patent purposes basis as other chemical compounds.’

⁵² In comparing ‘pure fibre when eliminated from the natural matric of the leaf or stalk or wood on which nature forms and develops’ and its impure natural form, it was held that the ‘chemical formula for this cellulose in all these variety of plants, I am advised, is the same’. *Ex parte Latimer* 46 OG 1638, 125, 126.

⁵³ The US Patent and Trademark Office (USPTO) adapted its requirement that a patent be useful in 2001 to say that rather than just demonstrating utility, a gene patent must demonstrate specific, substantial and credible utility. In practice this means that ‘a patent applicant provide a specific function for a DNA gene sequence’. The US Court of Appeals for the Federal Circuit declared ESTs were not patentable except ‘in the rare cases where the applicant showed a precise biological function sufficient to fulfil patent law’s utility requirement’. *In re Fisher* 2005 421 F.3d 1365.

that allowed them to be recognised and repeated by third parties at a distance. As we saw earlier, patent law adopted a two-fold strategy to deal with this problem. On the one hand, patent law allowed patentees to deposit and third parties to access physical manifestations of the patented invention. While in relation to biological subject matter this first occurred in relation to microorganisms, it was soon extended to plants and other biological organisms.

The second tactic that was used to allow patent law to accommodate the idiosyncrasies of biological subject matter related to the way the inventive process was configured. As we saw in Chapter 8, for the idiosyncrasies of plant innovations to be accommodated within intellectual property law the process of invention was reimagined. The starting point for this was the recognition of the positive role that nature plays in the creation of biological inventions. That is, patent law recognised that 'nature had done the heavy lifting, creating products and phenomenon with awesome capabilities'.⁵⁴ At the same time, patent law also reversed the roles played by the inventor and nature in the creation of the invention. While under the mechanical view of creation, nature provides the underlying material, which the human inventor then shapes into the resulting invention, with biological subject matter nature does the inventing, while the human agent is relegated to the task of identifying and reproducing nature's creations. In this context, nature and inventor operated like Siamese twins in the co-invention of biological inventions; neither was able to operate independently of the other to develop a novel invention.⁵⁵ It was only when the skill and effort of the two were combined that a biological invention's continued existence could be guaranteed. One of the consequences of this was that the subject matter and the inventor were bundled together both conceptually in terms of how the process of invention was configured and literally in terms of the physical manifestation of the invention deposited as part of the application process to ensure that third parties had access to the patented invention.

One of the first changes that occurred as a result of the molecularisation of biological subject matter was that the role that the human agent played in the inventive process was recast. Specifically, molecularisation changed the way patent law thought about how the inventor and nature interacted and the role that each played in the generation of biological inventions. While the role of the inventor working with plants had previously been limited to recognising and preserving nature's innovations, this began to change in the 1970s or thereabouts. The 1980 Supreme Court decision of *Diamond v. Chakrabarty* captured the change that took place in the way the process of invention was figured at the time. The case arose when General Electric attempted to

⁵⁴ Rebecca Eisenberg, 'Biotech Patents: Looking Backwards while Moving Forwards' (2006) 24(3) *Nature Biotechnology* 317.

⁵⁵ Burbank spoke of the breeder using his intelligence and skill in assisting Mother Nature. Luther Burbank, 'Prodigal Mother Nature' (June 1926) 134 *Scientific American* 365–66. 'Nature in such instances, unaided by man, does not reproduce the new variety true to type'. Joseph Rossman, 'Plant Patents' (1931) 13 *Journal of the Patent Office Society* 7, 18.

file a patent for a genetically modified bacteria (*Pseudomonas putida*) made by one of its employees, Ananda Chakrabarty. While in working with the *Pseudomonas* bacteria Chakrabarty had clearly made use of nature, there was no doubt in the litigation that in modifying the bacteria so that they could break down crude oil that Chakrabarty had created the artificial organism. Instead of speaking about how Chakrabarty had worked with nature to co-invent the new artificial bacteria, the focus was on evaluating the changes that Chakrabarty – the genetic engineer – had made to nature.

What occurred here was a subtle but important change in the way the inventive process was configured. While previously nature and inventor had been inextricably intertwined, with molecularization the inventor was unbundled from the subject matter. In minimising the role of nature-as-inventor while elevating the role of the human inventor, patent law fundamentally changed the way that the process of invention was presented. As a result, there was no longer any discussion of co-invention or of nature and inventor working side-by-side to create biological inventions. Instead, the focus was now on the relationship between inventor and nature, and the extent and manner in which the inventor had changed nature: an issue I return to below. One of the consequences of this was that the process of biological invention was recast so that it was comparable to the figure of invention used for mechanical inventions. As a result, the role of the biological inventor was now comparable to the structural chemist or the mechanical engineer.

While the unbundling of computer-related subject matter that started in the 1970s was instigated by legal interventions, the unbundling of biological (now molecularised) subject matter was a consequence of changes in the way biological innovations were seen. While for much of the twentieth century some forms of biological innovations, such as the development of new microbiological-based inventions, were characterised as scientific endeavours and treated as such, others, such as the breeding of new plants, were still seen as artisanal non-scientific practices. This began to change in the 1970s. In part this was because plant breeding was recast as a more-scientific activity. As one commentator noted, 'Now that plant innovation has become so much a matter of biochemistry and molecular genetics – so high-tech one might say – its structure and development has come to resemble that of other high-tech industries.' While many of the pejorative views about plant breeding persist, this has been masked by the shift to a molecular subject matter, which now stands in for plant subject matter. Whatever criticisms might be made of molecular biology, there is little doubt of its scientific credibility nor about the role that molecular biologists play in the generation of biological inventions.

While Chakrabarty had managed to modify nature to create something new and his status as creator had been elevated to something akin to a mechanical inventor, he was still unable to persuade nature to disclose its secrets; he was unable to reduce the design or principle of the invention to a written form so that third parties could recreate his discovery at a distance. To deal with this problem and to ensure that the invention satisfied the requirements of enabling disclosure, physical samples of the

invention were placed in publicly accessible locations. As Chakrabarty's patent states: 'Microorganisms prepared by the genetic engineering processes described herein are exemplified by cultures now on deposit with the US Department of Agriculture.'⁵⁶ In this sense *Chakrabarty* and many of the decisions that applied its logic to other types of biological organisms spanned two worlds. It is a decision firmly rooted in the physical, empirical patent law of the past century while, at the same time, a decision that marks the beginning of the shift to a dematerialised subject matter. To better understand the nature of this change, we need to look at the impact that molecularization had on the way biological subject matter was represented.

REPRESENTING MOLECULAR SUBJECT MATTER

One of the challenges that often arise in accommodating new types of subject matter in patent law is working out how new inventions are to be represented so that they can meet the various demands that the law makes of them. This includes ensuring that inventions are distinct enough for them to be examined, judged, and evaluated, and that third parties are able to repeat the patented invention without undue effort. The techniques used to represent plant-based subject matter to achieve these ends changed considerably over the twentieth century. After using the written description and the drawing of the plant in the patent to build a virtual-legal plant, intellectual property law came to rely on the deposit of the physical manifestation of the protected plant. As the subject matter was molecularised and attention shifted from the surface of plants to the interior molecular world, the way subject matter was presented to the law for scrutiny also changed.

In early molecular patents, gene-based inventions were expressly presented as chemical compounds. For example in what has been described as 'likely the first gene patent',⁵⁷ which was granted to Jack J. Manis, a researcher at the Upjohn Company in Michigan, for a patent 'claiming a purified version of a naturally occurring plasmid found in *Streptomyces spinosus*' (and deposited at the NRRL), the invention was described in the patent as a 'novel chemical compound, essentially pure plasmid pUC6, which is obtainable from a biologically pure culture of the microorganism'.⁵⁸ While the chemical reading of the gene prevailed until the 2013 Supreme Court decision *Association for Molecular Pathology v. Myriad Genetics*, at least in terms of how genes were judged, molecular subject matter began to give way

⁵⁶ Ananda M. Chakrabarty, 'Microorganisms Having Multiple Compatible Degradative Energy-Generating Plasmids and Preparation Thereof' US Patent No. 4,259,444A (31 March 1981).

⁵⁷ Jacob S. Sherkow and Henry T. Greely, 'The History of Patenting Genetic Material' (2015) *Annual Review of Genetics* 161, 166.

⁵⁸ Jack J. Manis, 'Plasmid and Process of Isolating Same' US Patent No. 4,273,875 (16 June 1981), Abstract. See also H. Yanagawa et al., 'Molecule Assigning Genotype to Phenotype and Use Thereof' US Patent No. 72,087 A1 (13 June 2002), Figure 3 (chemically-modified portions of the 3'-terminal ends of nucleic acid portions).

to more biological modes of representation from the outset. As is often the case with innovations in patent law, the techniques developed to describe molecular subject matter were initiated by patentees and subsequently endorsed by the Patent Office and the courts. While patentees used a range of different techniques to describe the (non-chemical) biological gene, three stand out.

While early gene-based inventions were described by patentees (and accepted by the courts) as types of chemical compounds, during this transitional period they were not represented using chemical nomenclature or structural formula (as chemical patents were). Instead, patentees employed a range of experimental techniques to represent their gene-based inventions. These included gel electrophoresis diagrams (Figure 9.1),⁵⁹ schematic representations (Figure 9.2), and cleavage maps which represent the sites where restriction enzymes cleave a DNA molecule (Figure 9.3).⁶⁰

A second technique that patentees used to ensure that molecular subject matter met the representational requirements of patentability was to deposit biological material at public depositories such as the American Type Cultural Collection or the Northern Regional Research Laboratory of the US Department of Agriculture.⁶¹ In some cases, patentees deposited biological source material such as bacteria, along with instructions for how the protected DNA (gene) could be extracted from that material using well-known techniques.⁶² More often, however, patentees deposited plasmids containing genes typically frozen in liquid nitrogen to preserve them at public depositories.⁶³

The practice of depositing biological material to describe and enable molecular inventions was formally recognised by the US Patent Office in the late 1980s when in making changes to accommodate biotechnological inventions, the Patent Office introduced new rules dealing with the deposit of biological materials.⁶⁴ While the

⁵⁹ The poor quality of this image, which the USPTO says is the best that is available, raises interesting questions about the effectiveness of the patent in disclosing the invention.

⁶⁰ Jack J. Manis, 'Plasmid and Process of Isolating Same' US Patent No. 4,273,875 (16 June 1981), Abstract. See also H. Yanagawa et al., 'Molecule Assigning Genotype to Phenotype and Use Thereof' US Patent No. 72,087 A1 (13 June 2002).

⁶¹ See USPTO, 'Deposit of Biological Material' 37 CFR 1.801–1.825 (Added, 54 FR 34880, 22 August 1989); USPTO, Manual of Patent Examining Procedure, 'The Deposit Rules', section 2402.

⁶² Jack J. Manis, 'Plasmid and Process of Isolating Same' US Patent No. 4,273,875 (16 June 1981) (the microorganism used to produce the claimed plasmid was deposited at the Northern Regional Research Laboratory of the US Department of Agriculture as NRRL 11439). Corina Herrnstadt et al., 'Cloning and Expression of *Bacillus thuringiensis* Toxin Gene Toxic to Beetles of the Order Coleoptera' US Patent No. 4,853,331A (1 August 1989).

⁶³ See *In re Lundak* 773 F.2d 1216 (Fed. Cir. 1985). Because of the uncertainties of reproducibility that inhere in such processes, at least in the present state of biotechnology, this invention is of the class covered by the deposit requirement'. Berge Hampar, 'Patenting Recombination DNA Technology: The Deposit Requirement' (1985) 67(11) *Journal of the Patent and Trademark Office Society* 569, 580.

⁶⁴ As the MPEP explained in introducing the 1990 Rules since most of the provisions of the rules reflect policy and practice existing prior to 1 January 1990, little change in practice or burden on applicants for patent and patent owners relying on the deposit of biological material has occurred. 2402 The Deposit Rules.

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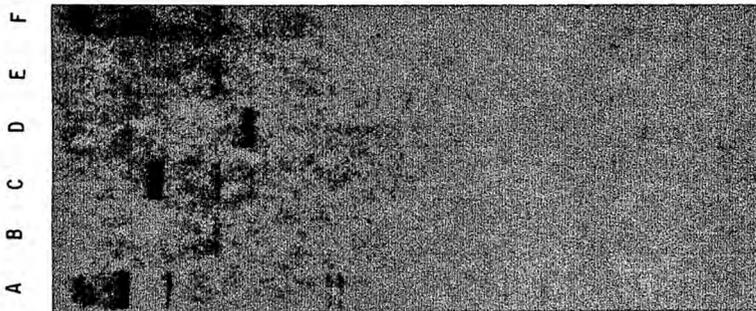
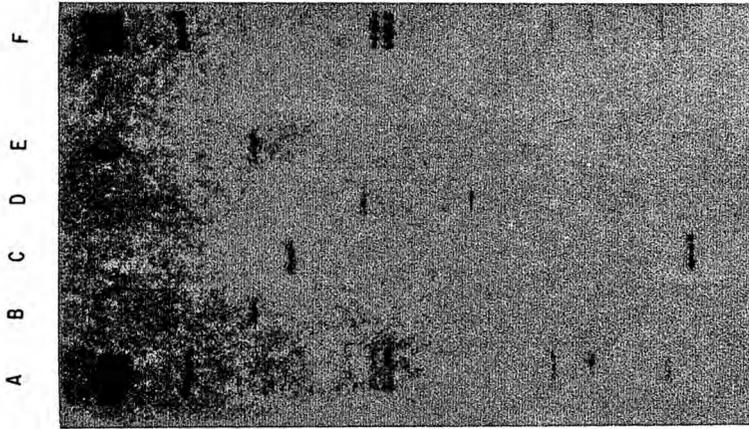


FIGURE 9.1 Autoradiogram of gel electrophoresis results
Howard Goodman, John Shine and Peter Seeberg, 'Purification of Nucleotide Sequences Suitable for Expression in Bacteria' US Patent No. 4,407,948 (4 Oct 1983).
Courtesy of the United States Patent and Trademark Office.

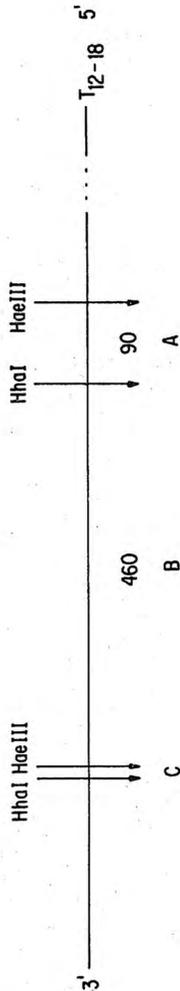


FIG. 2

FIGURE 9.2 Schematic representation of the nucleotide sequence Howard Goodman, John Shine and Peter Seeburg, 'Purification of Nucleotide Sequences Suitable for Expression in Bacteria' US Patent No. 4,407,948 (4 Oct 1983). Courtesy of the United States Patent and Trademark Office.

United States Patent [19]

[11]

4,273,875**Manis**

[45]

Jun. 16, 1981[54] **PLASMID AND PROCESS OF ISOLATING SAME**[75] Inventor: **Jack J. Manis**, Portage, Mich.[73] Assignee: **The Upjohn Company**, Kalamazoo, Mich.[21] Appl. No.: **17,812**[22] Filed: **Mar. 5, 1979**[51] Int. Cl.³ **C12N 1/20**[52] U.S. Cl. **435/253; 435/91; 435/317; 435/820; 435/886**[58] Field of Search **435/91, 317, 820, 253**[56] **References Cited****PUBLICATIONS**

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Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Roman Saliwanchik[57] **ABSTRACT**

A novel chemical compound, essentially pure plasmid pUC6, which is obtainable from a biologically pure culture of the microorganism *Streptomyces spinosus* biotype 23724a, NRRL 11439. The pUC6 plasmid is useful as a cloning vehicle in recombinant DNA work. For example, using DNA methodology, a desired gene, for example, the insulin gene, can be inserted into pUC6 and the resulting plasmid can then be transformed into a suitable host microbe which, upon culturing, produces the desired insulin.

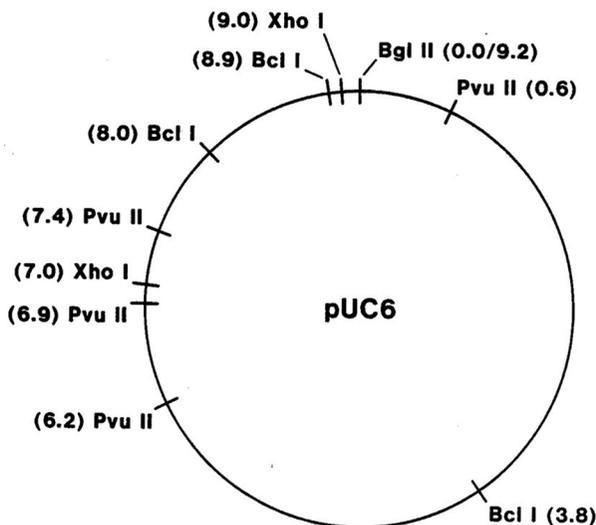
5 Claims, 1 Drawing Figure

FIGURE 9.3 Circular plasmid diagram

Jack Manis, 'Plasmid and Process of Isolating Same' US Patent No. 4,273,875 (16 June 1981). Courtesy of the United States Patent and Trademark Office.

Patent Office rules had previously been limited to the deposit of microorganisms, this was changed in 1988 to encompass ‘microorganisms and other biological material’.⁶⁵ This was followed in 1990 by the introduction of new rules for the ‘deposit of biological materials for patent purposes’.⁶⁶ For the purpose of the new rules, ‘biological material’ was defined to include material that was capable of self-replication either directly or indirectly after insertion into a host. Representative examples include bacteria, fungi, yeast, algae, protozoa, eukaryotic cells, cell lines, hybridomas, plasmids, viruses, plant tissue cells, lichens, and seeds.

Importantly, while plasmids – which are small, circular molecules of DNA that are able to replicate independently – were not included in the 1986 draft rules, they were added to the final rules promulgated in 1990. In making these changes, the US Patent Office formally recognised the deposit of plasmids as a way of ensuring that gene patents met the requirements of written description and enablement. In doing so, the patent office drew upon the scientific practice of using plasmids as tools (or vectors) to clone, transfer, and manipulate genes. This was made possible by the fact that researchers are able to insert DNA fragments or genes into a plasmid vector, creating a so-called recombinant plasmid. This plasmid can be introduced into a bacterium by way of the process called transformation. Then, because bacteria divide rapidly, they can be used as factories to copy DNA fragments in large quantities.

While the courts readily accepted that the deposit of a biological sample allowed third parties to repeat the patented invention (and thus ensured that that the disclosure was enabling), there were some lingering doubts about whether it ensured that patents satisfied the written description requirement.⁶⁷ In 2002, this question was addressed by the Federal Circuit in two decisions, *Enzo I* and *Enzo II*. The patent in dispute in these decisions was for nucleic acid (DNA) probes that were used to detect the bacteria that cause gonorrhoea, *Neisseria gonorrhoeae*. Rather than including either a structural description or the genetic sequences of the probes in the specification, the patent simply referred to the genetic material (the DNA probes) that Enzo had deposited at the American Type Culture Collection.⁶⁸ After being sued by Enzo for infringement, the defendants (Gen-Probe) argued that Enzo’s patent did not meet the written description requirement and as such that it was invalid.

In a surprising decision, the District Court of Southern New York in *Enzo I* agreed with the defendants that while the deposit made at the American Type Culture

⁶⁵ USPTO, *Manual of Patent Examining Procedure*, 5th edition, rev 8 (May 1988), 608 (1)(p)(C).

⁶⁶ U.S. Department of Commerce, Patent and Trademark Office, ‘Deposit of Biological Materials for Patent Purposes; Advance Notice of Proposed Rulemaking’ (1987) 52(174) *Federal Register* 34080–93. Final rules for deposits of biological materials for patent purposes was published in the *Federal Register*, 54 Fed. Reg. 34864 (22 August 1989) and in the *Official Gazette*, 1106 OG 37 (12 September 1989).

⁶⁷ Dennis J. Harney and Timothy B. McBride, ‘Deposit of Biological Materials in Support of a US Patent Application’ in (ed) A. Krattiger et al., *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices*, Vol. 1 (Oxford: MIHR and Davis, CA: PIPRA, 2007), sect 10, ch 10.10, para 1.2.

⁶⁸ The patent also described the three probes in terms of function. Given that it was accepted that a description of genetic material by function alone was insufficient, the question for the court was whether in depositing the probes at the ATCC Enzo had met the written-description requirement.

Collection ensured that the patent met the requirement of enabling disclosure, it did not satisfy the written description requirement and as such that the patent was invalid.⁶⁹ The court in *Enzo I* said that even though an invention had been reduced to practice and embodied in a physical form, it was still possible that it might fail to meet the written description requirement if the invention was not described in sufficient detail in the patent specification. As the court said: 'What the deposit does, in addition to enabling the practice of the invention, is tell the public where a sample of the invention can be found so that the invention can be carried out when the patent expires or used in other ways that may not infringe the patent'.⁷⁰ The problem for the patentee, however, was that the court held that this was 'not describing the invention in the patent ... the deposit here essentially contains the invention, and the invention must be described more than by stating that it exists in a depository'.⁷¹

Three and a half months later, in *Enzo II* the Federal Court readdressed the question of whether the written description requirement could be satisfied by the deposit of genetic material.⁷² To the relief of the biotech industry, the court reversed its earlier ruling and held that the deposit of a biological sample in a public repository could fulfil the written description requirement. This was on the basis that while 'deposit in a public depository most often has pertained to satisfaction of the enablement requirement', the court 'concluded that reference in the specification to a deposit may also satisfy the written description requirement with respect to a claimed material'.⁷³ Specifically, the court agreed with *Enzo* that 'reference in the specification to deposits of nucleotide sequences describe those sequences sufficiently to the public for purposes of meeting the written description requirement'.⁷⁴ In doing so *Enzo II* affirmed the long-held belief that a biological deposit could be used to satisfy the written description requirement.

The practice of depositing biological material at public depositories to satisfy the patentability requirements for molecular subject matter shares similarities with the deposit of chemical compounds discussed earlier. Despite this, there was no question in either *Enzo I* or *II* that the DNA probes deposited at the American Type Cultural Collection were biological materials.⁷⁵ While this may simply be a consequence of

⁶⁹ *Enzo Biochem Inc. v. Gen-Probe Inc.* 285 F.3d 1013 (Fed. Cir. 2002) (*Enzo I*) (2 April 2002).

⁷⁰ *Ibid.*, 1023.

⁷¹ *Ibid.*

⁷² *Enzo Biochem Inc. v. Gen-Probe Inc.* 296 F.3d 1316 (Fed. Cir. 2002) (*Enzo II*) (15 July 2002).

⁷³ *Ibid.*, 1326.

⁷⁴ *Ibid.*

⁷⁵ As Chief Justice Louries said in *Enzo II*, in 'light of the history of biological deposits for patent purposes, the goals of the patent law, and the practical difficulties of describing unique biological materials in a written description' a 'reference in the specification to a deposit in a public depository' of genetic material (purified chromosomal DNA) 'which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112'. That is, 'a deposit may be necessary, where 'the invention involves a biological material and words alone cannot sufficiently describe'. *Ibid.*, 1325.

a lack of appreciation for the historical role that chemical specimens played in patent law, it also reflects a shift to a (non-chemical) biological understanding of genes. This was evident in the way the Patent Office approached the question of how genes were described. In explaining what were soon to become the rules for deposit of biological materials the Commissioner of Patents, Donald J. Quigg, said: 'Chemical compounds, no matter how important or defined their biological activity, are not regarded as biological material within the scope of these regulations.' As a result, 'materials such as proteins, enzymes, or other complex organic materials need not be deposited where the written description alone is adequate to enable those skilled in the art to make and use the claimed invention'.⁷⁶

Although the deposit of biological material as a way of ensuring that gene patents met the requirements of written description and enablement is usually seen as a continuation of a practice that began with microorganisms in the 1930s and expanded over time to include other biological material, there are important differences. In particular, while biological materials such as microorganisms, seeds, and plant tissue were treated as if they were coextensive with (or were) the patented invention, molecular subject material was different. This was because unlike other types of biological deposits that were treated as if they were the invention, deposited plasmids housed the invention. As the court said in *Enzo I*, 'the deposit here essentially contains the invention'.⁷⁷ In this sense, it was not so much that the glass vials deposited at the American Type Cultural Collection contained frozen samples of the invention, so much as that the invention was located within the frozen physical material within the vials.

While the courts in *Enzo I* and *II* may have disagreed about what an applicant needed to do to satisfy the written description requirement,⁷⁸ they did agree on what and where the invention was; namely the way that the chemical compounds (nucleotides) expressed as the alphabetic symbols of As, Ts, Cs, and Gs were ordered within the deposited DNA substances. The difference between *Enzo I* and *II* was what the courts expected of the applicant in relation to the sequence information hidden within the frozen material in the glass vials. While the court in *Enzo II* was satisfied that because the deposited materials could, if someone wanted, be sequenced and the order of the chemical compound determined that the written description requirement was satisfied (that

⁷⁶ In 1988, PTO published proposed rules for deposit of biological materials for patent purposes U.S. Department of Commerce, Patent and Trademark Office, 'Deposit of Biological Materials for Patent Purposes; Notice of Proposed Rulemaking' (1988) 53(194) *Federal Register* 39420–32. 'Chemical compounds are capable of description at least through the identification of starting materials and explanation of appropriate procedures used in making the compounds. It must not require undue experimentation in order to make or use the chemical compound from the written description in the patent application'.

⁷⁷ *Enzo Biochem Inc. v. Gen-Probe Inc* 285 F.3d 1013, 1023 (Fed. Cir. 2002).

⁷⁸ The defendants also assert that the expert's opinion that the deposited genetic materials could actually have been sequenced did not cure the actual failure of the inventors to identify them by some distinguishing characteristic such as their structure.

is, that the disclosure inherently described the claimed nucleotide sequences), this was not enough for the court in *Enzo I* who expected the applicants to have actually sequenced the deposited materials and included the resulting sequence information in the patent.

In so far as the *Enzo* decisions saw the legal focus of attention shift from the material DNA substance towards the sequence information contained within that physical material, they mark a move towards a more dematerialised subject matter. Despite this, the subject matter in the *Enzo* decisions was still closely intertwined with the physical material deposited at the American Type Cultural Collection. (At the time, genes were also still seen ontologically as chemical compounds.) The process of dematerialisation took on a life of its own, however, with the third technique used by patentees to ensure that molecular subject matter met the representational requirements of patentability.

The third technique that patentees used to ensure that molecular subject matter satisfied the representational requirements of patentability was to describe the specific way that chemical molecules were organised within an organism: that is, they included the sequence information for the subject matter in the patent. Sequences took one of two forms depending on what was being described. In the case of claims for deoxynucleic acid (DNA), this information consists of the way the four chemical building blocks or nucleotides ('bases') that make up DNA were ordered ('nucleotide sequence information'). Specifically, it consists of the particular way that the four nucleotide building blocks of adenine, thymine, cytosine, and guanine (which are represented by the alphabetical letters A, T, C, and G) that make up a gene are ordered. In the case of proteins, the sequence information consists of the particular way that the twenty different amino acids (designated with either single or triple letter codes, such as the use of 'V' or 'val' to represent the amino acid valine) that are joined to form proteins are ordered ('amino acid sequence information'). In both cases, the use of sequence information to represent the molecular gene built on the discovery that the particular way nucleotides (within DNA) and amino acids (within protein) were ordered (their sequence) determined what the gene did.⁷⁹ Once they were identified, sequences were written out in a linear ticker-tape form as a series of As, Ts, Cs, and Gs in the case of DNA or in the case of amino acids as a series of single or triple letter codes (see Figure 9.4).⁸⁰

While scientists and breeders have long been able to stimulate change within biological subject matter, until the mid-part of the twentieth century, they were not in a position where they could explain the reasons for those changes. Because they could not explain the internal workings of biological subject matter, patentees had to focus on the external (phenotypical) features of biological organisms or to rely upon the

⁷⁹ The order or sequence of these bases determines what biological instructions are contained in a strand of DNA.

⁸⁰ John Baxter et al., 'Adrenocorticotropin-Lipotropin Precursor Gene' US Patent No. 4,322,499 (30 March 1982).

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15961  GATACCATGCAACATAAACCCTGATAAAGCTCCAGCAGGAAATGGCTGAACTAGAAGCTGTG
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16621  CCTTCTGCTGACAAGTTTGGAGTGTCTGCAGATAGTTCTACCAGTAAAAATAAAGAAC
16681  AGGATGGAAAAGtaagaacaactcaatgtaaaagatcgtgtgttatcagacattcttatt
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17161  agtgagtggtgtagatctcgnctcactgcaacctcgtctcccaggtccaagcaatttct
17221  ctgcctcagctcccagtagctgagatatacaggcgcagaccacacccagctactga
17281  cctgctctttvvvvvvvvvvaacagctgggagataggtgcctcagaccaaagccat
17341  gtatatgtcaaacctgacatattggcaggcaacatgaatccagactcttaggctgtcat
17401  ggggctctttttggcagtcattctgatctctctgacatgagctgtttcatttatgct
17461  ttgctgcccaggaagtagatttgccttcaacaattggtyggcaggttttctcctcctc
17521  catttatcttcttagtTCATCCCCTTTAAATGCCATCATTAGATGATAGGTGGTACAT
17581  GCACAGTTGCTCTGGGAGTCTTCAGAAATAGAAACTACCCTCTCAAGAGGAGCTCATTAA
17641  GGTTTGATGTGGAGGAGCAACAGCTGGAAGAGTCTGGGCCACAGATTGACGGAAAC
17701  ATCTTACTTGCCAAGGCAAGATCTAGGtaaatatttcatctgctgtattggaacaaact
17761  ytgattttactctgaatcctacataaagatattctggtaaaccaacttttagatgacta
17821  gtctatcatggacactttgttatacttaataagccactttagaaaaatagctcaagt
17881  gttaatcaaggtttacttgaaaaattatgaaactgttaatccatctataatttaattaat
17941  ggtttaaactaatgatattgaggatgwgaggctktygtgtactctamatgtattttca
18001  ggccagcagatagtggtcagcctggtaataccagtaaycmrgagcccaggcagggtgga
18061  gccagctgaggtcaggagtccaagactgtctggcacaatgggngaaacctgctctc
18121  tcttcaaaaaanacaaaaaaataactgggttgtgcttagtgnatgcccgnatccta
18181  gttnttcttnggggttagggaggagatcaenttggacccccagggggggggggggggng
18241  agcaggncaaaaacnagcccagctggggtggaagggaagcccactcnaaaaaanntnv
18301  vvvvvvvvvvtttttaggaacaagctactttggatttccaccaacactgtattcat

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FIG. 10F

FIGURE 9.4 Myriad patent sequence listing Mark Skolnick et al., '17Q-Linked Breast and Ovarian Cancer Susceptibility Gene' US Patent No. 5,747,282 (5 May 1998). One page of the genomic sequence for BRCA1 used in the patent application. The lower-case letters denote intron sequence (non-coding) while the upper-case letters denote exon sequence (coding). Courtesy of the United States Patent and Trademark Office.

deposit of (physical) samples of their inventions when they were describing their creations. The situation began to change as advances in molecular biology allowed scientists to unlock some of nature's secrets. As a result of a series of scientific and technical developments that began in the 1960s, there was a growing sense in which scientists had discovered the book of life: all that was left to be done was to find the relevant sequence information and everything else would follow. As John Toy said of the human genome project: 'We have discovered the human alphabet – what we now have to do is put the letters in the right order and make a sentence. Only when all of that is done shall we have the book of life to read'.⁸¹

One of the consequences of these changes was that prevision was no longer seen as a problem: there was a sense in which scientists were now in a position where they could explain why things had happened, why it was that a modified plant behaved in a particular way, why it fruited early, or why it was able to survive with less water. As the US Patent Office wrote in 1999, while 'the state of DNA inventions was once unpredictable, today the state of the art has advanced to the point where isolating nucleotide sequences is routine to persons skilled in the art, and therefore predictable'.⁸² Importantly, scientists were also now in a position where they could reduce biological subject matter to a written form that ensured that the subject matter could be identified and that third parties could replicate the invention at a distance. As a result, it was now possible to trust the immaterial representation of biological subject matter; it was no longer necessary for patentees to resort to the physical manifestation of the intangible or to focus on the external features of an organism when representing their innovations.

While there may initially have been problems with the accuracy of the sequence data in some patents,⁸³ there was never any doubt cast over its efficacy in representing molecular inventions. Sequence information first appeared in patents in the early 1980s.⁸⁴ However, the cost and difficulty of sequencing meant that this was relatively rare. As trust in sequence information grew and sequencing became cheaper, faster, and more accurate, so too did confidence in the ability of sequence data to represent the molecular subject matter. Initially, risk adverse patentees would submit both a physical deposit of the DNA and sequence information.⁸⁵ By the 1980s, however, there was a growing acceptance that in relation to a 'less complex life-form, such as a DNA

⁸¹ John Toy, *Medical Director of the UK's Imperial Cancer Research Fund* (26 June 2000). As cited in Judith Root, *The Poetics of DNA* (Minneapolis: University of Minnesota Press, 2007), 84.

⁸² See Patent & Trademark Office Society, 'Statement of the P.T.O.S. to the U.S.P.T.O. on Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, First Paragraph "Written Description" Requirement' (1999) 81 *Journal of the Patent and Trademark Society* 140, 141–42.

⁸³ For example see Myles Jackson, *The Genealogy of a Gene: Patents, HIV/AIDS, and Race* (Cambridge, MA: The MIT Press, 2015).

⁸⁴ For early examples see John Baxter et al., 'Adrenocorticotropin-Lipotropin Precursor Gene' US Patent No. 4,322,499 (30 March 1982); Graeme Bell et al., 'DNA Transfer Vector and Transformed Microorganism Containing Human Proinsulin and Pre-proinsulin Genes' US Patent No. 4,431,740 (14 February 1984).

⁸⁵ Berge Hampar, 'Patenting Recombination DNA Technology: The Deposit Requirement' (1985) 67(11) *Journal of the Patent and Trademark Office Society* 569, 608.

molecule (i.e., gene)' that 'a written description absent a deposit should suffice ... so long as the specification includes the nucleotide sequence or a procedure for isolating the molecule from genomic DNA'.⁸⁶ It was also recognised that 'sequences claims may be enabled' ... 'merely by stating the sequence, rather than by deposit of the host organism'.⁸⁷

While applicants may not have been under a formal obligation to use sequence data to represent molecular subject matter,⁸⁸ nonetheless it quickly became a defacto standard that was widely used in gene patents.⁸⁹ The use of sequence information to represent molecular subject matter was also endorsed by the courts. As the Federal Circuit said in *Eli Lilly* in 1997, adequately describing a cDNA (synthetic DNA) in a patent specification 'requires the kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA'. As the Federal Circuit said in *Chiron Corp v. Abbott Laboratories*, 'every case in which it analysed the conception of an invention involving DNA encoding a human protein, the Federal Circuit has held that an inventor does not have knowledge of the specific chemical structure (and thus conception) until the inventor knows the nucleotide sequence of the relevant DNA and has a viable method for obtaining it'.⁹⁰

Although patentees and the courts readily embraced the use of sequence information as a way of satisfying the representational requirements of patentability, the Patent Office experienced a number of problems. The reason for this was that while there might have been consensus by the 1980s that a gene patent that incorporated information about the way the nucleotides and amino acids were ordered satisfied the representational requirements of patentability, there was no agreement as to how that sequence information should be presented nor about the symbols that should be used to refer to the nucleotides and amino acids. This lack of uniformity created a number of problems for the Patent Office, which was concerned that undisciplined sequence data was slowing down the examination process (leading to a backlog of biotech patents at the end of the 1980s), increasing the cost, and undermining the effectiveness of the examination process. The lack of standardisation also made it difficult to compare what had been claimed in a patent application with what had been disclosed in the prior art, not least because it was impractical for an examiner searching a particularly lengthy sequence in a nonconforming format to accurately key the query necessary to search the sequence in a computerized

⁸⁶ *Ibid.*

⁸⁷ Iver Cooper, *Biotechnology and the Law* (July 2022 Update), § 5:67.

⁸⁸ 'Describing the complete chemical structure, i.e., the DNA sequence, of a claimed DNA is one method of satisfying the written description requirement, but it is not the only method ... Therefore, there is no basis for a per se rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequence disclosed'. USPTO, *Guidelines for Examination of Patent Applications under the 35 U.S.C. 112 Written Description Requirement* (2001), 41.

⁸⁹ John M. Lucas, 'The Doctrine of Simultaneous Conception and Reduction to Practice in Biotechnology' (1998) 26(4) *AIPLA Quarterly Journal* 381, 481.

⁹⁰ *Chiron Corp v. Abbott Laboratories* 902 F Supp 1103, 1120 (ND Cal 1995).

search. Faced with different formats, examiners had to convert the sequence data as it appeared in patent applications into formats that were consistent with those appearing in the prior art to evaluate the patentability of the inventions claimed in a patent application. These problems were compounded by the complexity and volume of the data that the Patent Office had to deal with. There were also concerns about the accuracy of the sequence data that appeared in the printed patent records. The reason for this was that patent printing procedures used at the time meant that the Patent Office could not simply cut and paste sequence information from an application into the official records. Instead, the sequence data had to be rekeyed from the material submitted by the applicant. Not surprisingly, this often resulted in the printing of erroneous sequences.

To address these problems, the Patent Office made a number of changes in the late 1980s. As well as changing the way biotechnological inventions were classified, the Patent Office also introduced a special biotechnology examining division (Group 180) equipped with a specialised computer system for searching sequences of amino acids and nucleotides.⁹¹ In 1990, the Patent Office introduced rules for '*Patent Applications Containing Nucleotide Sequence and/ or Amino Acid Sequence Disclosures*'. The rules were part of an ongoing coordinated effort between the private sector and the European, Japanese, and US Patent Offices to standardise the use of symbols and the format for sequence information in order to facilitate the exchange and use of published data.⁹² The rules set out a standardised format that had to be used when nucleotide and amino acid sequence data were submitted as a part of a patent application. The rules also specified the symbols that applicants had to use as shorthand for nucleotides and amino acids. The standardized format, which was mandatory, was needed to 'permit proper examination and processing of such applications and to improve quality and efficiency of the examination process, promote conformity with usage of the scientific community, and improve dissemination of sequence data in electronic form'.⁹³ While in drafting the sequence rules the Patent Office consulted with nucleotide and protein sequence data libraries generally, the rules were based on the data format and forms used at the GenBank Sequence Database (the open access collection of publicly available nucleotide sequences and their protein translations maintained by the National Center for Biotechnology Information). As the Patent Office said, the standardised format was as close to the GenBank format as the Office could come while accommodating the special requirements of patent applications.

⁹¹ Patent and Trademark Office, Biotechnology Examining Group, 'Patent and Trademark Office Creates New Biotechnology Examining Group' (May–June 1988) 7(3) *Biotechnology Law Report* 203.

⁹² 'Requirements for Patent Applications Containing Nucleotide Sequence and/ or Amino Acid Sequence Disclosures' (1 May 1990) 55(84) *Federal Register* 37 CFR Part 1, 18230.

⁹³ 'Requirements for Patent Applications Containing Nucleotide Sequence and/ or Amino Acid Sequence Disclosures' (Tuesday, 2 May 1989) 54(83) *Federal Register* Proposed Rules, 180671.

Applicants were also encouraged to use sequence identification numbers in the form SEQ ID NO: X as a shorthand way of claiming their inventions.⁹⁴ In addition to providing a paper-based version of the sequence information, applicants were also required to submit a copy of the sequence listing in computer readable form on floppy discs. The computer readable form was entered into the Patent Office's database for searching nucleotide and amino acid sequences. The electronic database enabled the US Patent Office to exchange patented sequence data in electronic form with the European and Japanese Patent Offices. To build a comprehensive database that allowed the Patent Office to properly assess the prior art, applicants had to provide sequence information for all sequences mentioned in an application, whether claimed or not. Sequence listings were also disclosed as part of the published patent application or issued patent. They were also provided to the National Center for Biotechnology Information for inclusion in their GenBank sequence database.⁹⁵

While the 1990 sequence disclosure rules resolved many of the problems that had arisen with sequence information, a number of problems remained: mostly associated with the requirement that applicants had to submit sequence data in both paper and a computer readable form. The continued use of paper-based disclosure created a number of logistical problems for the Patent Office. One reason for this was that the number of sequence listings that were being lodged at the Patent Office increased by over 100% per year in the 1990s.⁹⁶ Moreover, while early sequence listings were sometimes only 40 or so base pairs long,⁹⁷ by 1995 individual sequence listings of over a million base pairs were being lodged. Paper-based sequence listings of this size were not only unable to be searched by the human eye, they were also heavy, cumbersome, and voluminous. For example, in 1990 the Patent Office received a submission containing twenty-two thousand sequence listings, which required eight boxes of paper to print. The size and weight of paper print-outs of sequence listings, which were often thousands of pages in length and over a foot thick, meant that the patent office needed specialised carts to carry the applications to examiners for processing. Storage was also a problem. As the Patent Office complained: 'Considering that the growth rate of sequence listings is such that they now approach one foot per application, this would require one thousand linear feet of shelf space. With each rack holding twenty-four linear feet, the PTO would need

⁹⁴ 'Response to and Analysis of Comments, Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures' (Tuesday, 1 May 1990) 55(84) *Federal Register* 37 CFR Part 1, 18230. The final rules were published in the *Federal Register* at SS FR 18230 (1 May 1990) and in the *Official Gazette* at 114 OG 29 (15 May 1990) 18235. The sequence rules went into effect on 1 October 1990.

⁹⁵ 'Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures' (Monday, 22 April 2019) 84(77) *Federal Register* Notices, 16653.

⁹⁶ By 2002, the USPTO was processing more than 21,000 sequence listings per year. Robert Wax and James Coburn, 'Sequence Rule Compliance' (2003) 22 *Biotechnology Law Report* 397, 400.

⁹⁷ John Baxter et al., 'Adrenocorticotropin-Lipotropin Precursor Gene' US Patent No. 4,322,499 (30 March 1982).

forty-two ... racks for the application resulting from that one application. Clearly, something needs to be done to address this onslaught of paper.⁹⁸

While the electronic version of the sequence listing was treated as an unofficial copy of the official paper version, this was largely a pretence given that in practice the electronic version served as the basis for examination, printing, and making copies. Because the Patent Office was not in a position where it could undertake the laborious and expensive task of ensuring that the electronic and paper-based versions of a sequence were the same (something that was usually only ever done in litigation),⁹⁹ the concurrence of the electronic and paper-based versions of the sequence was assumed on the basis of a statement to that effect by a registered attorney or agent. Given the difficulty of maintaining the two independent versions of the sequence listing and the ‘irony that the official paper copy was effectively ignored while the unofficial electronic copy is the only that is used’, in 1999 the Patent Office eliminated the paper copy in ‘favour of the useful, handy and verifiable computer readable version’.¹⁰⁰

The use of digital sequence information to describe genetic inventions, which has been treated as a defining feature of molecular gene patents, fundamentally changed the way molecular subject matter was represented. In this sense it was not merely as the Patent Office wrote in 1999 that there was an inverse relationship ‘between the level of predictability in the art and the *amount* of disclosure necessary to satisfy the written description requirement’, so much as the *nature* of the disclosure changed.¹⁰¹ The reason for this was that in reducing biological subject matter to a string of digitized letters and symbols, sequence information represented the ‘virtualisation’ of biological labour and biological objects within patent law: organisms and genes become codes made up of zeros and ones.¹⁰² In this sense, it could be said that patent law’s acceptance of sequence information, which erased ‘the boundaries between life in vivo and life in silico’,¹⁰³ represented the informatisation or dematerialisation of biological subject matter.¹⁰⁴

While the adoption of sequence information in lieu of either structural chemical formula or physical deposit marked an important change in the way molecular subject

⁹⁸ USPTO, ‘Permitting Electronic Submission of Voluminous Material’ (5 January 1999) 1218 Official Gazette (37 CFR 1.96, 1.821), 193.

⁹⁹ *Ibid.*

¹⁰⁰ Rochelle K. Seide and Janet M. MacLeod, ‘Drafting Claims for Biotechnology Inventions’ in *Eight Annual Patent Prosecution Workshop: Advance Claim Drafting and Amendment Writing* (New York: Practising Law Institute, 1998), 337, 391.

¹⁰¹ USPTO, ‘Revised Interim Guidelines for the Examination of Patent Applications under the 35 U.S.C. § 112(1) “Written Description” Requirement’ (21 December 1999) 64 *Federal Register* 71427.

¹⁰² Hallam Stevens, *Life Out of Sequence: A Data Driven History of Bioinformatics* (Chicago: Chicago University Press, 2013), 5.

¹⁰³ Hallam Stevens, ‘On the Means of Bio-production: Bioinformatics and How to Make Knowledge in a High-Throughput Genomics Laboratory’ 6(2) (2011) *BioSocieties* 217, 241.

¹⁰⁴ Adrian Mackenzie, ‘Bringing Sequences to Life: How Bioinformatics Corporealizes Sequence Data’ (2003) 22(3) *New Genetics and Society* 315, 330.

matter was conceptualised, nonetheless it was only a partial process. This is because when it came to deciding the fate of genes as patentable subject matter, the subject matter was still grounded in the materiality of the gene as a chemical substance. Put differently, while epistemologically molecular subject matter had been reduced to a paper/digital form, ontologically molecular subject matter was still treated as a tangible physical chemical compound when deciding subject matter eligibility.¹⁰⁵

JUDGING MOLECULAR SUBJECT MATTER

One of the techniques that patent law used to allow it to deal with an ungriving biological subject matter was to bundle nature and inventor together. The process of invention was also figured accordingly: nature was seen to provide the inventive contribution while the role of the human inventor was relegated to recognising and preserving nature's innovation. The resulting co-inventions were judged accordingly. With molecularisation, biological subject matter was unbundled and the role of the inventor was recast in more familiar terms. As a consequence, it was now possible to isolate and evaluate what the inventor had contributed to the resulting invention. That is, it was now possible to judge biological subject matter in a manner similar to the way mechanical inventions were evaluated.

In thinking about what an inventor working with biological material needed to do to ensure that the end-results were patentable, patent law not only recast the figure of the inventor in more familiar terms, it also saw 'nature' emerge for the first time as a discrete legal category. While nature had previously made an appearance in patent law, it was predominately as a source of innovation and change (mutation, sports) – as the agent of invention – rather than anything like the way it is thought about today. And, even in the rare instances where unmodified plants, microorganisms, and bacteria were treated as natural things that were beyond the reach of patent law (as is the case now), there was no sense in which they belonged to some overarching legal category. To the extent that there was any sustained focus on natural inventions – and, again, this was rare – this was usually part of a broader discussion about how to configure empirical inventions so that they complied with the doctrinal rules that were imposed on them.

The situation began to change with the emergence of a more molecularised subject matter in the 1970s. As is often the case when patent law grapples with the products of scientific and technical innovation, the process of change was neither straightforward nor logical. While the 1980 *Chakrabarty* decision did see a more abstract grouping of biological subject matter emerge within patent law, nonetheless 'nature' still did not yet exist, at least in the way that it understood today. By the first decade of the twenty first century, however, the situation had changed: the focus of attention had shifted from living biological subject matter to a more general and more familiar grouping

¹⁰⁵ 'Patent law is ill suited to protecting the informational value of these molecules'. Rebecca Eisenberg, 'Do EST Patents Matter?' (October 1998) 14(10) *Trends in Genetics* 379, 380.

that consistently encompassed both animate biological matter as well as inanimate natural matter such minerals, metals, and elements. While patent law may not have invented nature as a legal category (although it is tempting to say so), it is safe to say that over the last 40 or so years that nature has been elevated in status, given a name, and a body of law. As part of the process, nature was also given a history.

Recognising that ‘nature’ has only recently emerged within patent law as a meaningful albeit confused and problematic category of excluded subject matter helps to explain why it is that the various attempts to write the history of the product of nature doctrine have proved to be so problematic; why it is that the doctrine has such divergent origins; why it is that the case law on natural subject matter ‘remains a kaleidoscope of doctrine’;¹⁰⁶ and why it is that ‘[a]nyone looking for a historical “right” answer on the product of nature question will probably be disappointed’.¹⁰⁷ The simple reason for this being that people are trying to write the history of something that did not yet exist.

One of the characteristics of the abstract legal category that emerged alongside molecular subject matter is that it included a wide range of nature-based innovations that spanned from oranges dipped in borax and wire made from tungsten and uranium, through to fibre extracted from pine needles, products made up of different strains of bacteria, and novel chemical compounds such as adrenalin and aspirin. One of the consequences of this diversity was that the product of nature doctrine potentially reached back in a range of different directions within patent law. This meant, for example, that a decision about the patentability of a human gene was now connected to earlier decisions about microorganisms, minerals, plants, and synthetic chemicals.

Another consequence of this diverse history was that it offered a number of different ways of potentially evaluating and judging the unbundled subject matter. As a result, and to the annoyance of textbook writers and doctrinalists, there is no easy way of determining how nature-based subject matter might be judged: there is no simple question that can be asked or litmus test that can be applied to determine whether nature-based subject matter is patent-worthy. Instead, different tests are used at different times, often seemingly chosen to suit the facts at hand. At different times decisions have turned on the nature of the invention and how it was classified,¹⁰⁸ on the type of labour used to create the invention, on the ability of the

¹⁰⁶ Christopher Beauchamp, ‘Patenting Nature: A Problem of History’ (2013) 16 *Stanford Technology Law Review* 257, 310.

¹⁰⁷ *Ibid.*

¹⁰⁸ In many cases, a decision that something is of the type or kind that warrants (or demands) it be classified as an unpatentable product of nature is not contentious. Thus, it has been readily and widely accepted that the discovery of a new mineral or a new plant found in the wild, or a human kidney removed from the body, would be products of nature and as such should be ‘free to all men and reserved exclusively to none’. *Diamond v. Chakrabarty* 447 U.S. 303, 309 (1980). For a discussion of the role and place of kinds in patent law (primarily in relation to patent claims) see Andrew Chin, ‘The Ontological Function of the Patent Document’ (2012) 74 *University of Pittsburgh Law Review* 263.

applicant to show that the invention in question was ‘markedly different’¹⁰⁹ from the raw material on which it was based, or on the way the invention was named (with a change of name being taken as being indicative of a change of kind and thus that the matter in question is patent-eligible).¹¹⁰

The confusion this creates is compounded by the fact that judges often switch between questions or rely on different factors to decide subject matter eligibility. In a single judgement a court may simultaneously focus on the labour of the inventor (and whether it is ‘inventive’), on the way the invention in question differs from the raw material on which it is based (is it markedly different?), and, at the same time, on the character of the invention (is it the right kind of invention?). Indeed, this is what happened in *Diamond v. Chakrabarty* where in finding that the disputed genetically engineered bacterium was patent-eligible, the Supreme Court not only highlighted the labour that Chakrabarty had used to create the modified bacteria and how ‘markedly different’ that genetically modified organism was from the starting material, the Court also took account of the fact that the bacteria had been christened with a new name: *Pseudomonas putida*.¹¹¹ As the Court said, the claim was ‘not to a hitherto unknown natural phenomenon, but to a non-naturally occurring manufacture or composition of matter – a product of human ingenuity “having a distinctive name, character [and] use”’.¹¹²

A similar multi-pronged approach was also adopted by the Supreme Court in its 2013 decision of *Association for Molecular Pathology v. Myriad Genetics*. While the patents being challenged in this case covered a range of subject matter – including isolated DNA sequences (BRCA1 and BRCA2), methods to diagnose propensity to breast cancer by looking for mutated DNA sequences, and methods to identify drug candidates using isolated DNA sequences – in line with the reductionist spirit that characterises the way patent law engages with molecular subject matter, the case and associated commentary focused on the patentability of Myriad’s claims over the BRCA1 and BRCA2 genes. Specifically, it focused on whether the isolated DNA segment was patentable.

While the Supreme Court in *Myriad* may not have been as promiscuous as it had been in *Chakrabarty* in terms of the factors that were used to determine patentability, nonetheless the Court did make use of a number of different factors in deciding that

¹⁰⁹ See *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office* 702 F. Supp. 2d 181, 222 (SDNY 2010).

¹¹⁰ For example, in *Intervet v. Meril*, it was held that DNA constructs encoding a type of porcine circovirus as a new type of virus ‘comports with the way that viruses are typically classified in the relevant art’. 617 F.3d 1282, 1288 (Fed. Cir. 2010).

¹¹¹ *Diamond v. Chakrabarty* 447 U.S. 303, 310 (1980).

¹¹² *Ibid.*, 309–10. In other situations, the fact that subject matter has *not* been given a new name has been taken to suggest that the subject matter is not patent-worthy. Thus, in *American Fruit Growers v. Brogdex*, the Supreme Court held that an orange dipped in a solution of borax to render the skin mould-resistant was not a manufactured article and thus not patentable. One of the reasons for this was that there was ‘no change in the name, appearance, or general character of the fruit. It remains a fresh orange fit only for the same beneficial uses as theretofore’. *American Fruit Growers v. Brogdex* 283 U.S. 1, 11–12 (1931). See also *In re Ewald* 129 F.2d 340, 342 (CCPA 1942) (a cored pear was not a manufacture because it did not possess a new name, character, or use).

‘naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated’. In explaining the reasons for this conclusion, Thomas J. compared the patentable invention in *Chakrabarty* with the non-patentable BRCA1 and BRCA2 genes saying that while due to the additional plasmids and resultant capacity for degrading oil, the Chakrabarty bacterium was new ‘with markedly different characteristics from any found in nature’, by contrast Myriad had not created anything.¹¹³ Thomas J. also compared the BRCA1 and BRCA2 genes with the bacteria-based invention at stake in *Funk Brothers* noting that the composition in *Funk* was held to be ineligible for protection because the patent holder did not alter the bacteria in any way.¹¹⁴

As is clear from even a cursory look at the literature, the *Myriad* decision has been cut and spliced in many ways. For some, the decision is tied up with discussions about doctrinal purity and questions of whether subject matter inquiry should be distinct from novelty and obviousness. For others, the key question is understanding how the Supreme Court managed to distinguish non-patentable isolated sequences from patentable synthetic lab-made cDNA¹¹⁵ (isolated sequences were functionally identical to those found in nature), whether the decision was policy masked as science,¹¹⁶ or whether the science relied upon in the decision was accurate.¹¹⁷ For others *Myriad* left open the question of what constitutes patent eligible cDNA and the extent to which cDNA needs to be altered for it to be patent eligible. While these are important questions, I wish to take a different tact. In particular, I want to shift the focus of attention away from the question of how the nature-based subject matter should be judged to focus on the way that the subject matter was construed and the impact this had on the ultimate decision. That is, I want to consider the relatively neglected question of the ontology of the gene in patent law.¹¹⁸

In contemplating the status of genes as patentable subject matter, intellectual property law makers were faced with competing interpretations of how the subject matter could be construed. This was a consequence of the gene’s ambiguous status whereby it was simultaneously thought of as a material chemical entity *and* as a carrier of information.¹¹⁹ As Sweet J. noted in the first instance decision in *Myriad*, genes are of

¹¹³ *Assoc. for Molecular Pathology v. Myriad Genetics* 569 U.S. 576, 577 (2013).

¹¹⁴ *Ibid.*, 591.

¹¹⁵ Dan L. Burk, ‘Are Human Genes Patentable’ (2013) *IIC* 747; See also Charles Lawson, ‘Patenting DNA Sequences after the Myriad Decision’ (2014) 33 *Biotechnology Law Report* 3.

¹¹⁶ Shubha Ghosh, ‘Myriad post-Myriad’ (2020) 47(5) (October 2020) *Science and Public Policy*, 638. (‘Deference to the Scientific Community Is Implicit in the Court’s Exegesis of the Science of DNA’).

¹¹⁷ Brief for Amicus Curia Eric S. Lander in Support of Neither Party, No 12–398, *The Association for Molecular Pathology v. Myriad Genetics*, 11–14. Mateo Aboy et al., ‘After Myriad, What Makes a Gene Patents Claim ‘Markedly Different’ from Nature?’ 35(9) (September 2017) *Nature Biotechnology* 820.

¹¹⁸ For a notable exception see Jane Calvert and Pierre-Benoît Joly, ‘How Did the Gene Become a Chemical Compound? The Ontology of the Gene and the Patenting of DNA’ (2011) 50(2) *Social Science Information* 157, 168.

¹¹⁹ See Hans-Jörg Rheinberger, ‘Gene Concepts Fragments from the Perspective of Molecular Biology’ in (ed) P. Beurton, R. Falk, and H. Rheinberger, *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press, 2000), 219.

double nature. On the one hand they are chemical substances or molecules. On the other hand, they are also physical carriers of information ‘where the actual function of this information is coding for proteins’. One of the consequences of this was that when deciding the fate of gene patents, the courts found themselves in a situation similar to the position they had been in with software-related inventions where they were presented with two very different ways of thinking about the subject matter. In this sense it was not only as Eric Lander said in his amicus brief in *Myriad* that the question before the Supreme Court was a scientific question about the subject matter, so much as that it was a choice between different scientific understandings of the subject matter.¹²⁰

Unlike the case with software-related inventions, the law did not attempt to merge the two approaches when dealing with the patentability of genes. Rather, patent law approached subject matter eligibility as an either/or decision. The consequences of which were clear. If the gene was seen as a chemical molecule – as the Federal Circuit did – the result was that isolated genes were almost inevitably patentable subject matter. The reason for this is that because when DNA is removed from the body chemical bonds are severed and replaced with new bonds, the isolated compound is chemically different from its natural equivalent. Because the isolated DNA was ‘markedly different’ to the natural DNA in the body, it was patentable subject matter. In contrast, if the gene is seen as a carrier of biological information – as Sweet J. at first instance and the Supreme Court did – the outcome was different. Because the gene in the body and the isolated gene both act as carriers of information,¹²¹ the isolated gene was not ‘markedly different’ from native DNA as it exists in nature. On this basis it was held that the isolated DNA was unpatentable subject matter.

Prior to the *Myriad* litigation, the status of the gene in patent law had been clear: a gene was treated as a chemical compound, which meant that when it was isolated from its natural state, it was markedly different from the raw material on which it was based and thus potentially patentable. Given that this view of the ontology of the gene had been unquestionably accepted in patent law for over 40 years, it is not surprising that Judge Sweet’s first instance decision in *Myriad* that ‘DNA represents the physical embodiment of biological information’¹²² caught so many people by surprise. While this may have been seen by some as a temporary aberration that was corrected by the Federal Circuit (which reinstated the chemical view of the gene and consequently upheld the validity of the patents), the new view of the legal gene was confirmed by the Supreme Court in 2013 when in declaring the gene patents invalid the court stressed that *Myriad*’s claim were ‘concerned primarily with the information contained in the genetic sequence, not with the specific chemical composition of a particular

¹²⁰ Brief for Amicus Curia Eric S. Lander in Support of Neither Party, No 12–398, *The Association for Molecular Pathology v. Myriad Genetics*, 2.

¹²¹ Jane Calvert and Pierre-Benoît Joly, ‘How Did the Gene Become a Chemical Compound? The Ontology of the Gene and the Patenting of DNA’ (2011) 50(2) *Social Science Information* 157, 158.

¹²² *Assoc. for Molecular Pathology v. USPTO* 702 F. Supp. 2d 181, 185 (SDNY 2010).

molecule'.¹²³ As Justice Thomas said, Myriad's claims were not 'saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a non-naturally occurring molecule'. The reason for this was that Myriad's claims were 'simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes'.¹²⁴ By prioritising biological information over chemical structure, the Supreme Court decision represents a continuation of the process that has seen subject matter shift from the organism to molecules, then from molecules to information, and finally from information to 'prescriptive script'.¹²⁵

When gene patents first appeared in patent law in the 1960's, genes were treated as chemical compounds both in terms of how they were described and how they were conceptualised and judged. That is, the gene was treated both epistemologically and ontologically as a chemical compound. While this remained unchanged when the inventor was unbundled from the subject matter, the situation began to unravel when patent law adopted sequence information as a way of describing, identifying, and enabling molecular subject matter. By accepting that it was now possible to repeat the invention from its paper/digital form, patent law also accepted that it was no longer necessary to deposit physical samples of the invention as part of the application process. While the adoption of sequence information in lieu of a physical deposit to describe and enable the gene marked an important change in the way molecular subject matter was conceptualised and a shift towards a more dematerialised subject matter, nonetheless when it came to deciding the fate of genes as patentable subject matter, the subject matter was still grounded in the materiality of the gene as a chemical substance.

The situation changed in 2013 with the Supreme Court decision in *Myriad*. By elevating biological information over chemical structure,¹²⁶ the Supreme Court completed the process that had begun in the 1980s of rendering molecular subject matter biological and informational.¹²⁷ The reason for this was that after *Myriad*, genes (DNA sequences) were no longer simply chemical molecules. Nor were they material chemical entities that carried information or instruction.¹²⁸ In the post-Myriad world, the utility of gene patents was based on the information

¹²³ *Assoc. for Molecular Pathology v. Myriad Genetics* 569 U.S. 576, 593 (2013).

¹²⁴ *Ibid.*, 577.

¹²⁵ Sakari Tamminen and Niki Vermeulen, 'Bio-objects: New Conjugations on Living' 21(5) (2019) *Sociologias* 156, 162.

¹²⁶ Bernhard D. Saxe, 'Gene Patent Decision: A Chemist's View' (2013) 33(15) *Genetic Engineering and Biotechnology News* 8, 12.

¹²⁷ On the role of information in biology see Lilly E. Kay, *Who Wrote the Book of Life?* (Stanford: Stanford University Press, 2000), 226.

¹²⁸ 'DNA sequences are not simply molecules, they are also information. Patent claims to information – even useful information – represents a fundamental departure from the traditional patent bargain.' Rebecca Eisenburg, 'Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences' (2000) 49(3) *Emory Law Journal* 783, 786.

provided by the DNA sequence, rather than the material substance. In a subtle but important change, genes were now informational both in terms of the way they are represented and also in terms of how they are conceptualised and judged.¹²⁹ While ‘information’ may have started out as a metaphor or analogy, it came to be treated as a thing in itself within patent law – as an ontology. And, as Jane Calvert said, when ‘something is taken as an ontology it becomes a potential object of patentability’.¹³⁰

In adopting the life-as-information paradigm, the subject matter of patent law underwent a radical transformation from organic into virtual form, as the subject matter of patent law was ‘displaced, with the molecule overtaking or territorializing the organism and getting plugged into the computer’.¹³¹ As a result, the material chemical molecule (which had supplanted plant-based subject matter) gave ‘way to molecules that contain the code for life and that information technologies have captured life’s vitality and transformed it into bits’.¹³² One of the consequences of this was that the legal gene, like its scientific equivalent, became ‘curiously intangible’.¹³³ One of the distinctive features of the new informational subject matter is that it is separate and distinct from the material physical form of the invention. Unlike the pre-*Myriad* molecular gene, which was rooted in the material chemical compound, the molecular gene post-*Myriad* was decoupled from its physical form. It was, in short, dematerialised as the subject matter was reconceptualised through its immateriality.¹³⁴

The shift from surface to subsurface, and then from chemical structure to genetic information, and then from gene as chemical compound to gene as carrier of information brought about a number of changes in biological subject matter. In the case of plants, for example, while patent protection had previously been limited to individual plants, this changed when the subject matter shifted below the surface and became informational. One of the consequences of this was that patentees were no longer tied to a claim that was taxonomically literate nor limited to individual

¹²⁹ In this sense the gene became informational both epistemologically in the sense of ‘*information about genes*’, which refers to the particular way that genes are represented; and ontologically in the sense of ‘*information encoded in genes*.’ Paul Griffiths, ‘Genetic Information: A Metaphor in Search of a Theory’ (2001) 68(3) *Philosophy of Science* 394, 409.

¹³⁰ Jane Calvert, ‘Patenting Genomic Objects: Genes, Genomes, Function and Information’ (2007) 16(2) *Science as Culture* 207, 217.

¹³¹ Richard Doyle, *On Beyond Living: Rhetorical Transformation of the Life Sciences* (Stanford: Stanford University Press, 1997), 1.

¹³² Sakari Tamminen and Niki Vermeulen, ‘Bio-objects: New Conjugations on Living’ 21(5) (2019) *Sociologias* 156, 163.

¹³³ ‘Introduction’ in (ed) P. Beurton, R. Falk, and H. Rheinberger, *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press, 2000), x. ‘The more molecular biologists learn about genes, the less sure they seem to become of what a gene really is. Knowledge about the structure and functioning of genes abounds, but also, the gene has become curiously intangible’.

¹³⁴ Sakari Tamminen and Niki Vermeulen ‘Bio-objects: New Conjugations on Living’ 21(5) (2019) *Sociologias* 156, 159.

organisms; patentees could and frequently did claim groups or classes of plants, or groups of plants that were united by the fact that they exhibited shared characteristics (such as being glyphosate resistant). While the validity of a patent for super-double nasturtiums had been questioned at a time when the focus of the law was on individual plants, the shift below the surface meant that it was now possible to patent a novel double flower gene in *Verbena* that produced flowers with additional petals.¹³⁵

The nature of plant-based subject matter was changed further by the use of sequence information to claim genetic innovations. While physical samples deposited as part of the application process provided or at least were treated as if they provided boundaries around the invention, these markers disappeared when the subject matter was represented using sequence information.¹³⁶ One of the consequences of this is that decisions needed to be made about the limits of sequence-based inventions. One option was to limit protection to identical, facsimile copies of the claimed invention. With these 'picture claims', protection would have been limited to nucleotide sequences that were identical to the sequences that were depicted in the patent.¹³⁷ One of the arguments made in favour of this approach was that if the line was 'not drawn at 100% sequence identity, these claims become a slippery slope with boundaries that must be individually defined'. To accept anything less would have opened 'a Pandora's box that the patent law is unable to control'.¹³⁸ It was also argued that as genes vary so much between and within species, yet are so closely related, any alternative approach to patenting genes, other than disclosing exact nucleotide sequences would have risked granting overly broad patent rights to single inventors.¹³⁹

Whatever advantages there might have been with this approach, it was not followed. One of the problems with limiting protection to 100% sequence identity was that it would have been relatively easy for would-be infringers to avoid a patent by making (non-functional) cosmetic change to the genetic structure of a biological organism which, in turn, would have changed the sequence information. To protect the equity of patented inventions, the courts decided that protection should extend beyond the literal sequence specified in the patent application to include related sequences.¹⁴⁰ As the Patent Office said, claims typically include the 'sequence and any sequence having a certain percentage identity or homology to the sequence or any sequences which hybridizes to the sequence'.¹⁴¹ That is, it was very common for patentees to

¹³⁵ Mitchell Eugene Hanes and Staislaw Naleoa, 'Double Flower Gene of *Verbena* and the Method of Producing Same' US Patent No. 6,150,591 (21 November 2000).

¹³⁶ See *Ajinomoto Co. v. Archer-Daniels-Midland* 228 F.3d 1338 (Fed. Cir. 2000).

¹³⁷ Diana Sheiness, 'Patenting Gene Sequences' (1996) 78(2) *Journal of the Patent and Trademark Office Society* 121.

¹³⁸ Margaret Simpson, 'The Evolution of the Enablement and Written Description Requirement under 35 USC Sec 112 in the Area of Biotechnology' (2000) *Berkeley Technology and Law Journal* 1233, 1261.

¹³⁹ *Ibid.*

¹⁴⁰ Guillaume Dufresne and Manuel Duval, 'Genetic Sequences: How Are They Patented?' (2004) 22 *Nature Biotechnology* 231.

¹⁴¹ Patent and Trademark Office, 'Notice of Hearing and Request for Comments on Issues Relating to Patent Protection for Nucleic Acid Sequences' (12 March 1996) 61(49) *Federal Register* 9980, 9981

claim sequences that have at least a threshold level of percentage with the specified sequence, for example, sequences that have at least 90% identity with the specified sequence.¹⁴²

One of the consequences of limiting patent protection to 100% sequence identity would have been that protection was limited to the individual invention that was disclosed in the patent. By allowing patentees to claim homology of less than 100% similarity, patent law opened up the possibility of extending the scope of the invention to groups of inventions, which were sometimes very large. For example, in one decision it was noted that a patent claiming 'a recombinant yeast with a coding region at least 90% identity with SEQ ID No 11' potentially covered 3.4×10^{41} variants.¹⁴³ As was the case with the shift to formula-based chemical inventions, this created further questions about the number of inventions that patentees needed to disclose to enable their inventions. This was part of a more general change whereby the subject matter became mathematical to the extent that the courts, the Patent Office, and others reading the patent claims were called on to decide questions of similarity and difference in mathematical terms.¹⁴⁴ Instead of deciding infringement or patentability by looking at the external traits of an invention or what the invention did, similarity and difference was now decided by relative degree of similarity. As a result, the question became where and how the level of homology or sequence identity should be set. If 80% similarity was enough, what about 79%? And so on.¹⁴⁵ The upshot of this was although on first blush the use of sequence information to identify biological inventions represents a continuation of the longstanding practice whereby questions in patent law are answered using scientific criteria, on closer inspection, the process was ironically rendered more legal.¹⁴⁶

¹⁴² Guillaume Dufresne and Manuel Duval, 'Genetic Sequences: How Are They Patented?' (2004) 22 *Nature Biotechnology* 231.

¹⁴³ *Ex parte Porro* (2008) BPAI Appeal 2008-9814 (11 March 2008).

¹⁴⁴ Guillaume Dufresne and Manuel Duval, 'Genetic Sequences: How Are They Patented?' (2004) 22 *Nature Biotechnology* 231.

¹⁴⁵ The threshold value for percentage of identity varies with some claiming rights over sequences with as little as 70% homology. Osmat A. Jefferson et al., 'Gene Patent Practice across Plant and Human Genomes' (2015) 33 *Nature Biotechnology* 1034.

¹⁴⁶ At least in the sense that the law could not rely upon science to provide an answer.