

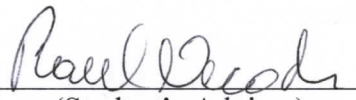
The Nomenclature Question: A Pre-History of the Human Genome Project

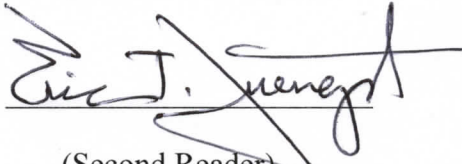
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Introduction

This thesis narrates a prehistory of the Human Genome Project, beginning with the intellectual underpinnings of scientific advancement in the middle to late twentieth century. Long before official discussions about a microscopic genetic “map” of the human body arose within the scientific community in the 1970s, a way array of intellectuals—from the physical and medical sciences, as well as philosophers and ethicists—developed a growing interest in this seemingly impossible task. Their engagement with the abstract vision of a prospective map reveals a complex chronology of debates and discussions that now form a multidimensional history of the Human Genome Project (HGP). These histories are intrinsically related to the language used to describe and present the body in various scientific contexts. This thesis reconstructs a pre-history of the Human Genome Project, with language as a lens for perspective. Through this lens, one can trace the transformation of scientific language from a tool for intellectual momentum in mapping the molecular body to a pivotal instrument in defining a genetic sequence as a patentable product. While narratives about the body can constrain and reconfigure our perceptions of self, the outcome of these narratives is never pre-ordained, but is instead contingent upon discourses and their power to reconfigure paradigms about the body. In a world driven by science, we must reconsider what it means to have a body.

The Human Genome Project formally began in 1990, when the U.S. Congress jointly funded the Department of Energy and the National Institutes of Health to map out the human genetic sequence. While the Department of Energy (DOE) was interested in the project as an opportunity to study the long-term genetic effects of nuclear radiation, the National Institutes of Health (NIH) wanted to maintain its reputation as a leader of American scientific research. As Dr. Bernadine Healy, Director of the NIH during the early years of the Human Genome Project,

boasted, “the [HGP] is one of the crown jewels of the NIH.”¹ With a strong sense of excitement from the scientific community, funding was not a concern in early discussions about a prospective human gene map.

The first report issued by the DOE and NIH outlined a fiscal and research-oriented plan to complete the project within fifteen years. The fact that the genome was nearly mapped four years prior to its intended completion date is indicative of the large-scale intellectual, financial, technological, and cultural resources afforded to the Human Genome Project. By 2001, the U.S. Department of Energy and the National Institutes of Health has invested approximately 2.7 billion dollars in the HGP.² A considerable amount of funding had been allocated to the development of new sequencing and database technologies to increase mapping efficiency and to reduce the cost of research. Still, scientists were inundated with new information; this resulted in questions of storage, access, and ownership of genetic information. All this was dependent on having a coherent system of classification for the mapped genomic regions, and a universal system of molecular nomenclature.

Perhaps one of the central challenges for the Human Genome Project- the creation and orchestration of its consortium of scientists, laboratories, institutions, and interested parties outside of the research community- was also its central accomplishment: the Human Genome Project created a dynamic network of collaborations, debates, applications, protests, and questions that involved not just scientists, but the community at large. This thesis analyzes the contested and complex origins of the HGP and argues that overcoming the challenge of linguistic conventions in molecular biology was critical to its development.

¹ Veggeberg, Scott. "Watson Departure Vexes Genome Experts." *The Scientist Magazine*. May 25, 1992.

² "2003 Release: International Consortium Completes Human Genome Project." National Human Genome Research Institute. April 14, 2003. News Release Archives

Therefore, I propose three new perspectives to understand the early history of the human genome mapping effort. Each perspective is related to language and systems of terminology in molecular genetics. Throughout the thesis, the term ‘nomenclature’ arises in a variety of contexts, both historical and contemporary. However, in each instance, nomenclature details a specific turning point in the Human Genome Project- from nomenclature’s vital role as a mechanism for the HGP’s intellectual momentum, to a precedent set by the cytogenetics community, to the actualized legal complications that arose from description of gene sequences in patent applications in the 1980s.

The first section focuses on early descriptions of genetics by public intellectuals. I argue that their visions about the possibilities and utilities of a gene map provided the intellectual momentum for a seemingly impossible task. The second chapter looks at “the nomenclature precedent”, that is, how the related field of cytogenetics developed a language classification system for DNA protein sequences during the 1960s. This section examines the relative ease with which the cytogenetics community developed a terminology system and discusses how well-established nomenclature facilitated organization, communication, progressive research, and intelligibility in cytogenetics. Finally, the third chapter considers language as a structural turning point in the right to ownership of bio-intellectual property. Specifically, the trajectory focuses on the Written Description requirement for patent applications and follows how a single court case revealed new questions about genetic research and transcended the patent structure in place during the 1980s.

It is my hope that these three perspectives collectively affirm the significance of language in configuring twentieth century paradigms of scientific value and standardization. After all, the

Human Genome Project is itself a history of the human body as it was constructed, contested, and redefined in the twentieth century.

Chapter One

Intellectual Momentum: Early Descriptions of a Gene Map

*“Every map offers only its own perspective on the world, however objective it may appear or claim to be, a perspective... implies a particular assertion of reality.”*³ –Geoff King

Mapping has long been a physical manifestation of human knowledge: an embodiment of the discovery process, an examination of geographic and spatial relationships, a depiction of scale and relativity, and a continued effort to understand and explore uncharted landscapes. Yet fundamentally, a map is a representation, a medium between reality observed and reality rendered. As historian Roy Porter suggests, “to a large degree our sense of our bodies, and what happens in and to them, is not first-hand but mediated through maps and expectations derived from culture at large.”⁴

In much the same way, the following chapters present a relatively recent account of how scientists have come to understand and map a fundamental element of the human body: genes. A history of the progress and challenges that predetermined mapping the human body is a literal taking of the term *human geography*. In this interpretation, body mapping is based not on the relationship of terrain-geography to human movement, but instead upon the ways in which intellectual development has demanded a greater understanding of the human body: its functions

³ King, Geoff. *Mapping Reality: An Exploration of Cultural Cartographies*. New York: St. Martin's Press, 1996.

⁴ Porter, Roy. *Flesh in the Age of Reason*. New York: W.W. Norton & Co., 2005.

and expressions, its capacities and limitations, and its utilities and possibilities. Even prior to the completion of the Human Genome Project in 2003, the gene map had been commended as, “the most important, most wondrous map ever produced by humankind.”⁵ Although the possibility of a comprehensive gene map was dazzling, the Human Genome Project was never a pre-ordained success. Instead, the project resulted from fifty years of contestation, innovation, and determination to map the human body in its most fundamental form.

A Time of Transition and Possibility

The earliest intellectual conundrum of the Human Genome Project presented itself in the mid-twentieth century, long before the Project’s official commencement in 1990. The task itself was immense; the genome would comprise a comprehensive map of every strain of genetic material found in the human body. Billions of microscopic nucleotides had yet to be discovered, and the first intellectual issue involved a question of how to map invisible and theoretical dimensions of the human body.

Although the body’s gross anatomy had been mapped centuries earlier, new information about the microscopic workings of the body presented unprecedented potential for research, as well as practical hurdles. The problem was a matter of discrepancy: although a number of scientists predicted a future of research in genetics, a number of practical concerns constrained the actualization of genome mapping. During the 1940s, geneticists remained uncertain of the structure, function, and location of genes in humans. Scientific instrumentation allowed for limited lens visibility and funding for research in the biological sciences had been significantly diminished in the wake of war. In 1945, the place of science in post-war America was highly

⁵ Address by President Bill Clinton, The East Room, Washington, DC, June 26, 2000.

uncertain.

Post–War Origins: Vannevar Bush’s Endless Frontier

*“To achieve [our] objectives...the flow of new scientific knowledge must be continuous and substantial.”*⁶ – Vannevar Bush

Intellectuals first envisioned gene mapping in the mid- twentieth century, when the end of the Second World War marked a time of transition in American scientific communities at large. From the development of radar systems to the widespread distribution of penicillin, scientists had formed a critical part of the war both at home and abroad.⁷ Applied physics had advanced American war efforts with the introduction of radiation technology, radar capabilities, trajectory guided missiles, and hydrophone submarine detection.⁸ In November of 1944, President Franklin D. Roosevelt famously wrote to then–Director of the Office of Scientific Research and Development Vannevar Bush to inquire about continued applications of science in a post-war society. Bush composed a lengthy response that he entitled *Science: The Endless Frontier*.⁹ In his manifesto about the future of science in twentieth century America, Bush argued that while most wartime scientific research had been applied (i.e. developed specifically to enhance military capacity), a new frontier of knowledge would emerge from universities that encouraged

⁶ Bush, Vannevar. *Science--the Endless Frontier: A Report to the President on a Program for Postwar Scientific Research*. Repr. May 1980. Washington, D.C.: National Science Foundation, 1980. Introduction Section 1.

⁷ Krige, John and Oreskes, Naomi. *Science and Technology in the Global Cold War*. Cambridge, Massachusetts: The MIT Press, 2014. 11.

⁸ For more information, see: Daniel J. Kevles’ “The Physicists: The History of a Scientific Community in Modern America”

⁹ Ibid

basic research (i.e. research for the benefit of common scientific enterprise).¹⁰ Furthermore, Bush argued that scientific advancement was the primary indicator of innovation, modernity, high standards of living, and a developed nation, which, "...[could] insure health, prosperity, and security as a nation in the modern world."¹¹ This vision marked a turning point in American science. During World War Two, applied physics made major contributions to the war effort. Whereas physics marked the zenith of scientific achievement in the first half of the twentieth century, genetics emerged as a form of basic research, responding to new questions about the body that could not be resolved solely with physics research and applications.

Furthermore, Bush described human disease as a pivotal factor during wartime, and suggested that science should support new efforts in understanding disease and infection. He noted that "the responsibility for basic research in medicine and the underlying sciences, so essential to progress in the war against disease, falls primarily upon the medical schools and universities. Yet we find that the traditional sources of support for medical research in the medical schools and universities, largely endowment income, foundation grants, and private donations, are diminishing and there is no immediate prospect of a change in this trend."¹² Bush called for a move to basic research, but he understood that most academic institutions could not support the large-scale research he had in mind. His letter to Franklin D. Roosevelt did much to sway both political and economic support for the enterprise of biological research. Although science was the vehicle of exploration, the human body was the '*endless frontier*'. Following the

¹⁰ Especially relevant to basic scientific research is a set of norms introduced in 1973 by sociologist Robert K. Merton in his work *The Sociology of Science: Theoretical and Empirical Investigations*. This landmark publication outlined ethical principles to guide modern scientific research.

¹¹ Bush, Vannevar. *Science--the Endless Frontier: a Report to the President on a Program for Postwar Scientific Research*. Repr. May 1980. Washington, D.C.: National Science Foundation, 1980.

¹² *Ibid.*

war, it was the writings of intellectuals from related scientific fields that reified genetics as an emergent, yet legitimate, scientific discipline.

A Novel Vision of the Genome

*"The world extended in space and time is but our representation"*¹³ –Erwin Schrodinger

In 1944, Austrian physicist Erwin Schrodinger delivered a series of lectures at Trinity College in Dublin entitled “What is Life? The Physical Aspects of the Living Cell.” In opening, Schrodinger asked his colleagues and students, “How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?”¹⁴ His question was directed toward minds interested in the study of cellular biology and quantum physics, yet his inquiry remained relevant decades after his lecture, when molecular biologists asked the same question of human genetics.

At the turn of the twentieth century the biological science community had rediscovered Mendelian inheritance, a finding that sparked further scientific inquiry into genetic inheritance in plants.¹⁵ However, by the 1940s, the field of human genetics had not yet attained the prestige of other biological disciplines. In comparison to fields such as physics, genetics was limited by inconsistencies and paradoxes. In 1944, for example, Schrodinger demonstrated that a paradox related to the recognition that genetic heredity (by definition) was continuous, and its inherent

¹³ Schrödinger, Erwin. *Mind and Matter*. University Press, 1958. 22.

¹⁴ Schrödinger, Erwin. "What Is Life? The Physical Aspect of the Living Cell." *The American Naturalist*, University of Chicago Press for The American Society of Naturalists 79, no. 785 (1945): 554.

¹⁵ Many reasons have been offered to explain the rediscovery of Mendel's work. Although Mendel's publications on hybrid studies were in print during his lifetime, historians have offered several conclusions for the lack of recognition Mendel received from his scientific contemporaries. These include: a lack of circulation among his contemporaries, continued publication in obscure journals, his status as a monk rather than a scholar associated with scientific communities, the fact that his work was not subsequently republished during his lifetime, and Mendel's lack of scientific colleagues and students to continue his work.

need to mutate in order to remain stable under changing internal conditions.¹⁶ According to Schrodinger, this paradox revealed that classical physics could not adequately explain how genetic material operated in the human body. The most logical description of human genetic structure, he instead suggested, would come from “an elaborate code-script...sufficiently large to embody a complicated system of determinations...with an unlimited number of possible arrangements.”¹⁷ Schrodinger hypothesized that such a code-script could account for the possibility of both stability and variability within human chromosomes. The code-script Schrodinger described, unbeknownst to him, existed in human chromosomes and served a specific function: to transmit and store genetic information.

Schrodinger found himself at a midpoint in scientific development: “The first half of our century belonged to quantum physics” he affirmed, “but the second half will belong to molecular biology and genetics. We have reached a point of dramatic change in our views of life and ourselves (and)...great discoveries (are) imminent. The implications (of genetics) will change our culture.”¹⁸ By “we” Schrodinger meant the biological, chemical, and physical scientific communities, that held certain principles that could no longer accommodate new and emerging knowledge about the genome. In addition to Schrodinger’s status as a quantum physicist, he was also a visionary of scientific prospects because he understood that invisible interactions of the quanta informed and even defined visible biological interactions.

Specifically, Schrodinger noted, “Within every group [of genes] a linear map can be

¹⁶ Symonds, N. “What Is Life? Schrödinger’s Influence on Biology.” *The Quarterly Review of Biology* 61, no. 2 (June 1986): 221–26.

¹⁷ Schrödinger, Erwin. “What Is Life? The Physical Aspect of the Living Cell.” *The American Naturalist*, University of Chicago Press for The American Society of Naturalists 79, no. 785 (1945): 554.

¹⁸ Götschl, Johann, ed. *Erwin Schrödinger’s World View: The Dynamics of Knowledge and Reality*. Theory and Decision Library, v. 16. Dordrecht; Boston: Kluwer Academic, 1992.

drawn up which accounts quantitatively for the degree of linkages between any two of that group, so that there is little doubt that they actually are located, and located along a line, as the rod-like shape of the chromosome suggests.”¹⁹ He was sure it was possible to construct a linear map to organize and catalog the genetic “code-script.” Schrodinger noted that the concept of mapping microscopic anatomical space was conceivable because “ the physical interactions between our system... must, as a rule, themselves possess a certain degree of physical orderliness, that is to say, they too must obey strict physical laws to a certain degree of accuracy.”²⁰ Schrodinger’s recognition of order in the human body created a visible slate to examine the internal microscopic landscape. Schrodinger envisioned “linkages” (connections between microscopic information) and used their spatial properties to justify his expectation that scientists would produce, ‘a sort of map of properties within every chromosome.’²¹

However, Schrodinger did not suggest that anatomical “code-scripts” existed in isolation. Rather, he believed they formed a “map of properties”²² that accounted for linkages that together produced a continuous “pattern of an organism...a whole.”²³ The map would have to be a compilation of its unitary microscopic structures (i.e. properties of genetic material) and their macroscopic counterpart (i.e. the compositional whole, the envisioned genetic map). He later observed that life, in its variety of forms, was, “not merely a piece of this entire existence, but in a certain sense the *whole*; only this whole [was] not so constituted that it [could] be surveyed in

¹⁹ Schrödinger, Erwin. "What Is Life? The Physical Aspect of the Living Cell." *The American Naturalist*, University of Chicago Press for The American Society of Naturalists 79, no. 785 (1945): 554.

²⁰ Schrödinger, Erwin. "What Is Life? The Physical Aspect of the Living Cell." *The American Naturalist*, University of Chicago Press for The American Society of Naturalists 79, no. 785 (1945): 554.

²¹ *Ibid.*

²² *Ibid.*

²³ *Ibid.*

one single glance.”²⁴ Parallel to his parable for life, Schrodinger conceived of ideas that were later elemental compilations of the genome project as a structured whole, although he never witnessed the human gene map to fruition.

Nevertheless, Schrodinger’s lectures at Trinity College Dublin represent one of the earliest visions of a human gene map, introduced in both an academic and public sphere. Delivered first to a public audience, Schrodinger examined a question that would come to deeply inform science in the twentieth century: “How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?” He was determined to find a molecular explanation for how the human body operated and changed in physical and temporal dimensions. His lecture series ended by affirming that neither the events of space nor time could be definitively accounted for by the principles and laws of existing scientific disciplines. Aided and limited by the laws of classical physics, Schrodinger introduced the possibility of a continuous genetic structure, composed of atomic-sized properties and complicated by the paradox of genetic heredity and mutation. Schrodinger’s prediction remains one of the earliest visions of a map of the human genome. The writings of Schrodinger furthered scientific thought about genetics from an “informational abstraction composed of all of the human genes... toward describing the genome as a discrete object.”²⁵ His vision not only advanced intellectual discourses regarding the nature and structure of the gene, it also brought the concept of genomic mapping out of the realm of scientific imaginings to that of legitimate scientific possibility.

²⁴ Schrödinger, Erwin. *My View of the World*. University Press, 1964. 28.

²⁵ Hogan, Andrew J. “The ‘Morbidity Anatomy’ of the Human Genome: Tracing the Observational and Representational Approaches of Postwar Genetics and Biomedicine The William Bynum Prize Essay.” *Medical History* 58, no. 3 (July 2014): 315

Mapping the Indeterminate

Much like early mapmakers of the sixteenth century had overestimated the expansive boundaries that defined the world, the scope of the human genome was not accurately predicted prior to the charting of its landscape. Estimates regarding the number of genes within the human genome varied drastically even beginning in the early 1960s, when German geneticist Friedrich Vogel published an estimate that the genome consisted of approximately 6.5 million genes.²⁶ Vogel derived this number by hypothesizing the weight of amino acids in a particular chromosomal chain. His prediction was based on research conducted by Swedish chemist and Nobel Prize recipient, Theodor Svedberg. Yet, consistent with Schrodinger's prediction, Vogel under-estimated the size of the genome because he relied on scientific principles that could not fully account for the undetermined structure and function of the genome. Indeed, Schrodinger's words echoed from the past. It was not until the outset of the Human Genome Project in 1991, that the National Center for Human Genome Research published a report estimating the actual number of genes in the genome to be closer to twenty two thousand.²⁷ Despite Schrodinger's vision, the size and scope of genetic material to be surveyed was unclear in the 1960s; this resulted in a temporary standstill for the scientific community.

In 1956, Albert Levan and Joe Hin Tjio successfully identified and published the 46

²⁶ Vogel, F. "A Preliminary Estimate of the Number of Human Genes." *Nature* 201, no. 4921 (February 22, 1964): 847–847.

²⁷ National Center for Human Genome Research (U.S.). *Understanding Our Genetic Inheritance: the U.S. Human Genome Project : the First Five Years, FY 1991-1995*. Bethesda, Md.: National Technical Information Service [distributor], 1990.

For a comprehensive history of efforts to numerate the genome, see: Pertea, Mihaela, and Steven L Salzberg. "Between a Chicken and a Grape: Estimating the Number of Human Genes." *Genome Biology* 11.5 (2010): 206.

human chromosomal structures from their studies with human lung fibroblasts.²⁸ At the time, similar studies in cytogenetics (the study of chromosomes) were halted due to uncertainties in the number of human chromosomes (many scientists maintained that the total number was 48, identical to the number of chromosomes in the chimpanzee, although scientists later discovered that most humans have only 46 chromosomes).²⁹ The findings of Tjio and Levan directly contradicted the widely accepted claim that there were 48 human chromosomes. In fact, as molecular biologist Stanley M. Gartler points out, Levan had himself published a paper at the Sloan Kettering Institute in 1956 (the same year of his collaborative publication with Tjio) that affirmed his prediction of 48 human chromosomes.³⁰

On the one hand, highly regarded geneticists of the early twentieth century, including Herman J. Muller and Theophilus Painter, utilized studies of insect and mammalian genes to draw conclusions regarding human genetics and their findings remained temporarily unscrutinized.³¹ Yet even respected scientists such as Painter indicated a degree of uncertainty in chromosome findings. Painter noted “in my own material the counts range from 45-48 apparent

²⁸ Tjio H. and Levan A., ‘The Chromosomes of Man’, *Hereditas*, 42, 1 (1956) For a detailed account, see: Hulten, M. A. "Numbers, Bands and Recombination of Human Chromosomes: Historical Anecdotes from a Swedish Student." *Cytogenetic and Genome Research* 96, no. 1-4 (2002): 14-9.

²⁹ In their *Hereditas* publication, Tjio and Levan mention a study of chromosomes in embryonic liver mitosis conducted by Dr. Eva Hansen and Yngve Melander, who halted her research because her team was only able to locate forty-six of the presumed forty-eight human chromosomes. For further information, see: Hartl, Harvard University Daniel L. *Essential Genetics: A Genomics Perspective*. Jones & Bartlett Publishers, 2009.

³⁰ Levan, A. “Chromosome Studies on Some Human Tumors and Tissues of Normal Origin, Grown in Vivo and in Vitro at the Sloan-Kettering Institute.” *Cancer* 9. 1956. 648–663

³¹ For further information on the history of chromosomal discoveries in early cytogenetics, please see: Gartler Stanley M, “The Chromosome Number in Humans: A Brief History” in Nature Reviews. *Genetics* 7, no. 8 (August 2006), 655–660.

(human) chromosomes, although the clearest...so far studied only 46 chromosomes have been found. There can be no question, however, that the diploid number falls between 45 and 48.”³²

From a methodological perspective, microbiologist Stanley M. Gartler retrospectively suggested a number of obstacles that might have prevented numerical confirmation of human chromosomes in the 1950s. Certainly, the rarity of accessible human tissue samples prevented large-scale quantitative studies. Furthermore, sperm cells, which were especially well suited for chromosome counting, were often difficult to obtain. Specimens could also be analyzed only within a short timespan before chromosomes merged together and were unable to be separated for counting. Finally, Gartler argues that “some investigators believed there might be a natural variation in human chromosome number” based on ethnicity.³³ The undetermined number of human chromosomes created many uncertainties in the human genetic landscape.

This uncertainty revealed a tendency in early cytogenetic studies to what Malcom J. Kottler has termed *preconception*, the tendency to determine a result based upon previous findings that have confirmed its premise³⁴. Many early studies of chromosomes reported 48 human chromosomes because investigators who conducted the studies expected to find this number. Indeed their work was consistent with (and even based upon) information that was regarded as scientifically legitimate at the time. Rather than to affirm uncertainty in the field, the work of early cytot geneticists mistakenly confirmed previously held conceptions that the number of human chromosomes totaled 48.

32 Painter, T. S., “The Y-Chromosome in Mammals.” *Science* 53, no. 1378, (New York, N.Y., May 27, 1921), 503–504.

³³ Gartler, Stanley M. “The Chromosome Number in Humans: A Brief History.” *Nature Reviews. Genetics* 7, no. 8 (August 2006): 655–60.

³⁴ Kottler, M. J. “From 48 to 46: Cytological Technique, Preconception, and the Counting of Human Chromosomes.” *Bulletin of the History of Medicine* 48, no. 4 (1974): 465–502.

Thus, the discovery of Tjio and Levan did more than substantiate the actual number of human chromosomes; it defined a territorial anatomic space with possibilities for further investigation, mapping, and clinical utility. The discovery became the foundation of future genetic studies, prompted by a new understanding of the chromosome as a structural entity, which contained genetic information relevant to disease and family inheritance studies. The very process of determining, printing, and distributing the chromosomal structures that contained genomic material gave rise to the possibility that the exploration of microbiology might continue in both depth and scale; that the internal and once imagined structure of the chromosome might yield information to help scientists discern the nature, structure, and functions of genetic material contained within each chromosome.

In this way, Tjio and Levan's discovery of 46 chromosomes in human lung fibroblasts marked the genesis of cytogenetics (the study of cellular structure and function) as an autonomous and respected scientific field. As Victor A. McKusick described "medical genetics, which really did not exist as a clinical specialty before 1956, was given its own organ, the nucleus...[from which it] evolved into a full-fledged clinical and academic field."³⁵ Tjio and Levan's momentous discovery yielded this rhetoric about the possibility of mapping genes on chromosomes. These figures affirmed, and later challenged a respected hypothesis of their era: that humans had fewer chromosomes than related species. Tjio and Levan's findings allowed cytogenetics to have a greater understanding of the microscopic and internal functions of the human chromosome. Once the number of chromosomes was accurately known, the boundaries of genetic study could be defined both spatially and visually—what Schrodinger had once imagined had transformed into visible reality. According to historian Andrew Hogan, Levan and Tjio's

³⁵ McKusick, V. A. "The Anatomy of the Human Genome: A Neo-Vesalian Basis for Medicine in the 21st Century." *JAMA* 286, no. 18 (November 14, 2001): 2289–95.

discovery transformed the genome from “an abstract way to identify an individual’s genetic material or genes, to referring to an observable and physically bounded anatomical entity”³⁶ that could be conceptualized in terms of human chromosomes. With a defined landscape, genetic mapping was no longer just a vision, but an actualized possibility.

Gilbert and the Advancement of Schrodinger’s Vision

*“To recognize that we are determined, in a certain sense, by a finite collection of information that is knowable will change our view of ourselves. It is the closing of an intellectual frontier with which we will have to come to terms.”*³⁷ –Walter Gilbert

One of the earliest proponents of human genet mapping was Walter Gilbert, a Harvard graduate and faculty member, and a pioneer in the field of molecular biology. Like Schrodinger, Gilbert had studied physics and chemistry as an undergraduate, and in 1957 he received a doctorate in Physics before accepting a tenure-track faculty position at Harvard. As a professor of physics, Gilbert learned about the advances in cytogenetics (i.e. the study of chromosomes) from collaboration with James D. Watson, co-discoverer of the double helical structure of Deoxyribonucleic Acid (DNA). Gilbert notably left his career as a physicist to study molecular biology, a relatively novel scientific discipline in the 1960s. Gilbert’s career transition illustrated the scientific shift Schrodinger had predicted in the mid-twentieth century; intellectual interests refocused toward the science of molecular human anatomy.

³⁶ Hogan, Andrew J. “The ‘Morbid Anatomy’ of the Human Genome: Tracing the Observational and Representational Approaches of Postwar Genetics and Biomedicine The William Bynum Prize Essay.” *Medical History* 58, no. 3 (July 2014): 315–36.

³⁷ Quoted in: Kevles, Daniel J., and Leroy E. Hood, eds. *The Code of Codes: Scientific and Social Issues in the Human Genome Project*. Cambridge, Mass: Harvard University Press, 1992. 96.

Gilbert understood that gene mapping embodied a paradox. To Gilbert, the genome represented the, “most basic or fundamental information [that]...could be available...”³⁸ and yet the task of gathering, storing, and mapping gene sequences was inconceivably colossal. Why were the simplest units of scientific information about the body the most difficult to extract and to understand? This paradoxical question led Gilbert in search of an answer and a method to sequence millions of proteins to understand the functions of DNA.

In addition to the intellectual challenges associated with mapping the genome, Gilbert was also concerned with the structural importance of genetic mapping, including a more nuanced view of gene functions. In a well-cited article from *Nature*, Walter Gilbert suggested that genes had an intronic structure, in reference to the intragenic region, the region inside the gene that could be spliced in order to be accurately transcribed.³⁹ This structure would allow molecular biologists to map proteins and to link strands of genetic material, similar to Schrodinger’s vision of linkages. The result of Gilbert’s findings, as he proclaimed in his writing, solved the problem of how to accurately duplicate genetic material under certain conditions. The intron model suggested that a second carbon copy of specific genetic material was located within the gene. Gilbert claimed that “introns are both frozen remnants of history and the sites of future evolution.”⁴⁰ He meant that one copy could be utilized for the study of contextual information (i.e. the gene as it normally functioned) and the second copy could be used to examine genetic material under changing conditions.⁴¹ Gilbert’s model of the intronic gene allowed molecular

³⁸ Ibid.

³⁹ Williams, Roy, Scott, and Walter Gilbert. “The Evolution of Spliceosomal Introns: Patterns, Puzzles and Progress.” *Nature Reviews Genetics* 7, no. 3 (March 2006): 211–21. doi:10.1038/nrg1807.

⁴⁰ Gilbert, Walter. “Why Genes in Pieces?” *Nature* 271, no. 5645 (February 9, 1978): 501–501.

⁴¹ For technical information on evolutionary genetics and introns, see Gilbert’s work: Roy SW, Gilbert W (March 2006). “The evolution of spliceosomal introns: patterns, puzzles and progress”. *Nature Reviews Genetics* 7 (3): 211–21.

biologists to understand a unique aspect of the human genome map—genetic expression in disparate conditions. One of the greatest challenges of print maps is in inability to account for a changing environment. If a natural phenomenon changed the landscape, an entirely new map would have to be constructed. Yet, Gilbert understood that a map of human genetics would have to be versatile in order to account for a plurality of conditions and expressions in individuals with diverse genetic materials. The intronic nature of the gene—its ability to remain preserved in its original context and to simultaneously be altered by changing genetic conditions—gave rise to the possibility of a versatile genetic map that could accommodate a wide range of expressions in the human genome.

Although a physical map of the genome served to identify the specific location of nucleotides, molecular biologists had not yet mapped the myriad possibilities for expression (although a gene may carry sequences for disease, certain environmental and health factors determine if and when the gene is expressed in the human body). In other words, scientists would be able to map sequences of DNA within the human genome, even though the functions of particular genes were not yet known in the 1980s. Furthermore, early methods for physical mapping were information-dependent, such that “the mapping of a gene to a specific chromosome requires previous knowledge of the location of another gene” further exemplifying the importance of locational accuracy in early stage intron mapping.⁴²

Yet Gilbert remained wary of the vast genomic landscape; he understood that the location of a single nucleotide basechange “at the boundaries of the regions to be spliced out, can change

⁴² Guston, David. *Reading the Atlas of Ourselves: Toward a Human Genome Initiative*. Cambridge, Mass: Harvard University. April, 1987. Original manuscript held by: Cold Spring Harbor Laboratory Archives and Genentech Center for the History of Molecular Biology and Biotechnology NY, USA

the splicing pattern, resulting in the deletion or addition of sequences of amino acids.”⁴³ From a geographic perspective, this was a warning against the possible outcomes of faulty mapping procedures, where a microscopic change could result in the complete misrepresentation of the mapped gene, both in terms of the spatial accuracy (i.e. boundaries) of the region being mapped, and in terms of the final product depicting an accurate representation of the base pair sequence. His argument highlighted the importance of locational accuracy, because this influenced function and the potential for mutations. Additionally, the geographic location of certain base pairs offered potential information that would be useful in identifying other sequences. Thus, the spatial accuracy of one sequence was not independent from the spatial accuracy of other sequences. Gilbert’s concerns over spatial accuracy were later complicated by the drive to map and catalog sequences efficiently. Furthermore, Gilbert was not unaware that the genome held significant potential for medical and biopharmaceutical applications.⁴⁴

As an early proponent of the Human Genome Project, Walter Gilbert firmly grasped both the intellectual paradoxes and the technical and regulatory challenges inevitable in the colossal project of mapping the human genome. From the intronic structure of genes to the importance of locational accuracy in mapping practices, Gilbert’s writings point to specific nuances that were central to debates at the outset of the Human Genome Project. Like his predecessors, Gilbert’s descriptions of a human gene map contributed the intellectual momentum that contributed to both the prospects and complications of a human gene map.

Morbid Anatomy: A New Application

“In summary, chromosome analysis, gene mapping, and complete sequencing of the genome

⁴³ Gilbert, Walter. “Why Genes in Pieces?” *Nature* 271, no. 5645 (February 9, 1978): 501–501.

⁴⁴ See chapter two: Gilbert and the Rise of Private Bioinformatics

provide an anatomic basis for all aspects of clinical medicine.”⁴⁵ – Victor McKusick

By the 1980s, much intellectual preparation had been completed to enable sequencing of the genome. Tjio and Levan had correctly enumerated and mapped all 46 human chromosomes, while Gilbert and many other microbiologists had developed techniques to rapidly sequence lengthy strands of DNA. Yet a new frontier was again on the horizon. In 1982, geneticist and Professor of Medicine Victor McKusick published an article entitled “The Morbid Anatomy of the Genome.”⁴⁶ His article described the genome as having an anatomy that could be mapped to better understand genetics and clinical medicine. In fact, McKusick published a map of each chromosome, labeled by section and known function. He proposed that such a map had immense utility for clinical medicine, and demonstrated that it was possible to link chromosomal location of genes to certain inherited diseases. McKusick’s map earned him a status as the “father of medical genetics.”

McKusick’s method utilized linkage family studies to create an epidemiological map of the genome, a physical map of inheritable diseases that could be correlated to certain chromosomes. The linkage family studies method utilized genetic information from related individuals most often to examine gene-disease associations (i.e. the genetic etiology of disease). Familial linkage studies involved an investigation into the likelihood of parent-offspring inheritance, chromosomal lineage, studies of gene variation and relatedness of affected family

⁴⁵ McKusick, V. A. “The Anatomy of the Human Genome: A Neo-Vesalian Basis for Medicine in the 21st Century.” *JAMA* 286, no. 18 (November 14, 2001): 2289–95.

⁴⁶ “The Morbid Anatomy of the Human Genome: The Current Status of the Human Gene Map”: Victor A McKusick; Sydney Brenner Collection (64) (15 Ap. 1987)
McKusick, V. A. (1986), The Human Gene Map 15 April 1986: The Morbid Anatomy of the Human Genome. *Clinical Genetics*, 29: 545–588.

members, and analysis to identify the probability of inheritance or mutation.⁴⁷ In fact, the first gene to have been mapped (in 1911) utilized a Mendelian method to identify the genetic characteristics of colorblindness (found by color-dyeing sex chromosomes) in *Drosophila*.⁴⁸ This achievement relied on an approach that was a precursor to familial linkage studies, and served as a basis for future mapping approaches.

McKusick had experience with linkage studies prior to his contributions to genetic mapping. In 1958, he conducted a population study on inhabitants of Tangier Island on the coast of Virginia. Four years later, his interest was redirected to studying hereditary disorders among the Pennsylvania Amish.⁴⁹ This work encapsulated part of the emerging field of population genetics, the study of genetic inheritance from a certain subgroup of a population. McKusick's correspondence indicated that the map of chromosomes he published had a number of international contributors. In November 1975, Walter F. Bodmer, a population geneticist at Oxford, wrote to McKusick to share his findings on chromosome six.⁵⁰ Given his research emphasis and collegial collaborations with population genetics, it is interesting that the map McKusick published was not specific to the genetic traits of a particular population, but instead catalogued potential disorders from a more normative chromosomal map. Like Schrodinger, McKusick was a visionary of the human genome map, and as a product of his era, McKusick had the ability and determination to help actualize the genetic map Schrodinger had envisioned three

⁴⁷ Pearson, Thomas A. . "Genetics for Epidemiologists Study Designs; Family-Based Studies." Lecture, Visiting Scientist-NHGRI, at University of Rochester School of Medicine

⁴⁸ Wilson, Edmund B. "Studies on Chromosomes. III. The Sexual Differences of the Chromosome groups in Hemiptera, with Some Considerations on the Determination and Inheritance of Sex." *Journal of Experimental Zoology* 3, no. 1 (February 1906): 1–40

⁴⁹ Lindee, S. *Moments of Truth in Genetic Medicine*. Baltimore, Md.: Johns Hopkins University Press, 2005.

⁵⁰ Bodmer, Walter F. Letter to Victor McKusick. 26 Nov. 1975. *The Victor A. McKusick Papers*. Bethesda: National Library of Medicine, 2014. *Profiles in Science*. Web.

decades earlier. With information on the locations of associated disorders, retrieved from colleagues, linkage studies, and population studies, McKusick ensured that the map could continuously be updated to accommodate new information.

From the outset, the map accounted for location (i.e. the site on the chromosome), symbols, status (i.e. confirmed, provisional, tentative), title, and what he termed the “MLM number.”⁵¹ The MLM was an acronym for the Mendelian Inheritance in Man, a compendium of identified human genetic disorders. The database included a description of type of disorder, its cytogenetic (i.e. chromosomal) location, a list of relationships to other genes, and a clinical synopsis to describe traits of physical inheritance. The Mendelian Inheritance in Man Catalogue represented an early endeavor to foment access to information about the progress of mapping inherited diseases on chromosomes. Prior to his direct work with the morbid anatomy of the genome, he understood the possibilities that would result in mapping human chromosomes. In 1969, McKusick attended a conference on congenital malformations. In his closing address, entitled “Birth Defects: Prospects for Progress” he pointed to genetics as the forefront of a new scientific frontier, and proposed a, “detailed exploration of the genetic constitution of man.”⁵² Like Schrodinger, McKusick was a visionary of future investigation of the human body. As a prominent medical scholar at Johns Hopkins, McKusick had the resources and the influence to ensure that the utility of the human genome involved clinical applications. Unlike Schrodinger, McKusick had the technological resources to pioneer an online inheritance database. From this, the body again transcended the processes of physical and spatial mapping; access to information

⁵¹ McKusick, V A, and J S Amberger. “The Morbid Anatomy of the Human Genome: Chromosomal Location of Mutations Causing Disease.” *Journal of Medical Genetics* 30.1 (1993): 1–26. Print.

⁵² International Conference on Congenital Malformations (3rd : 1969 : Hague, Netherlands). 1970. *Congenital Malformations: Proceedings of the Third International Conference, the Hague, the Netherlands, 7-13 September 1969*. P 407. Amsterdam;New York.

about the body could now be transmitted through machine, and the endless possibilities of the endless frontier emerged once again.

In 1945, Erwin Schrodinger, well renowned as a quantum physicist, gave a speech entitled “What is Life?” His inquiry was, in part, a recognition of the changing scientific landscape. The laws of quantum physics, which he understood well, could no longer fully explain the elaborate genetic code-script that he envisioned nearly four decades prior to the Human Genome Project. Fifteen years following his lecture at Trinity College, Schrodinger published a short manuscript, which seemed to offer a personal answer to his initial question. He wrote that, “The self is not so much linked to its ancestors, it is not so much the product, and merely the product, of all that, but rather, in the strictest sense of the word, the same thing as all that: the strict, direct continuation of it.”⁵³ This is perhaps how Schrodinger might have viewed the Genome Project: that the ideas and descriptions set forth by scholars such as Tjio and Levan, Gilbert, McKusick, and countless others were not merely linked to the Project, but instead provided the intellectual momentum for its actualization.

⁵³ Schrödinger, Erwin. *My View of the World*. University Press, 1964. 28.

Chapter Two

The Nomenclature Precedent: Implications of the Denver Conference

“To undertake a history of the sciences...is to show how the establishment of science, and perhaps its transition to formalization, have come about in a discursive formation. [Language reveals] a whole set of differences, relations, gaps, shifts, independencies, autonomies, and the ways in which they articulate their own historicities on one another.”

- Michel Foucault⁵⁴

Genetics and Language-Based Classification

Language is a fundamental component of scientific practice. Genetic research methods and the interpretation of genetic data is complex enough to constitute a language in itself. Like any discipline, the line of intelligibility in genetics is strongly related to language. The language scientists use to construct a question informs their answers, just as the ways in which evidence is presented influences its reception. In the specific case of genetics, the articulation of problems, the methods used to arrive at solutions, and the formation of conclusions depends upon the language geneticists use.

In the 1960s, the sub-field of cytogenetics (the study of chromosomes) prospered following the creation of a standardized naming system for chromosome maps. Yet by 1990, at the outset of the Human Genome Project, the mapping community had not developed a standardized language classification system for gene mapping, a task immensely more complicated than chromosome mapping. The result was, as Foucault might have predicted, a series of gaps, overlaps, independencies, complications, and duplications in mapping languages

⁵⁴ Foucault, Michel. *The Archaeology of Knowledge and the Discourse on Language*. Vintage Books Edition. Vol. Science and Knowledge. New York: Random House, 2010.

and systems. The lack of systematized nomenclature at the outset of the Project reveals much about early complications in the Human Genome Project and contributes more broadly to debates about scientific standardization and objectivity at the end of the twentieth century.

Early Cytogenetic Mapping Origins and the Denver Conference

By the mid-20th century, the discovery of smaller microscopic gene regions had introduced new spaces that contained vast amounts of complex chromosomal information. Such information was comprehensible and navigable, in part, because a common system of vocabulary existed. This system defined chromosome bands, landmarks, and regions, and held a single standard for identifying these areas. Thus, even as the map of chromosomes became increasingly complex with the accumulation of more information, the chromosome map remained intelligible and useful in facilitating further research.

Following Joe Hin Tjio and Albert Levan's landmark confirmation of 46 human chromosomes in 1956, the field of cytogenetics began to refine chromosome maps (i.e. karyotypes) for greater visible clarity and resolution. As different mapping methods were tested, it became possible to identify distinctions in chromosome forms; cytogeneticists speculated that form influenced function.⁵⁵ If scientists interested in gene location could map the structure of chromosomes, the results would reveal information about the purpose and utility of certain chromosomes, and a language-based classification system could be used to create maps that detailed chromosome form and function. By the 1960s, greater lens resolution led to more precise chromosome photographs and cytogeneticists speculated that genes on the chromosome might soon be studied in greater detail. If images of the chromosomes were to be translated into a

⁵⁵ To chronologically note these distinctions, please see Figures 1 and 2 (pages 29-30)

map of chromosomes, the information had to be intelligible and navigable.

According to a retrospective report from the Congressional Standing Committee on Human Cytogenetic Nomenclature, “by 1959 several laboratories were engaged in the study of human chromosomes and a variety of nomenclature and classification systems ha[d] been proposed ...this resulted in confusion in the literature and a need to establish a common system of nomenclature that would improve communication...in the field.”⁵⁶ Without a common system of vocabulary, cytogeneticists could not determine or reference the sections of chromosomes that had previously been studied or mapped. This had the potential to hinder progress on a detailed map of human chromosomes.

In 1960, four years following Tjio and Levan’s discovery, British cytogeneticist Charles E. Ford convened a meeting on chromosomal nomenclature in Denver, Colorado. With fourteen lead investigators, all of whom had published human karyotypes (i.e. chromosome images), the group decided to number the chromosomes and pair corresponding sets together, to demarcate the sex chromosomes with “X” or “Y” and to further categorize all chromosomes by size groups.⁵⁷ By the 1960s, cytogenetic studies had been linked to new information about the origins of down syndrome and leukemia, and the potential medical applications of these findings created exciting prospects for scientists and physicians alike. The nomenclature system developed at the Denver Conference remained in use for decades following its establishment, and emerged in

⁵⁶ Standing Committee on Human Cytogenetic Nomenclature. *An International System for Human Cytogenetic Nomenclature (1978): ISCN (1978) : Report of the Standing Committee on Human Cytogenetic Nomenclature, Hässelby Castle, Stockholm, Sweden, September 4-9th, 1977*. Basel; New York: S. Karger, 1978.

⁵⁷ Lindee, M. *Moments of Truth in Genetic Medicine*. Baltimore, Md.: Johns Hopkins University Press, 2005.

response to the need for a common scientific and medical vocabulary to further communication and organization in cytogenetics.

Eighteen years later, the Congressional Standing Committee on Human Cytogenetic Nomenclature again stated, “It is fair to say that the participants at Denver did their job so well that this report has formed the cornerstone of human cytogenetics since 1960, and the foresight and cooperation shown by these investigators prevented much of the nomenclature confusion which [now] marks other areas of human genetics.”⁵⁸ With a clear system of vocabulary and a consistent method to identify and categorize new information, cytogenetic research prospered.

Between 1960 and 1980, cytogenetic research confirmed that chromosome bands determined the structure and function of DNA. In a lecture delivered at the National Library of Medicine, genome architect Charles R. Cantor stated, “...as we make maps...what we look for in these maps are patterns. We hope that there will be some images in the maps which will provide clues to function... history, evolution, and organization. And there already is a striking pattern in the physical map of the human genome, even seen at this very crude level of resolution, it's these bands.”⁵⁹ Indeed, bands were a crucial part of chromosome mapping; the Congressional Standing Committee on Human Cytogenetic Nomenclature identified these bands because the intensity of lightness and darkness on the bands was clearly distinguished when the chromosome was stained.⁶⁰ Furthermore, stains indicated particular regions of each chromosome, defined by the committee as band *landmarks*. These landmarks represented greater visible specificity of

⁵⁸ Standing Committee on Human Cytogenetic Nomenclature. *An International System for Human Cytogenetic Nomenclature (1978): ISCN (1978): Report of the Standing Committee on Human Cytogenetic Nomenclature, Hässelby Castle, Stockholm, Sweden, September 4-9th, 1977.*

⁵⁹ Cantor, Charles. “Biotechnology Seminar Series: The Human Genome Problems and Prospects.” Bethesda, MD: National Library of Medicine, 1988.

⁶⁰ For further information on the original banding pattern, see the Paris Conference Report of the Standing Committee on Human Cytogenetic Nomenclature (1971)

chromosomal subregions, and cytogeneticists speculated that genes were located within these subregions.

In addition to clear definitions of chromosome band nomenclature, the committee also addressed topics of identification and definition of landmarks, the designation process for regions and bands, and comments on a diagrammatic representation of these newly discovered chromosomal subregions. In fact, the methodology for mapping chromosomes was highly intelligible: “In designating a particular band, four items [were] required: (1) the chromosome number, (2) the arm symbol (i.e. the short or long arm of the chromosome), (3) the region number, and (4) the band number within that region. These items [were] given in order without spacing or punctuation. For example, 1p33 indicated chromosome 1, short arm, region 3, band 3.”⁶¹ Cytogenetic chromosome maps became progressively more detailed with higher resolution images. Despite their complexity, these maps were intelligible because they followed a single system of nomenclature. Initial depictions of chromosomes evolved into regions and bands which served as landmarks for genetic diseases. Increased resolution and visibility led to more complex mapping spaces, and a set of standardized nomenclature, based on the Denver Conference, was utilized to facilitate chromosome mapping as a precursor to gene mapping.

However, the system developed by the Denver Conference in 1960 also had limitations. As historian Susan Lindee points out, the Denver Conference made a critical error when an incorrect measurement system misclassified the sizes of chromosomes 21 and 22. In fact, a member of the Denver Conference had “misidentified an important chromosome and his error was in effect institutionalized, so that the last two human chromosomes ha[d] the ‘wrong’

⁶¹ Region 1p33 has been linked to Miller syndrome, an extremely rare genetic condition that affects facial and limb development as well as severe respiratory problems. Human Genome Nomenclature Report 1978.15.

numbers.”⁶² The problem was that the group had identified the location of Down Syndrome on the incorrect chromosome and the gene that coded for Down Syndrome was referred to by the number 21 based on the Denver classification system, when, as a technicality, gene expression for Down Syndrome should have been mapped on Chromosome 22.⁶³ In medical literature produced in the decades following this misnomer, the precise location of the chromosome remained intentionally misidentified in order to preserve the structure of the nomenclature system. Cytogeneticists realized the value of continuity in having singular, coherent terminology to guide research. Despite its imperfections, the Denver naming system remained in place for decades following the Denver Conference, and its extensive use by the genetics community facilitated communication, organization, and precision in future cytogenetics research.

⁶² Lindee, S. *Moments of Truth in Genetic Medicine*. Baltimore, Md.: Johns Hopkins University Press, 2005.

⁶³ *Annals of Human Genetics*, London, 1960, vol. 24, p106-108



Figure 1:

A low-resolution karyotype of forty-six human chromosomes discovered by Tjio and Levan in 1956.

This image depicts chromosomes from a human lung fibroblast. From 1956-1978 cytogeneticists made remarkable strides in organizing chromosomes so that they could be mapped and studied in further detail. Although not visible at the time, high resolution photographs made chromosome bands later visible and created the possibility of further mapping investigations related to genetically inherited diseases. Yet without a nomenclature classification system, duplicate sections of the genome were still mapped.

Image reprinted with permission from BioMed Central, acquisitioned from Hereditas

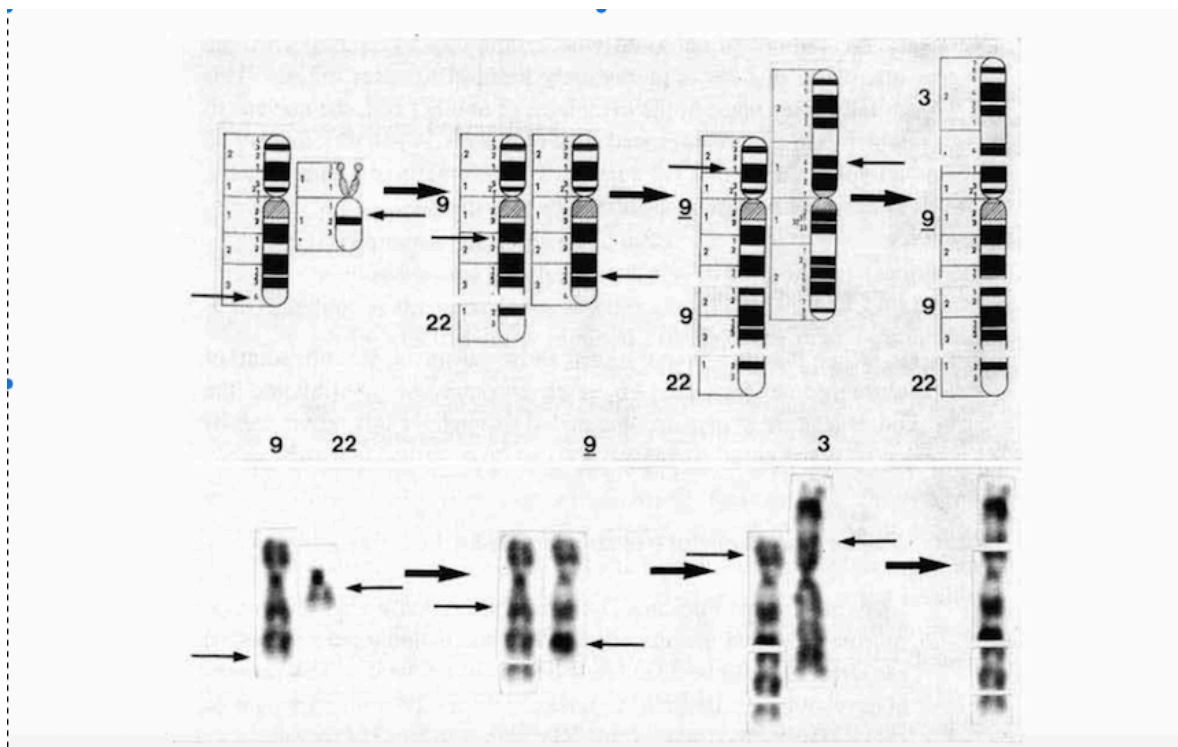


Figure 2: This image was published by the Standing Committee on Cytogenetic Nomenclature that met in Stockholm, Sweden in 1978. It depicts higher-resolution photographs of chromosomes 3, 9, and 22 and then-current mapping progress based on the standards developed at the Denver Conference in 1960. Note the visible difference in organization in contrast to the original 1956 karyotype (as seen above).

Image reprinted with permission from S. Karger AG, Medical and Scientific Publishers

Nomenclature and the Genome: Early Concerns

In the 1960s and 1970s cytogenetic research flourished: Francis Crick and Sydney Brenner discovered mutations on chromosomes and the function of messenger RNA was found to duplicate genetic information on the chromosome. However, by the 1980s, the system of chromosomal nomenclature could not accommodate the continuous discovery of new information that operated outside of the pre-existing structure devised at the Denver Conference.

The primary problem was one of scale: whereas the map of chromosomes depicted forty-six entities, each marked with bands and subregions, the DNA inside of the composite chromosomes totaled approximately 3.2 billion base pairs.⁶⁴

During the 1960s, rapid and simultaneous advances in genetics facilitated an unprecedented amount of data related to genetic sequences, protein synthesis, and gene expression. However, technological limitations for dealing with the magnitude of information presented yet another problem in the early stages of the Human Genome Project. As Vannevar Bush had so aptly anticipated, genetics appeared to be an endless frontier of information. Without computer operating systems, it would have likely been impossible to catalogue, archive, organize, analyze, and display the information as it was discovered.

Even so, not all scientists involved in the information-gathering stages of the HGP were convinced of the value of mass information collection. An article published in *Cytogenetics and Cell Genetics* noted that, in the early stages of the Human Genome Project, “the increase in numbers of newly identified genes [was] not...matched by an increase in functional information.”⁶⁵ Indeed, many believed that the search for information should be localized and comprehensive rather than general and expansive. In other words, some proponents advocated the collection of a sequence and its functional information so that map entries would comprise all available information about the gene studied. However, the approach most common in the Human Genome Project was instead the initial collection of as many sequences as possible. This presumed that functional information (about disease and inheritance and mutation) would be

⁶⁴ "Inside Life Science." Genetics by the Numbers. June 11, 2012.

<http://publications.nigms.nih.gov/insidelifescience/genetics-numbers.html>.

⁶⁵Wain, H., J. White, and S. Povey. "The Changing Challenges of Nomenclature." *Cytogenetics and Cell Genetics* 86, no. 2 (1999): 162-4.

added to the map after-the-fact. Accordingly, an entirely new nomenclature structure was required to accommodate this vast and uncharted genomic landscape.

Additionally, the nomenclature question was tied to a number of practical concerns about the project. Although sponsorship had been discussed by a number of national institutions, including the National Institutes of Health, the Department of Energy, and the National Science Foundation, the question of responsibility for the establishment and implementation of an intelligible language system was unclear. The result was multiple laboratories across the nation and the globe conducting research, but using different terms to refer to the same phenomena. Such language-based communication barriers hindered the collaborative nature of the endeavor, causing some research to be carried out repetitively, while leaving other tasks incomplete or unaddressed. More than just an intellectual ideal, the nomenclature issue was reflective of broader issues discussed at the outset of the Human Genome Project, including coordination between researchers, intelligibility of information, organized and collaborative research, institutional purview and implementation of standards to the broader genetics community.

Approximately one decade before the formal commencement of the Human Genome Project in 1990, American proponents of the HGP began to voice their concerns about nomenclature. Dr. Donald Lindberg, the first President of the American Medical Informatics Association, advocated for a system of standardized mapping nomenclature in genetics.⁶⁶ He asserted that a system of gene naming, similar to the system of cytogenetic nomenclature that had been highly successful in the 1960s, would advance networks of information sharing. The kind of coordination that Lindberg envisioned had the potential to standardize gene mapping and to allow for greater collaboration in the Human Genome Project. Proponents of a standardized

⁶⁶ Lindberg, DAB. *The Growth of Medical Information Systems in the United States*. Lexington: D.C. Heath and Company, Lexington Books, 1979: 194.

nomenclature system argued that it would significantly reduce the time and resources required to complete the human gene map.

In 1984, Frank Ruddle, Yale Professor and HGP proponent and architect, argued that, “increased knowledge of the gene map makes it easier to map new genes, [as] the techniques developed to map one gene are then available to map others.”⁶⁷ Ruddle believed in the significance of standardized mapping nomenclature and its influence on mapping methodology. If mapping techniques were not clearly communicated and shared, gene mapping could not progress efficiently.⁶⁸ Concerns over efficiency were likely related to the significant diversion of funding toward the genome project, particularly, some scientists felt, at the expense of other biological research. The Project was also in its planning stages during the global economic recession of the 1970s and 1980s, and efficient research offered the potential for economic stimulation in the fields of science, technology, and healthcare.

Just as cytogenetics had set a precedent for the gene map, genome nomenclature also held implications for the future of biology as an academic discipline. In 1982 Dr. Thomas B. Shows, the Co-Chair of the Human Genome Nomenclature Committee reported that, “an understanding of the human gene map should promote a genetic knowledge of how genes function individually and as coordinated sets...such information is essential for defining all aspects of normal and abnormal human biology and development.”⁶⁹ The standards of normalcy set by a system of

⁶⁷ Miller R, L, Partridge C, W, Kidd K, K, Ruddle F, H, The Yale Human Gene Mapping Library. Cytogenetic Genome Res 1984.

⁶⁸ The first genome-related methodology patent was granted in 1980 to Stanley Norman Cohen and Herbert Boyer for cloning the gene that codes for insulin. The licensing royalties for this patent exceeded three-hundred million dollars. See: Cell and Molecular Biology, Concepts and experiments / Gerald Karp –5th Ed (2008). pp. 976 - 977

⁶⁹ Shows, Thomas B., Alan Y. Sakaguchi, and Susan L. Naylor. “Mapping the Human Genome, Cloned Genes, DNA Polymorphisms, and Inherited Disease.” In *Advances in Human Genetics*, edited by Harry Harris and Kurt Hirschhorn, 341–452. Boston, MA: Springer US, 1982

nomenclature vested significant authority in genetics research. To return to the cytogenetics example, the Denver system defined a normal human being as one that possessed forty six chromosomes with particular bandwidths and strands. If these bands deviated from the system, it was an indicator of mutation and genetic disease. Thus, the power of a system to delineate normalcy from abnormality revealed the immense power of a set of nomenclature standards.

With such power at stake, the Project received scathing criticism from scientists concerned with the diversion of funding from other biological research. Between February and May of 1990, Michael Syvanen, a professor at the University of California at Davis, organized a petition concerning the funding for the Project: “The human genome project is not being funded with additional research appropriations; it is being funded with money that would otherwise fund the rest of biological research...we are facing an unprecedented crisis in American biological research funding.”⁷⁰ This funding crisis was in part a result of potential sponsorship for the Project as sponsorship contenders were the National Institutes of Health, the Department of Energy, and the National Science Foundation: the three primary sponsors of American scientific research. Although a system of standards emerged early on in other areas of genetic research, these standards did not reach the Human Genome Project until the 1970s.

Even after the formal commencement of the Human Genome Project in 1990, a standard system for genome vocabulary was still being discussed in academic circles and among potential institutional sponsors. The lack of a formally implemented nomenclature system created problems even in the first year of the HGP. In a letter to Dr. Elkye Jordan, then director of the National Center for Human Genome Research, Dr. Kenneth Kidd of Yale noted that, “the criteria

⁷⁰ National Center for Human Genome Research. Complaints and Criticisms File. Box BCD7. Human Genome Archives. National Reference Center for Bioethics at Georgetown. For further information, please see: Fortun, M. A. (1993). *Mapping and making genes and histories: The genomics project in the united states, 1980-1990*

used to select (genome) markers were different” for each mapping committee and that the HGP would require a coordinated effort to, “avoid presenting information in seemingly conflicting ways that might confuse others and retard effort toward...a complete and accurate genetic map.”⁷¹ By 1990, the first year of the Genome Project, no single or standardized system for genome mapping nomenclature had been agreed upon or implemented. Yet the problem was recognized within the mapping community. In a meeting held the same year, the Human Gene Mapping Workshop Executive Committee met at Saint John’s College, Oxford, to discuss the future of mapping meetings. Nomenclature was the first item listed in the meeting minutes. Due to the size of previous mapping workshops (specifically, the number of attendees and the amount of new material generated), the committee felt that an established system of nomenclature would allow standardization across subcommittees, many of which could not attend each individual mapping workshop.⁷² By the introductory year of the Human Genome Project, nomenclature debates influenced the structure and coordination of mapping workshops and meetings.

Nomenclature also revealed the technical difficulties of mapping genetic information with an unknown structure. Whereas function was generally known prior to the mapping of chromosomes, and the naming system was based on size and function, it was nearly impossible to map structures that were still being discovered within the genome. Thus, naming standards could not incorporate protein function into a genetic nomenclature system. This problem highlights an early criticism of the Project itself, that protein coding occurs in approximately 2% of the genome, while the remainder of the genome embodies non-coding (i.e. “junk”) DNA. Early critics of the Project posed a cost-benefit analysis that proved that 98% of information

⁷¹ Kidd, Dr. Kenneth, and Dr. Elke Jordan, October 23, 1990. NHGRI file 0141-026.P7. National Human Genome Research Institute.

⁷² Workshop on Human Gene Mapping. 1991. Workshop on Human Gene Mapping. Washington: U.S. G.P.O.

from the fully coded genome was not readily applicable to the Human Genome Project. Instead of mapping the 2% coding segment of the genome, researchers elected to map the sequences in their entirety, including the 98% of noncoding genes with no known biological function.

Unanticipated Consequences: Duplication and Pathology

Without a standardized system of nomenclature, discussions of the genome were difficult for both the scientific community and the public. In the absence of a common vocabulary, communication between institutions that collaborated on the Human Gene Project remained muddled. Without a common organizational system to classify, document, and exchange information about the progress of gene mapping, project architects had no clear method to exchange standardized information about mapping progress.

An article published in the midst of the project highlighted the problems of duplicated segments ingrained in the gene map. The Segmental Duplication research group found that 3.6% of the entire map was composed of duplicate segments. The report stated that these sections of the map were “over-represented in unordered and unassigned contigs (that is, overlapping DNA segments) indicating that duplicated sequences [were] difficult to assign to their proper positions.”⁷³ Studies had already confirmed the significant pathological and disease related consequences of duplicated segments. These mapped duplicates resulted in “new functional roles in the organism” and “local deletions, duplications, and inversions” of gene sequences.⁷⁴ Human cognitive and physical problems associated with genome sequence duplication included: color blindness, Emery-Dreifuss muscular dystrophy, Hunter Syndrome, Hemophilia, and spinal

⁷³ Bailey, J. A., Yavor, A. M., Massa, H. F., Trask, B. J., & Eichler, E. E. (2001). Segmental Duplications: Organization and Impact Within the Current Human Genome Project Assembly. *Genome Research*, 11(6), 1005–1017.

⁷⁴ Mazzarella, Richard, and David Schlessinger. “Pathological Consequences of Sequence Duplications in the Human Genome.” *Genome Research* 8, no. 10 (October 1, 1998): 1007–21.

muscular atrophy. Furthermore, pathological mutations were attributed to the, “mapping of the region in the vicinity of the breakpoints with...markers [that] show[ed] that some sequences are repeated in the areas that border the deletions.” Specifically, mapping data on Xq28 (i.e. the X chromosome, long arm, band 2, region 8) indicated that an estimated 10% of this sequence [was] duplicated at least once.⁷⁵ Yet the severe consequences of sequence duplication were not considered in reports published by the genome nomenclature committee. Without an organizational system to classify, document, and exchange information about the progress of gene mapping, researcher had no clear method to exchange standardized information about mapping progress.

In addition to concerns over standardization, and unlike the intelligible system outlined by cytogeneticists at the Denver Conference in 1960, genetic mapping language was highly inaccessible at the outset of the Human Genome Project in 1991. Genome contributors held varying degrees of scientific literacy and education, and there existed no shared system of vocabulary for the exchange of information. Thus, the majority of knowledge generated by the Project was incomprehensible to a non-specialist public:

As part of the pattern, for example, restriction mapping of the short arm of chromosome 16 has revealed that three different alleles of the α -globin gene lie, respectively, 170, 350, and 430 kb from the telomere (Wilkie et al. 1991). Polymorphic length variation at this locus is postulated to have arisen by nonhomologous exchanges between the subtelomeric repeats on different chromosomes. Furthermore, heterozygosity for the telomere polymorphism may have an effect on meiotic segregation. Because most nonhomologous pairing resulting in nondisjunction occurs at telomeres, trisomy of

⁷⁵ Ibid.

chromosome 16 may be more frequent in heterozygotes for the subtelomeric region (Speed 1988). Interestingly, trisomy of chromosome 16 is the most common trisomy seen in early natural abortuses.⁷⁶

This example illustrates that information produced about genetic mapping influenced communication standards, information-sharing, and intelligibility. The absence of a standardized system of nomenclature affected mapping efficiency, as non-named sections of the Genome were duplicated. This error not only produced inaccurate sections of the gene map, but directly affected the study and correct diagnosis of genetically-inherited diseases outlined in the map. Still, genetic nomenclature varied by laboratory, by region, and by working research groups. Similar to colloquial language variations, mapping language in the Human Genome Project was not formalized. Instead, several systems for identifying, classifying, and reporting new genetic research existed simultaneously. Certain research groups relied upon numeric classification systems, while other groups classified their findings based on size, estimated function, or geographic location on the physical gene map. The absence of a singular standardized nomenclature system highlights the Project as a cultural and social endeavor, subject to variations and inconsistencies. While nomenclature directly shaped the possibilities and limitations of the Human Genome Project to its completion, the genetic vocabularies that emerged in the twentieth century have now, “create[d] situations that transcend our legal structure and directly affect our social and moral fabrics. Thus there is a great need to continue dialogues between the judiciary, the legal community, the legislature, the interested public, and the scientific community to provide guidance in scientific developments that hold major impacts

⁷⁶ Ibid.

for society.”⁷⁷ Nomenclature is but a single example that reconfigures the Human Genome Project as a cultural and social project, defined and actualized by the language systems that enabled the creation of a long-envisioned human gene map.

Nomenclature and Standardization:

Throughout the early to mid-twentieth century, scientists envisioned the mapping of the human genome in different ways and the absence of a common vocabulary hindered the Project’s actualization. By the 1980s, many technological and scientific advances made the Human Genome Project feasible, and a number of renowned scientists and physicians, including Walter Gilbert and Victor McKusick, were involved in planning the mapping and sequencing effort.⁷⁸ Architects of the Project were also responsible for anticipating the large-scale organizational and structural complexities associated with the Human Genome Project. Other potential concerns included funding sources, collaborative efforts between public and private institutions, information-sharing, and the need for a committee to address ethical, legal, and social implications of the project. These concerns have largely been explored in a number of secondary historical writings and reveal intellectual debates that were addressed at the outset of the Project.⁷⁹ However, the issue of standardized genome nomenclature was not adequately anticipated in the wake of ethical and social concerns about mapping the genome.

⁷⁷ Kieff, Scott F, *Perspectives of Properties of the Human Genome Project*. Boston. Elsevier Academic Press, 2003: 11

⁷⁸ Watson, James. *The Double Helix A Personal Account of the Discovery of the Structure of DNA*. (1980 *Norton Critical Edition*), editor Gunther Stent, W.W. Norton.1980

⁷⁹ Cook-Deegan, Robert M. 1994. *The Gene Wars: Science, Politics, and the Human Genome*. New York: W.W. Norton & Co.

Kevles, Daniel J., and Leroy E. Hood, eds. *The Code of Codes: Scientific and Social Issues in the Human Genome Project*. Cambridge, Mass: Harvard University Press, 1992.

Loeppky, Rodney. 2005. *Encoding Capital: The Political Economy of the Human Genome Project*. New York: Routledge.

Central to the nomenclature debate was the question of standardization. The mapping process, reliant upon descriptions of genes and their relative locations on chromosomes, might have been significantly simplified by a standardized scientific language to describe, reference, catalog, transfer, map, and share information about the genome. In a letter written the commencement year of the Human Genome Project Dr. Phyllis McAlpine noted her “concerns about the release of developing maps...while [she did] not disagree in principle, with the rapid release of scientific information [she held] deep reservations about the process as no consideration appear[ed] to have been given to standardized nomenclature. [She] believe[d] that a major contributing factor to the authoritative nature and universal comprehension of the maps developed at the Human Genome Mapping workshops [could be] the insistence on standardized nomenclature so that all mapping information [could] be captured readily in the electronic databases of information pertaining to the map of the human genome.”⁸⁰ McAlpine later served as the chair of the Human Genome Nomenclature Committee, an international organization that advocated the necessity of standardized terminology for an endeavor as collaborative and as colossal as the mapping of the human genome. Established formally in 1979, the Human Genome Nomenclature Committee signaled an institutional acknowledgement that an established terminology was critical to the HGP’s organization and progress. Her perspective concerned both the logistical importance of standardized nomenclature for information-sharing and the “authoritative nature” that a singular terminology would produce.⁸¹ The authority of standardized

Sunder Rajan, Kaushik. 2006. *Biocapital: The Constitution of Postgenomic Life*. Durham: Duke University Press.

Murray, Robert F. 1996. *The Human Genome Project and the Future of Health Care*. Bloomington: Indiana University Press.

⁸⁰ McAlpine, Dr. Phyllis, and Dr. Elke Jordan. Professional Correspondence, August 31, 1990. National Human Genome Research Institute.

⁸¹ Ibid.

nomenclature had the potential to lend the genome project credibility (from consensus within the mapping community) and accessibility (to sequenced portions of the genome map). The completed map introduced opportunities for burgeoning biomedical and pharmaceutical economies, highly advanced medical research, the generation of new knowledge about human disease, and the academic prestige of mapping the human genome.

Even so, the human genome project relied upon, and even valued, processes of standardization to further ground the effort as objective and scientific. The methods used to establish this system of nomenclature were developed in the midst of the Project and cannot be separated from their historical setting. The work of M. Norton Wise provides a useful framework for understanding how precision and standardization of genome nomenclature reveals a matrix of discursive power, scientific values, and the subjectivity of human cartography.

In his work, *The Values of Precision* historian M. Norton Wise argues that precision and standardization in science are inseparable from cultural and historical values. He describes precision as a modern value that has a history closely related to scientific development. Wise is not the first historian to suggest that the scientific value of precision, far from ubiquitous and ahistorical, is a product of Enlightenment thought.⁸² Wise defines precision as, “responsible, nonemotional, objective, and scientific.”⁸³ He writes that precision requires reliability and must be agreed upon within a community. Precision, “requires an extensive set of agreements about materials...methods, and values that reach out into the larger culture.”⁸⁴ In order to form these agreements, and to arrive at a standard, a consensus much be reached from a network of

⁸² Everson, Ted. *The Gene: A Historical Perspective*. Westport, Conn.: Greenwood Press, 2007.
Hankins, Thomas L. *Science and the Enlightenment*. Cambridge; New York: Cambridge University Press, 1985.

Porter, Roy. *Flesh in the Age of Reason*. London: Allen Lane, 2003.

⁸³ Wise, M. *The Values of Precision*. Princeton, N.J.: Princeton University Press, 1995.

⁸⁴ Wise, M. *The Values of Precision*. Princeton, N.J.: Princeton University Press, 1995.

individuals. Precision, therefore, relies on a set of standards agreed upon by a community; this yields standardization. Ultimately, Wise argues that the process of standardization creates reliability, credibility, and makes numbers transportable beyond culture, and therefore valuable to a community concerned with precision and objectivity. As a historian of science, Wise's framework of precision and standardization is highly applicable to the Human Genome Project. There is utility in examining the debate about nomenclature in the Human Genome Project as a contribution to the contested history of standardization in modern science.

It is noteworthy that the mapping of the genome is only a recent example of how cultural and social values are reflected in scientific systems of classification and nomenclature. The classification system developed at the turn of the twentieth century to categorize ABO blood groups among individual populations remains a classic precedent of social values that influenced microbiological research. As authors Gannett and Griesmer describe, "'racial' classifications based on the physical characteristics of humans were subject not only to observations of the appearance of variation and difference, but also to judgments of categorical difference and to ethnic, cultural, and national biases that served as a priori classifications guiding sampling protocols for research on biological traits."⁸⁵ This is not dissimilar from mid-twentieth century speculations that human chromosome numbers were dependent upon race or ethnicity.⁸⁶

The lack of systematized nomenclature at the outset complicated the development of the Human Genome Project and contributed more broadly to debates about scientific standardization and objectivity at the end of the twentieth century. Thus, even as the map of chromosomes

⁸⁵ Gannett, Lisa and Griesemer, James R. *Classical Genetics and the Geography of Genes*. The Genetics of ABO Blood Groups. London; New York: Routledge, 2004.

⁸⁶ Kottler, M. J. "From 48 to 46: Cytological Technique, Preconception, and the Counting of Human Chromosomes." *Bulletin of the History of Medicine* 48, no. 4 (1974): 465–502.

became increasingly complex with the accumulation of more information, the chromosome map remained intelligible and useful in facilitating further research. Indeed, the importance of clear and structured mapping nomenclature was highly relevant to the map's continuity and progress. Without a common organizational system to classify, document, and exchange information about the progress of gene mapping, project architects had no clear method to exchange standardized information about mapping progress. Even so, the human genome project relied upon, and even valued, processes of standardization to further ground the effort as objective and scientific. As historians have accounted for racial, social, and political biases that influenced classifications for blood groups, historians now have the responsibility to account for cultural and social biases that rendered the Human Genome Project subjective to the intellectual zeitgeist of its era.

Chapter Three

Written Description: A Reconfiguration of Intellectual Property

“By the first decades of the twentieth century, the range of standard-setting institutions in many respects resembled our [current] situation...a decentralized and pluralistic constellation of institutions, each pursuing standardization to suit their own objectives within a dynamic and competitive context.”⁸⁷ – Andrew L. Russell

1960 marked the beginning of a decade defined by advancements in the field of genetics. A number of discoveries in microbiology further expanded opportunities for new research about the structure, function, and utilities of Deoxyribonucleic Acid (DNA). In 1960, just three years after Watson and Crick discovered the binary helical structure of DNA, Sydney Brenner, Francis Crick, François Jacob, and Jacques Monod solved a problem that had eluded geneticists for nearly a decade. Their research team, sponsored by the California Institute of Technology, had discovered Messenger Ribosomalnucleic Acid (mRNA), a set of molecules that were responsible for transferring genetic information to the cytoplasm, where genetic information is expressed.⁸⁸ The next year, thirty-four-year-old Marshall Nirenberg uncovered that the genetic code was comprised of chemical units of DNA that specify how protein molecules are constructed. By 1966, Dr. Nirenberg had identified the first sixty-three sequences of DNA.⁸⁹ Two years later, in 1968, Nirenberg and his colleagues were awarded the Nobel Prize in Physiology and Medicine for, “their interpretation of the genetic code and its function in protein

⁸⁷ Russell, Andrew L. *International Standardization as a Strategic Tool: Commended Papers from the IEC Centenary Challenge 2006*. Geneva, Switzerland: International Electrotechnical Commission, 2006.

⁸⁸ Crick FH, Barnett L, Brenner S, Watts-Tobin RJ (December 1961). "General nature of the genetic code for proteins". *Nature* 192 (4809): 1227–32.

⁸⁹ Wade, Nicholas. "Marshall Nirenberg, Biologist Who Untangles Genetic Code, Dies at 82." *New York Times*, January 21, 2010.

synthesis.”⁹⁰ The discoveries from the 1960s carried unprecedented individual import in the genetics community, but also collectively prompted new opportunities for discovering and assembling a map of the human genome. As individual research groups, laboratories, universities, and private institutions independently sponsored continued genome research, the issues of intelligibility and nomenclature norms remained unresolved.

Yet during this era of continuous discovery, no singular guidelines were in place to ensure that the information was uniformly treated. Several repositories existed to store newly collected information, although no nomenclature system existed to describe the location/structure/function of discovered genes. Certainly the need for a standardized system of nomenclature was discussed, and even advocated for in the midst of the Project. Its absence in the early planning stages of the Human Genome Project prompted several legal battles that transcended the existing legal framework for intellectual property in the life sciences.

By 1960, the field of cytogenetics had set a strong precedent for developing a standardized nomenclature system to facilitate and organize new information related to human chromosomes. The naming system developed in Denver was descriptive and intelligible to the extent that a lay person could locate a particular chromosome band and then retrieve hereditary information from their search. Despite its lauded success in the cytogenetics community, a nomenclature system was not established in the early stages of the Human Genome Project. However, the possibility of such a system was discussed several years prior to the formal commencement of the Human Genome Project. Indeed, the debate was not whether a system of nomenclature should be developed and utilized as an organizational tool, but how the system should be developed and implemented. Certainly it would seem that no single laboratory should

⁹⁰ Portugal, Franklin H. 2015. *The Least Likely Man: Marshall Nirenberg and the Discovery of the Genetic Code*. Cambridge, Massachusetts: The MIT Press.

have the authority or responsibility to establish such a system, but rather a prominent institutional sponsor.

On December 29, 1965 the National Institutes of Health received a manuscript from a team of geneticists working at Cold Spring Harbor Laboratories in Long Island. The seventy-six-page report was titled, “A Proposal for Uniform Nomenclature in Bacterial Genetics.”⁹¹ The proposal was developed from a paper published in 1953 at Brookhaven National Laboratory and sponsored by the U.S. Atomic Energy Commission that suggested a basic system for naming, referencing, and cataloguing genetic information.⁹² The paper defended the importance of a nomenclature system from a number of perspectives; it suggested that such a system was convenient and pragmatic (since individual research groups would not need to devise their own classification system), that it facilitated understanding and communication in the field, and it was malleable enough to accept new genetic information. The authors, a team of international geneticists, affirmed that:

“the aims of the present proposal are: uniformity, a unique designation for each strain, convenience for typing, editing, printing, record-keeping, and information retrieval; and adaptability, simplicity, and clarity, and comprehension by workers in all areas of biology; adaptability to new developments in the foreseeable future.”⁹³

The report concluded with an example of the system implemented; it contains a list of proposed standard symbols, based on known gene function. The report also included several

⁹¹ Demerec, M., E.A. Adelberg, A.J. Clark, and Philip E. Hartman. "A Proposal For Uniform Nomenclature in Bacterial Genetics." *Cytogenetics and Cell Genetics* 54 (July 1966): 61-76.

⁹² Dr. E.A. Adelberod, Department of Microbiology, Yale University, New Haven, Connecticut. W.A.J. Clark, Department of Molecular Biology, University of California. Dr. Philipe Hartmand, Department of Biology, The Johns Hopkins University, Baltimore, Maryland.

⁹³ Demerec, M., E.A. Adelberg, A.J. Clark, and Philip E. Hartman. "A Proposal For Uniform Nomenclature in Bacterial Genetics." *Cytogenetics and Cell Genetics* 54 (July 1966): 61-76.

recommendations for implementation. However, nine years passed before the nomenclature question was again discussed in mapping meetings.

Held in Rotterdam, the 1974 Human Gene Mapping Conference was the first formally recognized and collective call for a nomenclature system. Although no formal guidelines were established, a committee was formed to discuss the possibility of standardized terminology. The advantages were clear: increased organization in mapping, intelligibility and access to information, and a decreased likelihood that researchers in different labs would replicate research under various descriptions. The committee consisted of: Dr. Harry Harris from the University of Pennsylvania School of Medicine, Dr. Meera Khan of the Netherlands Department of Human Genetics, Tom Shows microbiologist and editor of *Cytogenetics and Cell Genetics*, and Dr. Victor McKusick of Johns Hopkins School of Medicine. Deemed the Committee on Terminology, the group determined that, "...guidelines need[ed] to be established for naming the human genetic markers, including the terms to be used for loci, genes, phenotypes, and polypeptide chains To provide time for the review, as well as subsequent discussion and appropriate review of existing terminologies, the members decided that a separate meeting of the committee would be required."⁹⁴

The committee met again the following year to discuss further the possibility of a nomenclature system, although one was not presented until the Human Gene Mapping Conference in Edinburgh in 1979. In the five years that had passed, two events had already shaped the future prospects of the Human Genome Project, and had revealed both the potentiality and the complexity of mapping without a single system of nomenclature.

⁹⁴ International Workshop on Human Gene Mapping (2nd : 1974 : Rotterdam, Netherlands). *Human Gene Mapping 2: Rotterdam Conference (1974)*. Basel; New York: S. Karger, 1975. 40.

After-the-Fact: NIH Standards and the Cambridge Gene Scare

1977 was a critical year in advancing the prospects of a Human Genome Project. The June before, researchers at Harvard and Massachusetts Institute of Technology had developed a technique known as gene splicing. The process allowed researchers to manually insert sections of foreign genetic material into pre-existing genetic material. Splicing was also used to create new genetic sequences. Combined with recombinant DNA techniques, gene splicing theoretically allowed geneticists to insert a gene sequence into a pre-existing sequence and then replicate this new segment widely. One of the earliest applications of gene splicing technology was a method to replicate human insulin.

By 1977, gene splicing caused a sensational controversy in both the media and scientific circles. The New York Times reported that, “the primary fear of the area’s residents is that new, particularly durable viruses could escape from a laboratory...attention was [also] focused on commercial concerns, which are not subject to the Government regulations that control gene-splicing research at federally financed universities or hospitals.”⁹⁵ In response to what later became known as the “Cambridge Gene Scare” the Cambridge Public Health Department and Cambridge Town Council issued a set of ordinances regulating activities related to gene splicing. In the months prior to this regulation, the Town Council had issued a moratorium on gene splicing research within the city.⁹⁶ The February 1977 issue of *Science* outlined the various local protocols developed in response to growing concerns over gene splicing technology. In a matter of months, Massachusetts, New York, California, Michigan, New Jersey, and Wisconsin had each issued protocol for gene splicing practices in regional laboratories.

⁹⁵ "Gene-Splicing Concern in Boston." *The New York Times* (New York City), May 31, 1981. <http://www.nytimes.com/1981/05/31/us/gene-splicing-concern-in-boston.html>.

⁹⁶ Wade, Nicholas. 1977. “Gene-splicing: Cambridge Citizens OK Research but Want More Safety”. *Science* 195 (4275). American Association for the Advancement of Science: 268–69.

“Having held public hearings on the gene splicing technique, the state attorney general’s environmental health bureau has prepared a bill to control the research. The bill...would require everyone engaged in gene-splicing research or production to obtain a certificate from the state health commissioner, who would also specify training... [and monitor] containment facilities.”⁹⁷

Just one month earlier, in January of 1977, the National Institutes of Health had revised their guidelines for recombinant DNA research.⁹⁸ The updated guidelines, later given federal authority as legislation, included regulations on genetic splicing and replication.⁹⁹ Public fear was not only related to the health and safety of communities where gene splicing research occurred, but also to its potency as a weapon of biological warfare.¹⁰⁰ After an outbreak of public dissatisfaction, the National Institutes of Health (NIH) authorized national standards for gene splicing.

The gene splicing ordinances issued by the NIH involved the consolidation of many local practices for gene splicing. The Cambridge Gene Scare also roused the attention of several national organizations, including the Occupational Safety and Health Administration, the Environmental Protection Agency, and the Food and Drug Administration. The creation of a single standardized system yielded uniform guidelines about gene splicing safety occurred only

⁹⁷ Wade, Nicholas. 1977. “Gene-splicing: At Grass-roots Level a Hundred Flowers Bloom”. *Science* 195 (4278). American Association for the Advancement of Science: 558–60.

⁹⁸ Office of the Director, NIH (1977). National Institutes of Health Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part One (147 pp.) and Part Two (appendices, 438 pp.); for sale by Superintendent of Documents, U.S. Govt. Printing Office, Washington, D.C. 20402, and available in about 600 public libraries of the GPO depository system.

⁹⁹ For a comprehensive history of Recombinant DNA Guidelines issued by the NIH, please see: Fredrickson, D.S. *A History of the Recombinant DNA Guidelines in the United States*. Report. Bethesda: US Department of Health in Collaboration with the National Institutes of Health, 2005.

¹⁰⁰ Wade, Nicholas. "Gene Splicing: Congress Starts Framing Law for Research." *Science* 196, no. 4285 (April 1, 1977).

after public outrage prompted changes in regulation. However, in addition to the consolidation of local regulatory practices, each federal department also issued independent regulations. As historian Andrew Russell described in the context of national electric regulations the “proliferation of standards committees ironically began to undermine their underlying purpose of providing greater cooperation and organization.”¹⁰¹ This marked the second critical turning point in the nomenclature debate of the 1970s. The Cambridge Gene Scare revealed a sense of public distrust about the ability of large agencies to regulate gene splicing research. While local communities called for a moratorium on gene splicing research to be endorsed by major scientific institutions, researchers resented the multitude of national regulatory standards with authority over locally developed regulatory practice. Dissatisfaction in gene splicing norms in both the public and academic spheres later contributed to institutional reluctance to establish standards in the early decades of the Human Genome Project.

The Frontier Re-discovered: McKusick’s Morbid Anatomy of the Genome

Victor McKusick was a driving force in determining the future course of the Human Genome Project. McKusick was considered the father of medical genetics. A cardiologist by training, McKusick opted to leave the well-established field of cardiology in favor of a career in the fledgling field of genetics, a decision his colleagues considered ill-advised. One of McKusick’s foremost interests was nosology, the study and classification of genetic diseases and malformations. McKusick acknowledged the importance of a classification system to medical diagnosis, treatment and genetic counseling, and raising attention in the medical community to the possibilities of collaboration between medicine and genetics.

¹⁰¹ Russell, Andrew L. *International Standardization as a Strategic Tool: Commended Papers from the IEC Centenary Challenge 2006*. Geneva, Switzerland: International Electrotechnical Commission, 2006.

In 1973, McKusick collaborated with his fellow Johns Hopkins colleague Frank Ruddle to plan the first Human Gene Mapping (HGM) workshop. The workshop aimed to centralize information sharing about the progress and potentiality of a coordinated human gene map by discussing recent mapping efforts. During his career at Johns Hopkins, which spanned over five decades, McKusick became the foremost proponent of medical genetics, a field that combined the academic expertise of classically-trained geneticists with the best medical knowledge and research available on disease pathology. McKusick referred to the result of his endeavors as the morbid anatomy of the human genome, that is, the study of genetic mutations and their relationship to human disease acquisition.¹⁰² In addition to creating the Mendelian Inheritance in Man, an online catalog of known linkages between regions of DNA and inheritable diseases, McKusick also organized international mapping meetings to discuss collaborative interest in a human genome mapping effort. By 1976, at least one gene had been mapped to each chromosome and exactly one decade later, American scientists had discovered the specific genetic mutation that caused Huntington's Disease.¹⁰³ As the first chair of the Division of Medical Genetics at Johns Hopkins, McKusick was keen in his enthusiasm regarding the field:

As human geneticists we are privileged to work in a scientifically important field and a field of intellectual challenge. This is a field with particular fascination because it involves the most fundamental and pervasive aspects of our species. To have... the opportunity to contribute to human welfare and to be of service to families and individuals through medical genetics and clinical genetics is a privilege.¹⁰⁴

¹⁰² McKusick, V.A. "The Human Genome through the Eyes of a Clinical Geneticist." *Cytogenetic and Genome Research* 32, no. 1–4 (1982): 7–23.

¹⁰³ Wexler, Alice. 2008. *The Woman Who Walked into the Sea: Huntington's and the Making of a Genetic Disease*. New Haven: Yale University Press.

¹⁰⁴ McKusick, Victor. Human genetics: The last 35 years, the present and the future. *American Journal of Human Genetics* 50:663–670.

McKusick's centrality to the Project is further evidenced in his participation in a committee on prospective gene mapping sponsored by the National Research Council. Along with James Watson and Sydney Brenner, McKusick's committee concluded that the gene mapping project should be initiated immediately, and completed within fifteen years of its commencement. McKusick encouraged shifting the course of the early human genome project to focus on the medical and pharmaceutical applications of gene sequencing. This offered pharmaceutical companies an opportunity to begin research and development projects closely related to the Human Genome Project.

Interest in a Human Genome Project was well-established by 1976, and the stakes were high. Three general categories of interest emerged from debates about the potentiality of mapping the human genome, and their collision created fireworks in the scientific, political, and corporate spheres. These three categories were: private interest in developing profitable biomedical applications; academic interests in continued scientific research; and the public interest in ethical and moral implications of human gene mapping. By 1976, the debate over genetically-modified insulin created tensions in each sphere surrounding intellectual property and ownership. These tensions created an intellectual property conundrum related to genome nomenclature, and set legal standard for the future course of the Human Genome Project.

Private Interest: A Brief History of Eli Lilly and Co.

Although new to the Human Genome Project in the 1970s, pharmaceutical giant Eli Lilly and Company held a long-standing interest in the creation and distribution of human insulin. In 1921, Eli Lilly and Co. sponsored Canadian surgeon Frederick Banting to pursue research that

would allow him to isolate and extract natural portions of the human pancreas that produce insulin. By January of 1922, the first patient at the Toronto General Hospital had proven Banting's success: the patient had awakened from a comatose state with the injection of insulin.¹⁰⁵ By November of that same year, Eli Lilly and Co. had refined the extraction and purification process, and it was the first major pharmaceutical company to offer insulin on the market.

Fifty years later marked a renewed scientific interest in human insulin development, and Eli Lilly and Co. was determined to remain at the forefront of its re-emergence. In 1976, private interest in the Human Genome Project gained a significant foothold, when Herbert Boyer left his position as assistant professor of biochemistry at the University of California to found Genentech. Boyer modeled Genentech as the first genetic engineering company in the United States. The first major research initiative sponsored by Genentech was a method to genetically engineer synthetic human insulin. Prior to 1976, the insulin produced by Eli Lilly and Co. relied upon extractions from mammals, most often canines. Genetically engineered insulin from human beings held a number of benefits. Primarily, it was more cost effective to produce than insulin derived from canines. Moreover, synthetic insulin led to fewer allergenic reactions among human users than the insulin produced from canines. Within two years of its establishment, Genentech had collaborated with scientists at the Beckmann Research Institute to produce synthetic human insulin. Meanwhile, as the Lilly Company prepared to market Humulin, the pharmaceutical brand name for synthetic insulin, researchers at the University of California had developed a new mechanism for sequencing and cloning human insulin.

¹⁰⁵ Clark, Roscoe Collins. *Threescore Years and Ten: a Narrative of the First Seventy Years of Eli Lilly and Company, 1876-1946*. Chicago: Privately printed, [The Lakeside Press, R.R. Donnelly & Sons Co.], 1946.

Academic Sphere: The University of California

In 1977, Australian born biochemist John Shine was completing a postdoctoral fellowship in the departments of Biochemistry and Biophysics at the University of California, San Francisco.¹⁰⁶ His research had led him to develop a Recombinant DNA (cloning) technique (known as a ligase catalyzed reaction), a crucial step in the human insulin replication process. On May 27, 1977 Shine and a group of colleagues at the University of California filed a patent application for the process the research team had developed.¹⁰⁷ In September, Shine filed a second related patent application related to the purification of a protein sequence, specifically the sequence associated with insulin production.¹⁰⁸ Both patents were on behalf of the Regents Of The University of California. By April 1978, Shine had filed yet another patent, this time related to the recombinant (cloning) bacterial plasmids that coded specifically for insulin genes. The research for this patent had been funded by a grant from the California Department of Health, Education, and Welfare.¹⁰⁹ Specifically, this patent claimed the recombinant DNA process, “to contain a nucleotide sequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.”¹¹⁰ The application included a claim over vertebrates having the nucleotide sequence and structure of transcribed insulin from the rat gene for insulin. The application also included two claims that the method for coding synthetic insulin was applicable to a microorganism where the vertebrate was a mammal, and a microorganism where the vertebrate was a human. Thus, the patent application included mammals, microorganisms,

¹⁰⁶ Shine J, Seeburg PH, Martial JA, Baxter JD, Goodman HM. Construction and analysis of recombinant DNA for human chorionic somatomammotropin. *Nature* 1977; 270: 494-499

Ullrich A, Shine J, Chirgwin J, Pictet R, Tischer E, Rutter WJ, Goodman HM. Rat insulin genes: construction of plasmids containing the coding sequences. *Science* 1977; 196: 1313-1319

¹⁰⁷ Patent Application: US 05/898,887

¹⁰⁸ Patent Application: US 06/346,123

¹⁰⁹ USP: 4,652,525

¹¹⁰ Patent Application: US 06/508,651

and humans in its periphery. As the patent description states, Shine and his colleagues were interested in the right to, “present [an] invention related to the isolation of the insulin gene, its purification, transfer, and replication in a microbial host and its subsequent characterization.”¹¹¹ The work on recombinant DNA conducted at the University of California was unprecedented; indeed it was “the first time the entire genetic sequence for an insulin gene had been spelled out.”¹¹² While the University of California moved forward with its method patents for the extraction, isolation, and purification of insulin, testing primarily on rodents to study whole system outcomes of the research, Lilly scientists prepared to test a new form of synthetic insulin extracted from portions of human bacterial growth.

A Civil Attempt

By 1977, the University of California Regents had agreed to license the recombinant DNA patents for human insulin to Genentech, the first California-based genetic engineering start-up. Lilly was headquartered in Indianapolis and Genentech was based in San Francisco, but both companies were well aware of one another’s research endeavors in creating a synthetic insulin product. On August 25, 1978 Eli Lilly and Co. and Genentech Inc. entered into a contract regarding their respective research on synthetic insulin. The agreement stated that Genentech had established a scientifically valid method for the extraction, purification, and synthetic re-creation of human insulin, and that Genentech held license to the related patent rights filed by John Shine and his research colleagues at the University of California. As was later described, “the Insulin

¹¹¹ USP: 4,652,5,

¹¹² Marshall, Eliot. "A Bitter Battle Over Insulin Gene." *Science* 277 (August 22, 1997): 1028-030. (remarks of William Rutter, former University of California, San Francisco scientist and current chair of Chiron Corporation, Emeryville, California).

Agreement gave Lilly access to Genentech biological material which Lilly in turn was to use in developing and marketing synthetically produced human insulin.”¹¹³ Under Article VI of the Insulin Agreement, Genentech agreed to allow Lilly the exclusive patent, “to use its biological material for the limited purpose of manufacturing, selling, and using Recombinant insulin without regard to Genentech patent rights.”¹¹⁴ Lilly agreed to disburse royalties to Genentech, and proceeded to production.

From 1977-1980 Eli Lilly and Co. had invested over sixty million dollars on manufacturing facilities that were equipped to produce and distribute Humulin on a rapid and systematic scale.¹¹⁵ The company projected that once Humulin reached the market, worldwide pharmaceutical sales would apex at 1.1 billion dollars, and synthetic insulin was the catalyst intended to propel the pharmaceutical industry into a new frontier. On July 15, 1980 Eli Lilly authorized the first medical application of their new drug, Humulin, on a human diabetic patient at Guy’s Hospital in London. The patient, like other diabetics, had a known allergic reaction to the insulin produced from animals, and a chemical duplicate of the insulin produced from bacteria of the human pancreas was a strong prospective solution.

Exactly one decade following Lilly’s successful test of Humulin in London, legal turmoil erupted. In early 1990, Genentech filed suit against Eli Lilly Co. and contended that, “Lilly’s research and production exceeded the scope of [the] limited patent license...[and furthermore] used the biological material referred to in the agreement to...develop a human growth hormone

¹¹³ Eli Lilly and Co. v. Genentech, Inc. United States District Court Database Indiana (United States District Court, S.D. Indiana, Indianapolis Division. July 17, 1990). Nos. IP 87-219-C, IP 88-1463-C.

¹¹⁴ Ibid.

¹¹⁵ Nelson, Gary L. *Pharmaceutical Company Histories*. Bismarck, N.D.: Woodbine Pub., 1983.

See also:

Khan, EJ, Jr. *All In A Century, The First 100 Years of Eli Lilly and Company*. Indianapolis: Eli Lilly and Company, 1976.

in order to compete with Genentech's human growth hormone product. Genentech assert[ed] that such a production was beyond the scope of the license...and a breach of the parties' contract."¹¹⁶

A Return to Nomenclature

The suit became one of several filed by Genentech against Eli Lilly and Company; grievances included infringement of contractual terms of use, violation of patent, and the attempt to repurpose biological material licensed by Genentech to create an unrelated product. In each hearing, the legal decisions of the court hinged upon the question nomenclature. The court agreed with Lilly in grievances related to the contract, and noted that the University of California, along with Genentech, had only outlined limited terms of use in the contract with Lilly, and had not sufficiently described the negative covenant, that is, the terms by which the contract could not be used. Judge Flaum of the Federal District Court of Indiana (Southern District) granted Lilly patent rights outside of the contract established with Genentech, because the latter had failed to sufficiently describe the specific parameters of use in the contract:

“As a general rule covenants may only be implied into an integrated agreement when the implied term is not inconsistent with some express term of the contract and where there arises from the language of the contract itself, an inference that it is absolutely necessary to introduce the term to effectuate the intention of the parties.”¹¹⁷

¹¹⁶ United States District Court, S.D. Indiana, Indianapolis Division. Contract Action No. IP 88-1463

¹¹⁷ Eli Lilly & Co. et al. v. Genentech Inc. et al., U.S. District Court for the Central District of California. 1997.

See also: Hughes, Sally Smith. *Genentech: The Beginnings of Biotech*. Chicago: University of Chicago Press, 2011.

Perhaps the most contested episode over nomenclature occurred in 1990, when the University of California again brought suit against Eli Lilly and Co. for claims of infringement of section 525 of the patent for recombinant human insulin. The 525 patent, also known as the Written Description Requirement, was first applied as an amendment to the Patent Act of 1793.¹¹⁸ The Written Description requirement ensured that the inventor could not extend the claims or benefits of the invention beyond its actual scope. It was also a standard proof to ensure that those seeking a patent could intelligibly explain the method for arriving at the end product. However, as many legal scholars have acknowledged, the significance and application of written description changed considerably following *Regents of the University of California v. Eli Lilly and Company*- a legal battle that ensued well into the first decade of the Human Genome Project.

The legal debate between the University of California and Eli Lilly and Co. revealed that both institutions had developed synthetic insulin based on tried and true scientific tests. The first tests were completed on rodents, and allowed John Shine and fellow researchers to uncover the exact DNA sequence that coded for insulin. The Insulin Agreement between the two parties then allowed Lilly to create Humulin, a product later tested on human diabetic patients. The court never debated whether each party had created something considerable- rather, it determined which institution had the legal right to patent the product. And the basis for this determination was 525, the Written Description agreement. Although the University of California adhered to the traditional expectation that the 525 written description would outline an intelligible method for the extraction, isolation, and purification of insulin, Lilly argued that the outcome itself (i.e. the actual nucleotide sequence for insulin) had not been included in the 525 section of the patent application. Lilly subsequently determined that description provided by the University of

¹¹⁸ Schroeder, Jacob Adam. "Written Description: Protecting the Quid Pro Quo since 1793." *Fordham Intellectual Property, Media & Entertainment Law Journal* 21.1 (2010-2011): 63-110.

California had outlined the method used for insulin extraction on rodents, rather than on humans. However, the extended nucleotide sequence between rodents and humans varied by only a single nucleotide on the gene that coded for insulin. As legal scholar Janice M. Mueller remarked, “Although UC included in the 525 patent a constructive or prophetic example describing a method that could be used to obtain the human insulin used to encode cDNA, as well as amino acids of human insulin, UC did not actually isolate and sequence cDNA until two years after the 1977 filing date.”¹¹⁹

This left two caveats: first, that the University of California had obtained the nucleotide sequence for human insulin by the time the case was heard in 1997, and second that the initial decision heard by the District Court in San Francisco significantly changed the expectation for written description in patent applications to include not just a description of the method but also a description of the product itself. As Mueller concluded in her report, “Lilly aptly illustrate[d] the increased widening of the gulf between the norms of business and scientific communities and the U.S. patent system, as users of the later come to understand that the patent system no longer reflects the realities of scientific contribution.”¹²⁰ Those proficient in the field of genetics were aware of the biological nature of the work completed at the University of California; the method utilized to create a synthetic form of insulin in humans was based upon (and conceptually identical) to the method utilized to create the synthetic insulin in rodents. Yet the University of California did not anticipate that the standard set by written description required, for the first time, a description of both the method and the product itself. One opinion issued by the decision

¹¹⁹ Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 *Berkeley Tech. L.J.* 615 (1998).

¹²⁰ Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 *Berkeley Tech. L.J.* 615 (1998).

noted, “rather than awarding patent protection to the first to make it possible to clone a particular gene family, the written description standard of *Lilly* require[d] that the patent right go to the first firm to sequence a number of the genes (and accurately describe this sequence). This firm...reap[ed] the benefits of an invention made possible by the research of others.”¹²¹ Although the University of California was in possession of a novel method for synthetic insulin production and later the nucleotide sequence for human insulin, the way researchers at UC described their achievements ultimately prevented a claim over ownership of intellectual property.

Implications

In the span of time required to amend the initial patent held by the University of California, Eli Lilly and Co. had utilized the sequence information from the Insulin Agreement to establish the number of human nucleotides in insulin and file a patent with a specific written description of their findings.¹²² Corporate competition had deterred academic innovation and Lilly was granted a twenty year premium over insulin research. In one year alone, Eli Lilly recorded a net profit of 1.114 billion dollars on Humulin, charging more than twice the expected market price for non-synthetic, animal-based insulin.¹²³ The decision in *Regents of the University of California v. Eli Lilly and Co.* hinged on the written description requirement for patent applications, although the parameters of 525 were significantly altered to include description not only of the method to arrive at the invention, but also a highly detailed description of the novelty itself (thereby implying authentic discovery and inventive ownership). This case spurred debates

¹²¹ Ibid.

¹²² US 09/096,247

¹²³ Eli Lilly & Co. 2001 10-K.

See also: Altman, Lawrence K. "A New Insulin Given Approval for Use in U.S." *New York Times*, October 30, 1982. <http://www.nytimes.com/1982/10/30/us/a-new-insulin-given-approval-for-use-in-us.html>.

over the nature of ownership: could scientists own a specific method, or had written description become inclusive enough to include ownership of biological material? If the later were true, what mechanisms were in place to govern the ethical, legal, and social utility of biological material? Furthermore, if public taxpayer dollars had contributed to the research at the University of California, could a District Court re-appropriate the research to a private, for-profit corporation?

Predictions aside, *Regents of the University of California v. Eli Lilly Co.* indicated a fundamental change in scientific research and its relationship to bureaucracy. On December 12, 1980, ten days after the University of California and Genentech were issued a patent for an early recombinant DNA method, the United States Bayh-Dole Act was passed. The legislation supported patent and license applications granted to private (biotechnology) companies that were the product of federally funded (often academic) research. The Bayh-Dole Act was an attempt to spur economic growth by allowing federally-held patents to be licensed for commercial use. The debate over synthetic insulin was an indicative precursor of the relations between government, academia, and the private sector at the outset of the Human Genome Project. Dr. Mildred Cho of Stanford indicated that as a result of the Bayh-Dole, “university research is [now] skewed toward marketable products and not basic research.”¹²⁴

By 1979, the international community had attempted to resolve the nomenclature question. During the fifth international Human Gene Mapping Conference in Edinburgh, a committee on gene nomenclature developed a set of guidelines to ensure that gene naming was consistent and intelligible to the gene mapping community. This committee was led by Dr. Phyllis McAlpine, who helped to create guidelines and standards for gene nomenclature in scientific publications and reports. McAlpine also introduced these standards to foster

¹²⁴ Schacht, Wendy. 2005. The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology.

collaboration and communication between the multitude of international organizations and laboratories working on the gene map.

However, just one year before the Edinburgh guidelines were issued, Eli Lilly and Co. had entered into contract with Genentech and the University of California in an agreement related to gene sequences for human insulin. The agreement marked a transformation in molecular nomenclature from a useful organizational tool to a critical component of the 525 patent requirement that all biological products be described in an intelligible and systematic manner. In the absence of a clear nomenclature system, the University of California lost the opportunity to claim rights over the discovery of insulin's genetic sequence. When the nomenclature question was addressed in 1979, the public and private biotechnology sectors were already embroiled in heated disputes over ownership rights and intellectual property. Furthermore, debates over nomenclature reveal how the body became a contested terrain in the midst of the Human Genome Project.

Conclusion

The nomenclature question revealed a set of structural inconsistencies between the scientific community, the legal sphere, and the private sector. Legal scholars have suggested that the debates over intellectual property in the Human Genome Project transcended the structural legal framework in place to respond to emerging debates over biological property and ownership. The alteration of written description, from a method description to a comprehensive product description, set precedent for future cases involving genetic research and ultimately reconfigured the boundaries and limitations of scientific discovery at the outset of the Human Genome Project.

Although Vannevar Bush predicted an accurate trend in basic research following the end of the second World War, perhaps genetic advancements now trended again toward applied scientific research. While Bush and Schrodinger both predicted a new era of scientific discovery, the Human Genome Project was never preordained. Instead, the Project culminated from half a century of debates over the future of biological research, the transition from basic to applied research, advancements made in the cytogenetics community, and the pivotal role of nomenclature in configuring intellectual property as a central component of genetic research. The Human Genome Project engaged not only the scientific community, but the academic and research world at-large, the medical community, the corporate sphere, as well as legislators, ethicists, and the interested public. Debates about the Human Genome Project emerged and re-evolved over the course of fifty years because the implications were both extensive and profound.

Tracing the intellectual development of the Human Genome Project confirms that the modern body cannot hold the same spatial and ontological existences as the body of yesterday. Cultural and intellectual discourses and past processes of transformation inevitably shape bodies. The Human Genome Project emerged as one of the most critical catalysts for understanding the human body in the twentieth century. The Project is the embodiment of an era, marked by bioethical scholarship, concerns of legal patentability, technological and scientific advances in molecular biology and computational software, and institutional encounters between public and private spheres. Although the Human Genome Project yielded ethical, legal, social, technological, and scientific implications (many yet to be revealed) the human body remained the fulcrum of human genomic possibility. Indeed, it was from the Human Genome Project, its

integration into systems of knowledge and power¹²⁵ and its theoretical and tangible nature, that a new narrative of self-hood emerged, which simultaneously expanded the known territory of the body and constrained its spatiality through definitions, standards, and categories of language in molecular biology.

¹²⁵ Cooter, Roger. "The Turn of the Body: History and the Politics of the Corporeal." *Arbor* 186, no. 743 (June 30, 2010): 393–405.

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