A HISTORY OF MUSCULAR DYSTROPHY:

THE BIOSOCIAL NATURE OF DISEASE

by

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Muscular dystrophy (MD) is one of the most frequently inherited diseases, yet few science, technology, and society (STS) scholars have attempted to study it. In particular, there is a significant gap in the literature regarding how sociocultural contexts have shaped biomedical perspectives on the disease. Therefore, this thesis adopts Paul Rabinow's notion of biosociality and traces the history of muscular dystrophy to draw conclusions about how and what kinds of knowledge about MD are produced as biological fact. The first chapter, which analyzes early descriptions of muscular dystrophy, demonstrates that modern perspectives on correct ways of knowing in turn influence who scientists credit with "discovering" MD. Similarly, the second chapter reveals how diagnostic technologies help define the boundaries of disease. Ultimately, this thesis serves as a case study to prove that science does not stand apart from culture; indeed, it is profoundly shaped by "the social."

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Table of Contents

List of Figures

Introduction

When Conner Curran was four years old, a doctor told his parents, "Take your son home, love him, take him on trips while he's walking, give him a good life and enjoy him…"[1] The implicit message was clear: Conner's days were numbered. He had just been diagnosed with Duchenne muscular dystrophy, a debilitating disease that meant he would be fortunate to survive to early adulthood.[2]

Today, scientists and medical professionals use "muscular dystrophy" as a blanket term to cover a large group of diseases characterized by progressive muscle weakness. In everyday language, however, muscular dystrophy (MD) more commonly refers to the dystrophinopathies, a subcategory of MD that includes Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), which are both characterized by weakness in the limbs, enlarged calves, and eventual heart failure.[3] The group of myopathies included under the umbrella of muscular dystrophy is ever-evolving, largely because MD, like many diseases, is now being analyzed at the genetic level; as of late 2019, scientists believed muscular dystrophy could be connected to the disfunction of more than forty genes, and thus more than forty diseases.[4] As the scientific understanding of MD continues to evolve, so, too, do ideas about its

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[1] Jon Hamilton, "A Boy with Muscular Dystrophy was Headed for a Wheelchair. Then Gene Therapy Arrived," Shots: Health News from NPR, NPR, July 27, 2020, https://www.npr.org/sections/health-shots/2020/07/27/893289171/a-boy-with-muscular-dystrophy-was-headed-for-a-wheelchair-then-gene-therapy-arri.

[2] Basil T. Darras, David K. Urion, and Partha S. Ghosh, "Dystrophinopathies," in *GeneReviews*, ed. Margaret P. Adam, Holly, H. Ardinger, Roberta A. Pagon, Stephanie E. Wallace, Lora J. H. Bean, Ghayda Mirzaa, and Anna Amemiya (Seattle: University of Washington, Seattle, 2000), https://www.ncbi.nlm.nih.gov/books/NBK1116/.

[3] Darras, Urion, and Ghosh, "Dystrophinopathies."

[4] Eugenio Mercuri, Carsten G. Bönnemann, and Francesco Muntoni, "Muscular Dystrophies," *Lancet* 392, no. 10213 (2019): 2025-2038, doi: 10.1016/S0140-6736(19)32910-1.

classification and diagnosis. Accordingly, this thesis aims to study the changing narrative of "disease" in the Western history of muscular dystrophy. What did it mean to have muscular dystrophy before scientists began to fully characterize its genetic bases, and how do these answers differ in the postgenomic age of the 21st century? Addressing these and related questions will demonstrate that muscular dystrophy does not exist in a purely "scientific" vacuum, as science itself is inevitably molded by society. Furthermore, some of the conclusions drawn from this research will be able extend to other genetic diseases and disorders, as the technologies and societal changes that have helped shape how biomedical professionals view muscular dystrophy have undoubtedly influenced perceptions of other diseases with genetic components.

Literature Review

Although muscular dystrophy is a thriving area of research for scientists, little work has been done to move studies of MD beyond the biomedical into a cultural context. This is surprising considering the incidence of the Duchenne type alone is between 1 in 3,500 and 1 in 5,000, making it one of the most common heritable diseases in the world.[5] The limited research on MD outside of a scientific realm has bifurcated into two main foci: studies of MD organizations and ethnographies of patients' experience, particularly within "the clinic," as popularized by Michel Foucault.[6] In the first category, French sociologists and frequent collaborators Vololona Rabeharisoa and

[5] Alan E. H. Emery, "Population Frequencies of Inherited Neuromuscular Diseases – A World Survey," *Neuromuscular Disorders* 1, no. 1 (1991): 21, doi: 10.1016/0960-8966(91)90039-U; Simon Guiraud et al., "The Pathogenesis and Therapy of Muscular Dystrophies," *Annual Review of Genomics and Human Genetics* 16 (2015): 281-308, doi: 10.1146/annurev-genom-090314-025003.
[6] Michel Foucault, *The Birth of the Clinic: An Archaeology of Medical Perception*, trans. A. M. Sheridan (London: Routledge, 1989).

Michel Callon have been particularly influential. Their first book, *Le Pouvoir des Malades: l'Association Française Contre les Myopathies & la Recherche* traces the history of the French Muscular Dystrophy Association (AFM) and examines the ways in which laypeople and specialists interact with each other.[7] Their subsequent English-language publications have continued to research the influence of the AFM in producing biomedical knowledge.[8] In comparison, other scholars have moved away from studying organizations to studying patient identity. Two Canadian ethnographies have explored how MD affects patients' personhood, both within the rehabilitation clinic and in a broader societal context,[9] and scholar Masae Kato has investigated the impact of culture on MD patients' attitudes towards personalized medicine, or gene-based treatments that have promise for treating the dystrophinopathies.[10] Like Kato,

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[7] Vololona Rabeharisoa and Michel Callon, *Le Pouvoir des Malades: l'Association Française Contre les Myopathies & la Recherche* (Paris: Presses de l'Ecole des Mines de Paris, 1999).

[8] Michel Callon and Vololona Rabeharisoa, "The Growing Engagement of Emergent Concerned Groups in Political and Economic Life: Lessons from the French Association of Neuromuscular Disease Patients," *Science, Technology, & Human Values* 33, no. 2 (2008): 230-261, doi: 10.1080/0308514042000176711; Vololona Rabeharisoa, "From Representation to Mediation: The Shaping of Collective Mobilization on Muscular Dystrophy in France," *Social Science & Medicine* 62, no. 3 (2005): 564-576, doi: 10.1016/j.socscimed.2005.06.036; Vololona Rabeharisoa, "The Struggle Against Neuromuscular Diseases in France and the Emergence of the 'Partnership Model' of Patient Organisation," *Social Science & Medicine* 57, no. 11 (2003): 2127-2136, doi:10.1016/S0277-9536(03)00084-4; Vololona Rabeharisoa and Michel Callon, "Patients and Scientists in French Muscular Dystrophy Research," in *States of Knowledge: The Co-Production of Science and Social Order*, ed. Sheila Jasanoff, 142-160 (New York: Taylor & Francis Group, 2004).

[9] Thomas Abrams, Jenny Setchell, Patricia Thille, Bhavnita Mistry, and Barbara E. Gibson, "Affect, Intensity, and Moral Assemblage in Rehabilitation Practice," *BioSocieties* 14, no. 1 (2019): 23-45, doi: 10.1057/s41292-017-0061-4; Barbara E. Gibson, Nancy L. Young, Ross E. G. Upshur, and Patricia McKeever, "Men on the Margin: A Bourdieusian Examination of Living into Adulthood with Muscular Dystrophy," *Social Science & Medicine* 65, no. 3 (2007): 505-517, doi: 10.1016/j.socscimed.2007.03.043.

[10] Masae Kato, "Genomics and Cure: Understanding Narratives of Patients with Duchenne Muscular Dystrophy in Japan," *Anthropology & Medicine* 25, no. 1 (2018): 85-101, doi: 10.1080/13648470.2018.1427695. See also Masae Kato and Margaret Sleeboom-Faulkner, "Cultures of Marriage, Reproduction and Genetic Testing in Japan," *BioSocieties* 4, no. 2-3 (2009): 115-127, doi: 10.1017/S174585520999010X; Masae Kato and Margaret Sleeboom-Faulkner, "Motivations for Seeking Experimental Treatment in Japan," *BioSocieties* 23, no. 1 (2018): 255-275, doi: 10.1057/s41292-017-0067-y.

Callon and Rabeharisoa have also examined the "mutual entanglements" of culture and patients' beliefs about disease and treatment, but on Réunion Island instead.[11]

While there has been a boom in work by scholars of science, technology, and science (STS) on muscular dystrophy since Rabeharisoa and Callon's first publications on the AMF, the current literature is lacking one critical perspective: that of the biomedical professionals who are so often presumed to objectively discover new truths about MD. Additionally, the vast majority of studies have focused on hyper-specific cultural contexts – France, Australia, Japan, and Réunion Island. This emphasis is understandable; after all, the last letter of STS stands for "society." However, there is also value in "zooming out" and trying to understand the creation of MD itself in the minds of scientists and doctors, as these biomedical professionals are arguably the most important people involved in MD knowledge production. How did medical professionals think about MD when the dystrophies were first discovered, and how has that perspective influenced professional understanding of MD today? In the opposite direction, how do present ideas about muscular dystrophy impact how scientists view its past? This temporal, rather than spatial, perspective is perhaps the realm of historians rather than anthropologists and sociologists.

Yet the few historical treatments of muscular dystrophy that do exist were written by biologists who, naturally, approached the subject with a different framework than either a historian or a social scientist would use. The geneticist Alan E. H. Emery and his wife, Marcia L. H. Emery, who also has a scientific background, have written

[11] Michel Callon and Vololona Rabeharisoa, "Gino's Lesson on Humanity: Genetics, Mutual Entanglements and the Sociologist's Role," *Economy and Society* 33, no. 1 (2004): 1-27, doi: 10.1080/0308514042000176711.

by far the most extensive work on the discovery of muscular dystrophy. Their book, *The History of a Genetic Disease: Duchenne Muscular Dystrophy or Meryon's Disease*, is the current authoritative source on the history of MD, but the authors themselves admit that rather than make any grand analytical claims, their work instead aims primarily to recognize the achievements and contributions of the English physician Edward Meryon, who was the first to systematically describe (the evidently poorly named) Duchenne muscular dystrophy.[12] After arguing for the preeminence of Meryon as the father of MD, the book reads as a timeline of major scientific findings—which is not unexpected, as their target audience is likely biologically minded as well. Finally, the neurologists Kenneth L. Tyler, J. M. S. Pearce, and Corrado Angelini have also contributed to the literature on the early descriptions of MD, but none of these authors go much beyond retracing the path forged by the Emerys.[13] Therefore, there remains a significant lacuna of scholarship by those in the humanities on how and why biomedical professionals' views of muscular dystrophy have changed so radically since MD was first described; it is this gap that this research attempts to fill.

Analytical Framework

The scholarship on muscular dystrophy completed here complements the work of other STS scholars who have, in taking an anthropological and/or historical approach

[12] Alan E. H. Emery and Marcia L. H. Emery, *The History of a Genetic Disease: Duchenne Muscular Dystrophy or Meryon's Disease*, 2nd ed. (New York: Oxford University Press, 2011), xv.
[13] Kenneth L. Tyler, "Origins and Early Descriptions of 'Duchenne Muscular Dystrophy,'" *Muscle & Nerve* 28, no. 4 (2003): 402-422, doi: 10.1002/mus.10435; J. M. S. Pearce, "Early Observations on Duchenne-Meryon Muscular Dystrophy," *European Neurology* 54, no. 1 (2005): 46-48, doi: 10.1159/000087386; Corrado Angelini, "Muscular Dystrophy," in *Handbook of Clinical Neurology*, ed. S. Finger, F. Boller, and K. L. Tyler (Edinburgh: Elsevier B.V., 2010) 95: 477-488, doi: https://doi.org/10.1016/S0072-9752(08)02131-3.

to studying various other illnesses, stridently argued for the recognition of the biosocial, rather than strictly biological, nature of disease.[14] The belief in the importance of studying the social aspects of disease reflects a larger trend in STS studies. The theory of "coproduction," as pioneered by Sheila Jasanoff and Jenny Reardon, proposes that scientific knowledge "is not a transcendent mirror of reality. It both embeds and is embedded in social practices, identities, norms, conventions, discourses, instruments and institutions – in short, all the building blocks of what we term the social."[15] The idea that science is somehow subject to "the social" is foreign to many outside of STS studies; the anthropologist Emily Martin has aptly described the natural sciences as citadels because they "are heir to processes that have left most of us thinking they are set apart from the rest of history and society."[16] But arguing in favor of coproduction is not to make the case that society and culture create immutable biological fact. The code of DNA is made of four distinct chemical bases; that was true (although unknown) two hundred years ago just as it is today and just as it will be two hundred years from now, regardless of time or place. Instead, to use a lens of coproduction is simply to suggest that there is something valuable in situating scientific discovery and innovation in a larger social, cultural, or even political context.

Instead of speaking in terms of coproduction, the motivation for this methodological approach can also be stated more generally by borrowing from the

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[14] Credit for the notion of biosociality belongs to Paul Rabinow, "Artificiality and Enlightenment: From Sociobiology to Biosociality," in *Anthropologies of Modernity: Foucault, Governmentality, and Life Politics*, ed. by Jonathan Xavier Inda, repr. (New York: Blackwell, 2005; New York: Zone, 1991), 181-193, doi: 10.1002/9780470775875.ch7. Citations refer to the Blackwell edition.
[15] Sheila Jasanoff, "The Idiom of Co-Production," in *States of Knowledge: The Co-Production of Science and Social Order*, ed. Sheila Jasanoff (New York: Taylor & Francis Group, 2004), 3.
[16] Emily Martin, "Anthropology and the Cultural Study of Science," *Science, Technology, & Human Values* 23, no. 1 (1998): 26, https://www.jstor.org/stable/689947.

sociologist Nikolas Rose. Drawing from the philosopher Ludwik Fleck's ideas on styles of thought, Rose writes:

> A style of thought is a particular way of thinking, seeing, and practicing. It involves formulating statements that are only possible and intelligible within that way of thinking… A style of thought is not just about a certain form of explanation, about what *it is* to explain, it is also about what *there is* to explain. That is to say, it shapes and establishes the very object of explanation, the set of problems, issues, phenomena that an explanation is attempting to account for. The brain, for the contemporary sciences of the brain, is not what it was in the 1950s; the cell, in cellular biology, is not what it was in the 1960s; 'the gene'—if it still makes sense to call it that—is not what it was before genomes were sequenced, and so on. The new style of thought that has taken shape in the life sciences has so modified each of its objects that they appear in a new way, with new properties, and new relations and distinctions with other objects."[17]

Here, Rose is arguing that new styles of thought not only change the *discourse* around a subject but also the *meaning* of a subject; this is strikingly clear when considering the life sciences. Just as the brain and the gene are envisioned completely differently now than they were fifty years ago, disease, and, on a smaller scale, muscular dystrophy, are different at their core than they were in the pre-genomic age. It is this evolving language—what Kaushik Sunder Rajan calls the "shifting grammar of life itself"—and its effects that I investigate in this research.[18]

[17] Nikolas Rose, *The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century* (Princeton: Princeton University Press, 2009), 29.
[18] Kaushik Sunder Rajan, *Biocapital: The Constitution of Postgenomic Life* (Durham: Duke University Press, 2006), 14.

Background on Muscular Dystrophy

Today, biomedical professionals understand the dystrophinopathies as recessive diseases caused by mutations in the *dystrophin* gene, which is located on the X chromosome. As a note, scientific convention dictates that genes are italicized while proteins are not; therefore, *dystrophin* refers to the gene, while dystrophin refers to the protein. Because the gene associated with DMD and BMD is X-linked and recessive, the dystrophinopathies almost exclusively affect boys, as males who inherit a dysfunctional copy of *dystrophin* from their mothers do not have an extra X chromosome that can compensate by producing normal dystrophin protein. Normally, dystrophin is involved in a large protein complex that physically links structural components of a cell, called the cytoskeleton, to a supporting network of proteins and sugars outside of the cell, called the extracellular matrix. Because skeletal muscle cells are constantly contracting and relaxing, the muscle cell membrane, called the sarcolemma, experiences enormous stress. The dystrophin protein acts as a spring, allowing the sarcolemma to stretch and change shape without tearing (Figure 1).

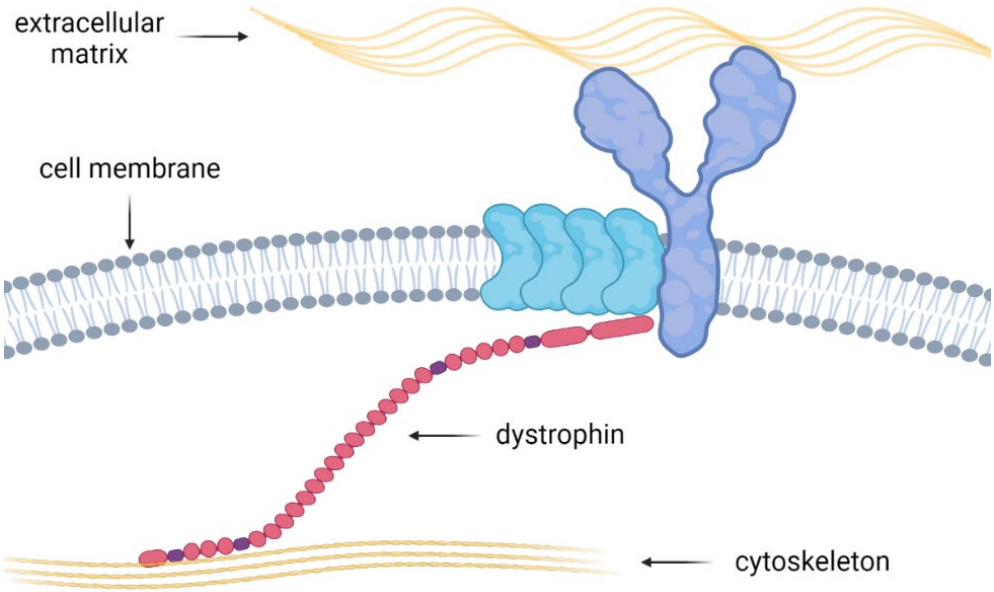

Figure 1: Dystrophin Links the Cytoskeleton to the ECM

A highly simplified diagram of how dystrophin connects a muscle cell's cytoskeleton to the extracellular membrane via a protein complex, thus allowing the cell membrane to stretch without tearing.

In cells that produce zero (i.e. skeletal muscle cells from DMD patients) or only minimal (i.e. skeletal muscle cells from BMD patients) functional dystrophin protein, the cell membrane is susceptible to wear and tear. If the sarcolemma does not remain intact, small molecules that are toxic to the muscles can freely enter the cells, resulting in cell death. This cell death triggers constant skeletal muscle regeneration, which in turn signals prolonged inflammatory responses and fibrosis, which is the build-up of connective tissue in inappropriate places.[19]

The continual cycle of cell death and fibrosis therefore explains one of the most distinctive clinical features of the dystrophinopathies: although DMD and BMD patients

[19] Guiraud et al., "The Pathogenesis and Therapy," 281. While a number of more recent reviews on the pathogenesis of muscular dystrophy exist (this one was published in 2015), Guiraud et al. was written in collaboration by the primary investigators of the three labs that were in competition to discover *dystrophin* and its protein product; they have remained at the forefront of MD research ever since.

have unusually large muscles, especially in the calves, they are extremely weak. In DMD patients, this weakness is noticeable in early childhood; by the time DMD patients are three to five years old, the muscle damage is irreparable. The muscle weakness progresses to the point where afflicted children are completely wheelchair-dependent by age twelve and die of heart failure at around eighteen years of age. Becker patients, on the other hand, experience later-onset skeletal weakness. Depending on their levels of dystrophin deficiency, some people with BMD can remain ambulatory into adulthood and survive well into middle age.[20]

While most treatments for muscular dystrophy merely attempt to manage symptoms, more effective therapeutics are soon on the horizon. In 2015, just three weeks after being the first to undergo a novel gene therapy treatment, Connor Curran was running up the same stairs that he could not walk up before. Five years later, he was playing and jumping like any nine-year-old boy. And as of August 2020, three "exon-skipping" therapies, designed to allow DMD patients to make truncated, yet still functional, dystrophin had been FDA-approved.[21] While hopes for a "cure" for muscular dystrophy are still distant dreams,[22] significant improvements to lifespan and overall quality of life are already well within reach.

[20] Darras, Urion, and Ghosh, "Dystrophinopathies," 1-3.
[21] Sujatha Gurunathan, "Once a Wild Idea, Successful First-Generation Exon-Skipping Therapies Pave the Way for Personalized Treatments," MDA, Muscular Dystrophy Association, Nov. 17, 2020, https://strongly.mda.org/once-a-wild-idea-successful-first-generation-exon-skipping-therapies-pave-the-way-for-personalized-treatments.
[22] Louis M. Kunkel, in conversation with the author, March 8, 2021.

Chapter 1: Discovering Muscular Dystrophy

Gaetano Conte and L. Gioja: Clinical Descriptions

In 1836, two physicians from Naples, Professor Gaetano Conte and Dr. L. Gioja, published a study on two brothers who, from between the ages of 8 and 10, had been experiencing progressive enlargement of the muscles, particularly in the calves and deltoids, and weakness in the legs. The older brother died with signs of cardiomyopathy as a young teenager, while the younger brother, Nicola, who appeared to be less heavily afflicted by the disease, had survived to adulthood before he was transferred out of Conte and Gioja's care.[23] However, Nicola's condition had deteriorated so much that as of his last appointment with Conte and Gioja, he was unable to voluntarily move any of his limbs; the only movements came from severe muscle contractures that radiated throughout his body.[24] When speculating on the cause of the boys' illness, Conte and Gioja hypothesized that the cold climate and the boys' physically challenging lifestyles "caused spasm of the lymphatic vessels so that their valves closed and they could no longer carry away muscle waste. The waste products remained in the muscle, causing abnormal growth, and spilt over into the blood. The muscular infiltrations resulted in increased intermuscular pressures that caused paresis."[25] Much to the doctors' dismay, no autopsy for the older boy was available, meaning they were unable to examine the

[23] John R. Bach, "The Duchenne de Boulogne - Meryon Controversy and Pseudohypertrophic Muscular Dystrophy," *Journal of the History of Medicine and Allied Sciences* 55, no. 2 (2000): 168, https://muse.jhu.edu/article/15181
[24] Tyler, "Origins and Early Descriptions," 403.
[25] Gaetano Conte and L. Gioja, "Scrofola del Sistema Muscolare," *Annali Clinici dell'Ospedale degli Incurabili de Napoli* 2 (1836): 66-79, quoted in Bach, "The Duchenne de Boulogne – Meryon Controversy," 168.

connective intramuscular tissue, which they believed would allow them to determine if their theory of a malfunctioning "nutritional" (metabolic) process was correct.[26] Despite the lack of histological evidence, the clinical details of the case, from the boys' growing weakness in the limbs to the hypertrophic muscles to the signs of heart failure, suggest that the patients suffered from what would eventually be known as muscular dystrophy. Yet Conte and Gioja never continued their studies; perhaps they never again came across individuals who exhibited similar symptoms. Ultimately, the lack of data (and the paper's improper citation in a book summarizing foreign medical studies) pushed their work into obscurity.[27] A decade would pass before another presumable case of MD was documented.

Richard Partridge: Macroscopic Histological Analysis

Richard Partridge was the next to present a case study of what was most likely Duchenne muscular dystrophy. In a briefing given to the Pathological Society of London in November of 1847, Partridge spoke of a 14-year-old boy who, over the past five years, had increasingly experienced general paralysis. Unlike Conte and Gioja, however, Partridge had access to autopsy results:

> On the post-mortem examination the spinal canal was found to contain about 3ss. of fluid, the cord being healthy… The deltoid and sternomastoid muscles had undergone fatty degeneration. The calves (which were larger than natural, and had, during the progress of the paralysis, become permanently contracted) presented a greater degree of fatty degeneration in their muscular structure than the upper extremities, the soleus and gastrocnemius being more affected also than the flexor

[26] Tyler, "Origins and Early Descriptions," 403.
[27] Tyler, 402-403.

> longus pollicus; neither the nerves or [*sic*] tendons had undergone change.[28]

Like most DMD patients, the boy that Partridge examined had a normal spinal cord and nerves, and he exhibited the characteristic enlarged, weakened calves. However, it is also important to note that Partridge's phrasing indicates that he only observed the tissues *macroscopically* and not *microscopically*. Thus, while many recognize Partridge for providing the first autopsy results of a Duchenne muscular dystrophy patient, the lack of microscopic evidence raises a sliver of doubt about the accuracy of a DMD diagnosis.

William J. Little: Microscopic Histological Analysis

In the same year that Partridge's briefing on his presumed MD patient was published, surgeon William J. Little was also taking note of two brothers who were experiencing similar symptoms. In fact, the timing of Little's initial observations, which came two months before Partridge's, in addition to similarities between the autopsy results, has led the Emerys to suggest that the elder of the two brothers was in fact the same patient that Partridge described.[29] Little's findings, which were not published until 1853, detailed the case of two brothers, aged twelve and fourteen. Neither had been born paralyzed or with any visible deformities, but over time, their conditions had steadily declined. The elder of the brothers had fared the worst, and Little described him as having a "peculiar" gate, with calf muscles that looked as if they should have belonged to a grown man. By the time Little had the chance to observe them, both

[28] Richard Partridge, "Fatty Degeneration of Muscle: Report of Proceedings to the Pathological Society of London," *London Medical Gazette (New Series)* 5, no. 29 (1847): 944, http://opacplus.bsb-muenchen.de/title/10431646/ft/bsb11043535?page=968.
[29] Emery and Emery, *History of a Genetic Disease*, 25.

brothers' conditions had advanced so far that, when pulled up into a standing position, they could not stand on their own.[30]

While Little's detailed clinical descriptions mostly reiterated what Conte, Gioja, and Partridge had previously described, a single sentence in his report suggests that he was the first to request a microscopic analysis of the tissues. Under Little's direction, a Dr. Parker had "kindly submitted these structures to a minuter [*sic*] examination [and] detected 'granular' evidences of inflammation in the matter scraped from the arachnoid [a membrane surrounding the brain and spinal cord]."[31] Despite having new, if extremely limited, evidence about the brothers' affliction, it seems that Little was no longer interested in studying the disease himself; after all, the details of the case were relegated to a footnote in a book that he published six years later. However, he may have used some of his lingering curiosity to direct a colleague's attention to the boys' "fatty degeneration of muscle"; only five years later, Edward Meryon, a fellow member of the Royal Medical and Chirurgical Society, would revisit the family of the brothers that Little had studied.

Edward Meryon: Clinico-Pathological Analysis

Although others before him had described patients with dystrophinopathies, Edward Meryon was the first to conduct both clinical and pathological studies of the disease systematically. As the Emerys write, "it was Meryon's great contribution to realize the similarity among the various cases and, most significantly, that they

[30] William J. Little, *On the Nature and Treatment of the Deformities of the Human Frame: Being a Course of Lectures Delivered at the Royal Orthopaedic Hospital in 1843* (London: Longman, Brown, Green & Longmans, 1853), 14-16, https://archive.org/details/b21289141/page/n5/mode/2up?q=feed.
[31] Little, *On the Nature*, 16.

represented a specific and unique disease entity."[32] Besides claiming that muscular dystrophy, which he called granular degeneration of the voluntary muscles, was a pathology distinct from other muscle-degenerating, paralytic diseases, Meryon also recognized that MD is caused by a problem in the muscles themselves (i.e. not in the spinal cord) and that it frequently appears in families, almost always in males. Given these many early contributions, Meryon is often considered to have produced the first "complete" clinico-pathological description of MD.[33]

Considering Meryon's eminence in the medical field, both in his own time and today, surprisingly little is known about his early life. There are ample records, however, from his time in medical school. Meryon was evidently an outstanding student, receiving a gold medal and first certificate in anatomy, a certificate of honor in physiology, and a certificate of honor in practical anatomy.[34] Notably, the classes in which Meryon received awards covered both "changes produced in the structure of the muscular system from disease" and "spasmodic and paralytic affections."[35] His excellence in these subjects, along with his membership in various well-respected professional organizations, including the Royal Medical and Chirurgical Society (to which both Partridge and Little belonged), would serve him well as he began to grow interested in muscle diseases.

On December 9th, 1851, Meryon presented a paper titled "On Granular and Fatty Degeneration of the Voluntary Muscles." Meryon believed that the work he was about

[32] Emery and Emery, *History of a Genetic Disease*, 34-35.
[33] Angelini, "Muscular Dystrophy," 479.
[34] Emery and Emery, 61.
[35] Emery and Emery, 34.

to present was "of more than ordinary interest," as he had found individuals from three different families who seemed to share the same unfamiliar disease.[36] He had discovered family "P" in 1848 when he was asked to consult on the case of a boy who, despite having progressed normally until late childhood, had begun to lose the ability to walk. When Meryon examined the child, simply known as the "Hon. Geo. P.," he found that "the power of the muscles of the upper extremities was diminishing also, notwithstanding that the muscular mass of the body and limbs did not appear to have diminished, but, on the contrary, he had grown well and had gained in flesh."[37] Just two years after this initial assessment, Geo. P. died, unable to walk or even stand. Meryon was immediately informed upon his patient's death and was able to conduct an autopsy just twenty-two hours later.[38] The macroscopic examination of the spinal cord and muscle tissue revealed the results expected of Duchenne MD patients: the spinal cord and membranes appeared to be perfectly healthy, while the voluntary muscles were atrophied and clearly diseased. However, microscopic analysis revealed that "the striped elementary primitive fibres were found to be completely destroyed, the sarcous element being diffused, and in many places converted into oil globules and granular matter, whilst the sarcolemma or tunic of the elementary fibre was broken down and destroyed.[39] To illustrate these findings, Meryon included hand-drawn images of what he saw under the microscope (Figure 2).

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[36] Edward Meryon, "On Granular and Fatty Degeneration of the Voluntary Muscles," *Medico-Chirurgical Transactions* 35 (1852): 73, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2104198/pdf/medcht00052-0111.pdf.
[37] Meryon, "On Granular," 74.
[38] Meryon, 75.
[39] Meryon, 76.

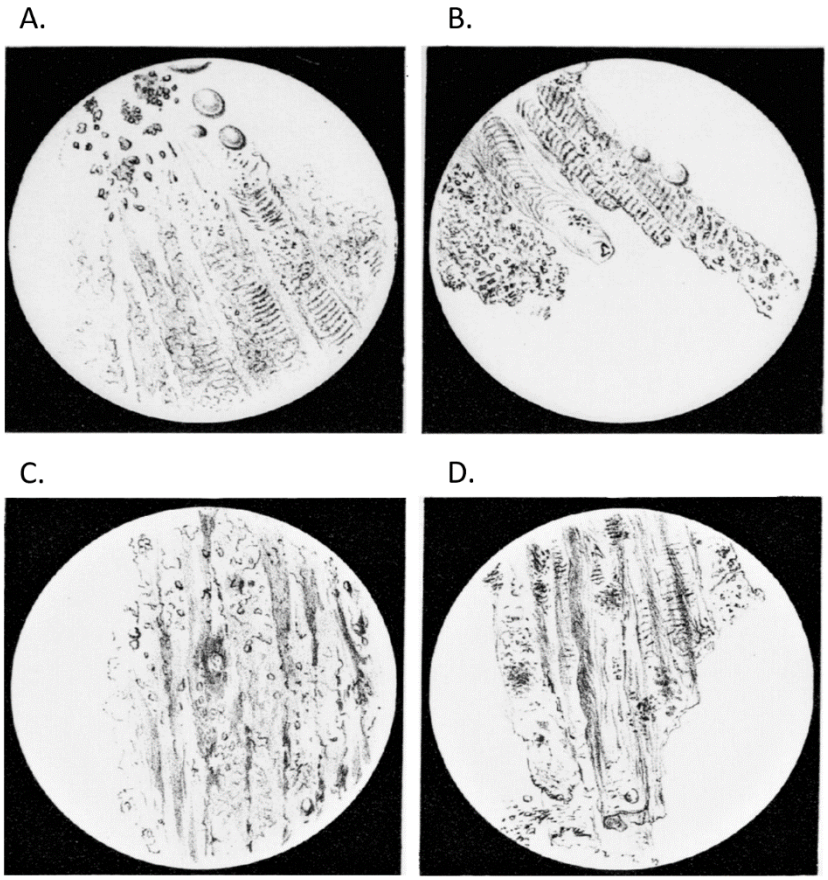

Figure 2: "Degeneration of the Voluntary Muscles"

Meryon's original captions for these illustrations are as follows: A. "Diseased Muscles, the transverse striae appearing faintly in places. Drawn from the preparation." B. "Diseased Muscle from the upper extremities, the transverse striae beginning to disappear and granular taking their place." C. "Diseased Muscle from the lower extremities, the transverse striae having disappeared." D. "Diseased Muscle from the lower extremities, showing little more than granular matter."[40]

Meryon's work was ground-breaking not only because he was the first to study the affected tissues at a microscopic level, but also because he had uncovered a string of other patients who suffered from the same symptoms. His interviews with Geo. P.'s parents revealed that they had three younger sons who had all started to show the same

[40] Meryon, 84.1.

signs of weakness in the extremities, while their six daughters remained unaffected.[41] Additionally, two other families also reported having two sons each with similar conditions; the oldest boy from family "H" was in fact the same patient that Partridge and Little had previously observed.[42] These results led Meryon to conclude that this degeneration of the voluntary muscles ran in families and exclusively affected males; that is, the disease was heritable.

Duchenne de Boulogne: The "Discoverer" of DMD

Considering all of Meryon's contributions to understanding the dystrophinopathies, including being the first to recognize DMD as a distinct, previously undescribed disease, it is curious that it is not his name associated with this form of muscular dystrophy. Instead, the eponymous honor belongs to Guillaume-Benjamin Amand Duchenne, better known as Duchenne de Boulogne. By his own admission, Duchenne did not come across his first patient with DMD until 1858; he then published his findings in 1861.[43] Notably, this was a decade after Meryon and two decades after Conte and Gioja had documented their discoveries of muscular dystrophy. Furthermore, his work only began to extend beyond the clinic ten years after he consulted with his first DMD patient when he observed autopsy reports. Even then, the autopsy reports were not for patients of his own; they were from two separate publications, one in 1863 and the other in 1866, on two German boys who had died from the same symptoms that

[41] Meryon, 76-77.
[42] Meryon, 80-81.
[43] George Vivian Poore and Guillaume-Benjamin Duchenne, *Selections from the Clinical Works of Dr. Duchenne (de Boulogne)* ([London?]: New Sydenham Society, 1883), 173-174, https://www.google.com/books/edition/Selections_from_the_Clinical_Works_of_Dr/mucEAAAAQAAJ?hl=en&gbpv=0.

Duchenne had observed.[44] In response to criticism over his lack of anatomical evidence, Duchenne finally observed muscle tissue from a DMD patient for himself in 1865 using a device of his own invention: the "histological harpoon," as it was known in England, which was the first instrument designed to collect muscle tissue samples from live patients.[45] While the development of a muscle biopsy tool was significant, in many ways Duchenne's work did little more than retrace what Conte, Gioja, Partridge, Little, and Meryon had cumulatively described years before him.

Although he was not nearly the first person to describe DMD, Duchenne seemingly had no qualms about claiming the title of "discoverer" for himself, even though he explicitly stated his familiarity with Meryon's work.[46] While some, like the Emerys, have given Duchenne the benefit of the doubt,[47] it is clear that he purposely tried to undermine Meryon's findings. In three separate publications, Duchenne wrote that Meryon had in fact observed *atrophie musculaire graisseuse progressive*, a term Duchenne used to describe various neuromuscular diseases like poliomyelitis and spinal muscular atrophy, rather than the disease that would eventually be classified as DMD.[48] Neurologist John R. Bach in particular has stridently criticized Duchenne, scathingly remarking that "The fact that subsequent historians and neurologists credited him with priority is not due to Duchenne de Boulogne's achievement in science, but rather his skill in deliberately obscuring the contributions of others and claiming, falsely, the glory

[44] Tyler, "Origins and Early Descriptions," 408.
[45] Tyler, 411; Angelini, "Muscular Dystrophy," 481-482.
[46] Poore and Duchenne, *Selections from the Clinical Works*, 77.
[47] Emery and Emery, *History of a Genetic Disease*, 88-90.
[48] Bach, "The Duchenne de Boulogne-Meryon Controversy," 171.

for himself."[49] As Bach summarizes, Duchenne repeatedly disparaged the work of other early neurologists who were studying muscular and neuromuscular diseases, alluded to unpublished and apparently nonexistent memoires in which he described DMD cases predating Meryon's discoveries, claimed to have cured at least one DMD patient, and discredited Meryon by arguing that Meryon had mistakenly diagnosed his patients.[50] In sum, the evidence indicates that Duchenne consciously obfuscated the true origins of the discovery of the dystrophinopathies.

Forgetting Meryon: 19th Century Attitudes Surrounding Microscopy

Considering Duchenne's actions, an obvious question arises: how and why was Duchenne so successful in claiming the discovery of DMD for himself? Situating Meryon and Duchenne in the social and technological contexts of their time may provide an answer. Today, the microscope is arguably one of the most popular tools associated with scientists; STS scholar Ann La Berge states that it may have been *the* primary symbol of biomedicine for a century before the rise of genetic technologies in the 1960s.[51] Yet this was not always the case. Following the deaths of the classical microscopists at the end of the 18th and beginning of the 19th centuries, microscopy experienced a dramatic decline. The microscope became associated with "popular" science and was "primarily an instrument of amateurs to be used either for display or entertainment. In a word, it was a toy."[52] Across continental Europe, scientists

[49] Bach, 158-159.
[50] Bach, 175.
[51] Ann La Berge, "The History of Science and the History of Microscopy," *Perspectives on Science* 7, no. 1 (1999): 111, doi:10.1162/posc.1999.7.1.111.
[52] La Berge, "The History of Science," 119.

continued to view microscopy as a recreational, social activity well into the early 1800s. Men would meet at each other's homes and spend their evenings fiddling with microscopes and other hobby instruments.[53] Although there is significant debate over what caused this century-long break from using microscopes for "serious" science,[54] one factor was that it was difficult to see clear images through them. Through the 18th and early 19th centuries, there were no significant improvements to the microscope. Thus, people were stuck with the same glass quality and lens size of the same simple microscopes that made men like Anton van Leeuwenhoek famous more than a hundred years before.[55]

The issue of microscope quality was solved in 1826, when British physician Joseph Jackson Lister (not to be confused with his son, Joseph Lister, who would become famous for pioneering antiseptic surgical techniques) designed an achromatic compound microscope that eliminated the spherical aberrations that had previously limited the instrument's practical value.[56] However, the invention of this new microscope was not associated with an immediate recognition that it could be used to study disease, or even that it could be used to study tissue. First, the cost of the achromatic microscope was prohibitive, so it did not become widely available until the

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[53] Jutta Schickore, *The Microscope and the Eye: A History of Reflections, 1740*-1870 (Chicago: University of Chicago Press, 2007), 105.
[54] C.f. Catherine Wilson, *The Invisible World: Early Modern Philosophy and the Invention of the Microscope* (Princeton: Princeton University Press, 1995); Marian Fournier, *The Fabric of Life: Microscopy in the Seventeenth Century* (Baltimore: Johns Hopkins University Press, 1996); Edward G. Ruestow, *The Microscope in the Dutch Republic: The Shaping of Discovery* (New York: Cambridge University Press, 1996).
[55] Gerard, L'E Turner, "Eighteenth-Century Scientific Instruments and Their Makers," in *The Cambridge History of Science*, ed. by Roy Porter, 4:509–35, (Cambridge: Cambridge University Press, 2003), doi:10.1017/CHOL9780521572439.023.
[56] Patricia Helen Bracegirdle, "The Establishment of Histology in the Curriculum of the London Medical Schools, 1826-1996," (Ph.D. diss., University of London, 1996),15, https://discovery.ucl.ac.uk/id/eprint/1381833/1/388986.pdf.

1850s.[57] Secondly, there was little interest in histology at the time anyway. Although a theoretical framework of tissue classification, pioneered by the French anatomist Marie François Xavier Bichat, had been broadly accepted in British medical schools by the 1820s, the first English-language series to provide a description of the microscopic anatomy of the tissues was not completed until 1844.[58] Furthermore, differential staining, which improves tissue visibility under a microscope, was not developed until 1852.[59] Finally, histology was not incorporated into lessons on general anatomy across all British medical schools until 1854, and it took another twenty years before schools were required to teach the study of tissue as its own, separate course.[60] The slow progress between the founding of histology and its mandatory teaching in medical institutions suggests that for much of the 19th century, few recognized the importance of studying tissue for understanding pathology. Suspicions about the utility of histology, and the microscope in general, lingered well into the 1850s in London.[61]

Since Meryon's first observations on muscular dystrophy occurred between 1848 and 1851, he was working at a pivotal time in the history of modern microscopy and histology; while some in London were beginning to see the microscope's potential for providing insight into disease pathogenesis, many others still viewed microscopy as merely a gentleman's hobby. Meryon, as one of the founders of the Microscopical Society of London, was firmly in the first camp.[62] When he presented his case studies to

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[57] Bracegirdle, "The Establishment of Histology," 377-378.
[58] Bracegirdle, 17.
[59] Brian J. Ford, "The Royal Society and the Microscope," *Notes and Records of the Royal Society of London* 55, no. 1 (2001): 39, doi: 10.1098/rsnr.2001.0124.
[60] Bracegirdle, "The Establishment of Histology," 25-219.
[61] La Berge, "The History of Science," 137.
[62] Gerard L'E. Turner, *God Bless the Microscope: A History of the Royal Microscopical Society Over 150 Years* (Oxford: Royal Microscopical Society, 1989).

the Royal Medical Society, however, his histological findings, while intriguing, were probably not the most interesting aspect of his talk for many of the members present. And when his findings made their way to France, his comments on the muscle tissue anatomy of his patients would have met an audience even more indifferent, if not hostile, to the microscope.

The microscopic revival of the 19th century was even slower to reach France than England. Like in England, microscopes, especially the new achromatic ones, were expensive. However, resistance to microscopy, and therefore anatomical pathology, was also driven by the still-prevailing theories of humoral pathogenesis (which could not be studied via microscope) and "radical empiricism," which prioritized the pure senses, unobstructed (or unaided) by any tools.[63] If microscopy was beginning to gain more widespread acceptance in London from the mid- to late 1850s, tensions between the upstart microscopists and the established, anti-microscopy clinicians were coming to a head in Paris. From 1854 to 1855, the Academy of Medicine held thirteen debate sessions dedicated to discussing the utility of microscopy; the older, anti-microscope faction won.[64] However, tides changed in the 1860s as France began to feel pressure from Germany, whose own surgical techniques, anatomical and physiological research, and overall medical training had rapidly surpassed those of France. National feelings of inferiority and "French degeneracy" sparked competition and paved the way for the acceptance of new technologies and medical instruments, including the microscope.

[63] Ann La Berge, "Dichotomy or Integration: Medical Microscopy and the Paris Clinical Tradition," in *Constructing Paris Medicine*, ed. by Anna La Berge and Mordechai Feingold (Amsterdam: Rodopi, 1998), 276.
[64] La Berge, "Dichotomy or Integration," 279.

Thus, it was only until the mid-1860s that French physicians, about a decade after British doctors, grew to see microscopic histological analysis as an essential part of the biomedical research process.[65]

France's history with microscopy explains in part why Duchenne was able to brush Meryon's work aside. The first time Duchenne publicly disagreed with Meryon's diagnoses was in 1855, the last year of the Academy of Medicine's debates on microscopy.[66] Duchenne was not one of these early adopters of the microscope, as part of his criticism included Meryon's heavy focus on anatomical pathology rather than clinical symptoms.[67] There would have been few established French physicians that would have disagreed with him. Yet soon after, Duchenne himself came under fire from colleagues abroad for his lack of pathological evidence in his various publications on potential new muscular and neuromuscular diseases. This may have been what led him to provide some, if very little, histological evidence in his 1861 edition of a book on "new" degenerative diseases.[68] However, it was not until 1872 that he fully addressed this criticism: "I have been much blamed abroad for having, in the different pathological investigations which I have published neglected and despised pathological anatomy, that branch of science inseparable from all good clinical work. I recognised the reproach, and wished to expose myself to it no longer."[69] While it is difficult to determine if Duchenne truly had a change of heart concerning microscopy or if he was

[65] Ann La Berge and Mordechai Feingold, introduction to *Constructing Paris Medicine*, ed. Ann La Berge and Mordechai Feingold (Amsterdam: Rodopi, 1998), 19-20.
[66] Bach, "The Duchenne de Boulogne -Meryon Controversy," 171.
[67] Bach, 172.
[68] Tyler, "Origins and Early Descriptions," 411.
[69] Poore and Duchenne, "Selections from the Clinical Works," 174.

simply responding to his London associates' pressure, by 1872, the resurgence of microscopy was well under way in France. Unsurprisingly, Duchenne's histological analyses of DMD patients yielded the same results that Meryon had described much earlier before: an increase in fibroid and connective tissue, fat vesicles in the sheaths of the sarcolemma, and disruptions in the transverse striations of the muscle fibers.[70] Yet Duchenne had already succeeded in sweeping Meryon under the rug, his microscopic descriptions discredited and forgotten. Notes from George Poore, who in 1883 compiled and translated into English selections from many of Duchenne's publications, demonstrate the irony of the situation:

> Duchenne seems to have been blamed because he devoted his attention more to bed-side observation than to microscopical anatomy. The fact was that he had no special talent for the pursuit of morbid histology, and although latterly he devoted some attention to the subject, and was one of the first who attempted to fix microscopic results by the aid of photography, he did not succeed in adding to our pathological knowledge, and one cannot but feel that anything which took a man of his habit of mind away from the bed-side, where he was unequalled, did not, to say the least, help the advance of medical science. A wise division of labour has been, and will be, a powerful cause of the advance of knowledge, and a great clinical observer should rather be encouraged than otherwise to leave the delicate work of histology to those whose natural talents lead them to devote their best energies to the pursuit of it.[71]

Poore gently reproaches Duchenne's lack of histological evidence, balancing his critique by emphasizing Duchenne's unparalleled clinical skills. It should be up to more a skilled microscopist, he writes, to study the diseased tissue. These detailed descriptions of DMD histology, though, had already been completed by a "skilled microscopist" – Edward Meryon. Yet later in the text, he explicitly states that Meryon's

[70] Poore and Duchenne, 176.
[71] Poore and Duchenne, xi-xii.

"case of muscular degeneration in the Medico-Chirurgical Transactions for 1854 and 1866 refers in reality… to pseudo-hypertrophic paralysis," a disease that was already well-documented.[72] By the early 1880s, Meryon's observations had been forgotten; from then on out, Duchenne's name would be associated with this form of muscular dystrophy.

What Does it Mean to "Discover" a Disease?

Largely thanks to the Emerys, the current works on the history of muscular dystrophy are nearly unanimous in their belief that Duchenne should not be credited as the first to discover MD. However, none of the literature has attempted to explain how "Duchenne" became the eponym. By placing Meryon's and Duchenne's in a broader social context, it becomes clear that the microscope, in conjunction with the newly emerging field of histology, is responsible for the name of the disease. However, it is also worth considering why these same scholars are so quick to name Meryon as the "true" discoverer of the disease; he certainly was not the first to provide a detailed clinical description. Neither the Emerys, Tyler, Pearce, Accardo, nor any other scientist who has written about the discovery of muscular dystrophy, to my knowledge, explicitly addresses this concern. The circular answer seems to be that Meryon should be credited simply because Duchenne should not be. Yet once again, understanding the connections between microscopy and muscular dystrophy reveals why scientists have argued for Meryon's primacy.

[72] Poore and Duchenne, 64-65.

When the Emerys published the first edition of their book on DMD (or, as they would call it, Meryon's disease), doctors were still using tissue analysis as the final step in diagnosing muscular dystrophy.[73] The resurgence of microscopy that had begun in the 1800s continued for another century as microscopy continued to gain respect and became an important tool for diagnosing the dystrophinopathies. Thus, it appears that 20th century conceptions about DMD pathology were reflected onto the past, influencing who biomedical professions labeled the "discoverer" of MD. As a result, scientists do not credit Partridge as the father of muscular dystrophy because he only examined tissue samples from an MD patient macroscopically. Similarly, Little's discovery is dismissed (even though some scholars have suggested that Little's clinical descriptions of the progression of DMD were even more detailed than Meryon's)[74] because he only used the microscope in a limited manner and did not present his histological observations as essential to his conclusions about the disease. Conte and Gioja do not figure into the conversation of discovery at all, as they solely focused on clinical descriptions since they did not have the opportunity to observe the diseased tissues.

The work of the famed neurophysiologist Charles Bell provides further support for the argument that current medical understandings influence the conception of disease discovery. Bell almost certainly described a single case of Becker muscular

[73] Leslie A. Morrison, "Dystrophinopathies," in *Muscular Dystrophies*, ed. by Robert C. Griggs and Anthonty A. Amato, vol. 101 of *Handbook of Clinical Neurology* (Amsterdam: Elsevier B. V., 2011): 19, doi: 10.1016/B978-0-08-045031-5.00002-5.
[74] Pasquale J. Accardo, "An Early Case Report of Muscular Dystrophy: A Footnote to the History of Neuromuscular Disorders," *Archives of Neurology* 38, no. 3 (1981): 144-146, doi: 10.1001/archneur.1981.00510030038004.

dystrophy, which is the milder of the two dystrophinopathies, in 1830, six years before Conte and Gioja's description of a Duchenne muscular dystrophy patient and more than a century before BMD was recognized as distinct from DMD.[75] In his book, *The Nervous System of the Human Body*, Bell describes…

> … a young gentleman about eighteen. All the muscles of the lower extremities, the hips, and the abdomen, are debilitated and wasted… The upper part of the body, the shoulders, and arms, are strong… There is a slight curvature or projection of the lumbar part of his spine. He is weak, and subject to palpitations on going up stairs; his tongue is coated… The paralytic debility of the muscles came on gradually: he was first sensible of it at a public school, about eight years ago. It began with a weakness in the thighs, which disabled him from rising; and it is now curious to observe how he will twist and jerk his body to throw himself upright from his seat.[76] (clxiii).

Bell's observations, combined with the boy's extended lifespan and later onset, align perfectly with clinical descriptions of BMD today; he even describes the odd technique the teenager used to maneuver himself from a chair into a standing position, part of classical physical tests for muscular dystrophy. Yet as with the doctors before Meryon, namely Conte and Gioja, Partridge, and Little, who described DMD, experts have been reluctant to give Bell credit for his discovery. But why? As the Emerys write at the end of their discussion about Bell, despite the fact they obviously believe Bell did indeed observe a BMD patient, "Without muscle pathology, however, the diagnosis of muscular dystrophy cannot be certain."[77] From Duchenne until the late 20th and early 21st centuries, the authority of the microscope has clearly influenced the way scientists

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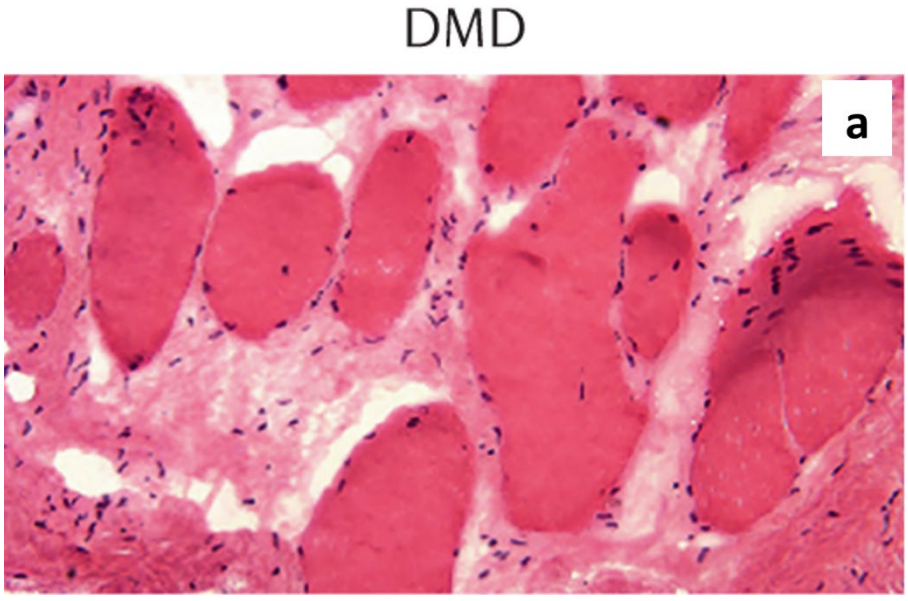
[75] Emery and Emery, *History of a Genetic Disease*, 133.
[76] Charles Bell, *The Nervous System of the Human Body: Embracing the Papers Delivered to the Royal Society on the Subject of the Nerves* (London: Longman, Rees, Orme, Brown, and Green, 1830): clxiii. https://archive.org/details/b21270508/page/n5/mode/2up?q=disabled.
[77] Emery and Emery, *History of a Genetic Disease*, 18.

discuss the history of MD. In short, the technology that is perceived to most accurately describe the disease determines who is credited with its discovery. This theme of the importance of technology in shaping conceptions of disease holds true not only when discussing the discovery of MD, but also when considering how ideas about diagnosis have changed over time; this is the subject of the next chapter.

Chapter 2: Methods of Diagnosis

Diagnosing the Dystrophinopathies: From Microscopy to DNA Sequencing

When Meryon sketched what he saw under his microscope after observing the muscle tissue of his first DMD patient, little did he know that he was foreshadowing the future of Duchenne and Becker muscular dystrophy diagnosis for the next one hundred and fifty years. Until the end of the 20th century, the primary way to confirm that an individual had either DMD or BMD was by conducting a muscle biopsy;[78] a trained pathologist could easily observe the differences between normal and healthy skeletal muscle tissue (Figure 3).



[78] Morrison, "Dystrophinopathies," 19.

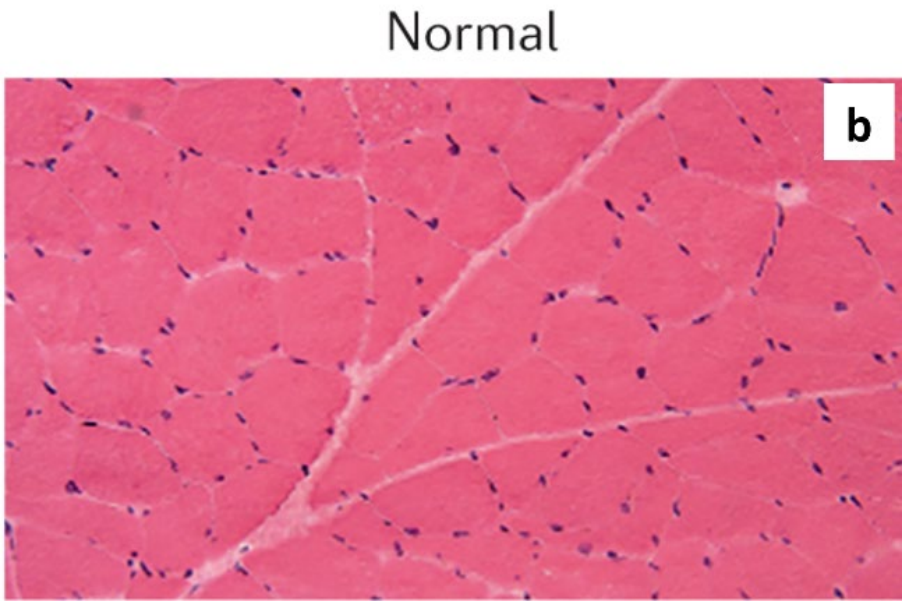


Figure 3: Skeletal Muscle Histology: DMD vs Normal Biopsy Samples

The DMD tissue on the top, clearly distinguishable from the healthy skeletal tissue on the bottom, shows fat (white) and muscle degeneration (pink) around the myocytes (red).[79]

Yet the resurgence of the microscope had other long-lasting effects on MD diagnosis. The development of histology precipitated a dramatic change in how physicians examined their patients, as studying tissue samples was an entirely new way for doctors to collect clinical data. As a result of this shift from focusing solely on the outward expression of disease, "the boundaries between 'laboratory' and 'clinical' practices became increasingly fuzzy, and changes in patients' tissues and vital fluid became part of the 'pathological signs' of a disease."[80] Thus, while muscle biopsy remained the definitive method to diagnose a patient with DMD or BMD, scientists also began

[79] Dongsheng Duan et al., "Duchenne Muscular Dystrophy," *Nature Reviews Disease Primers* 7, no. 13 (2021): 3, doi: 10.1038/s41572-021-00248-3.
[80] Ilana Löwy, "Labelled Bodies, Classification of Diseases and the Medical Way of Knowing," *History of Science* 49, no. 3 (2011): 301, doi: 10.1177/007327531104900304.

pursuing other laboratory-based assays for identifying patients with muscular dystrophy.

By the late 1940s, scientists began to consider the idea that there might be a way to diagnose MD by analyzing patients' blood. French scientists Jean-Claude Dreyfus and Georges Schapira started by studying the enzymes involved in muscle glycolysis, which is the process by which muscle cells turn sugar into energy.[81] Although they found that serum levels of various enzymes were elevated in muscular dystrophy patients, the most sensitive serum enzyme test was not created until 1958. A group of Japanese biochemists led by Setsuro Ebashi found that out of nineteen patients with progressive muscular dystrophy (a term which includes DMD and BMD), approximately 70% showed significantly increased levels of creatine phosphokinase activity.[82] Creatine phosphokinase, often abbreviated as either CK or CPK, is primarily present in muscle tissue and helps muscles contract. When there is muscle damage, however, CK leaks into the bloodstream and therefore leads to elevated serum levels.[83] After Ebashi et al.'s initial discovery, more and more sensitive assays for detecting elevated CK levels were devised, significantly improving the reliability of CK tests. In fact, Victor Dubowitz, famous for his work in pediatric muscle diseases, was so confident in the diagnostic abilities of CK testing that in 1976, he concluded that "Duchenne muscular dystrophy can be diagnosed with confidence before it is clinically

[81] Emery and Emery, *History of a Genetic Disease*, 155.
[82] Setsuro Ebashi et al., "High Creatine Phosphokinase Activity of Sera of Progressive Muscular Dystrophy," *The Journal of Biochemistry* 46, no. 1 (1959): 103, https://www.jstage.jst.go.jp/article/biochemistry1922/46/1/46_1_103/_pdf.
[83] Emery and Emery, *History of a Genetic Disease*, 156.

apparent, and excluded with certainty where it may have seemed clinically obvious."[84] This is a critical point; for the first time, scientists had created a test that they believed could not only *diagnose* patients with DMD, but could also *predict* which patients would eventually show the symptoms of the disease.

While biochemists were studying enzyme levels of muscular dystrophy patients, other scientists were interested in the genetic component of MD; these researchers were some of the first molecular biologists. Although Meryon recognized that MD often ran in families and almost exclusively occurred in males, the language of genetics did not yet exist. By the late 1950s, however, the X-linked mode of inheritance of muscular dystrophy had been well established, and interest in the potential genetic underpinnings of the disease skyrocketed.[85] A few decades later, the development of new genetic technologies and the work of countless scientists culminated in 1986 and 1987, when Louis Kunkel and associates identified the location, or locus, of the "DMD gene," the gene itself, and the gene's protein product, which they decided to name "dystrophin." Furthermore, they discovered that BMD was associated with mutations in the dystrophin gene as well.[86]

It is difficult to overstate the astounding nature of Kunkel's lab's findings. For the few other diseases that had been genetically mapped at this time, scientists had already known with relative certainty the identity of the mutated protein product

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[84] Victor Dubowitz, "Screening for Duchenne Muscular Dystrophy," *Archives of Disease in Childhood* 51, no. 4 (1976): 249, doi: 10.1136/adc.51.4.249.
[85] Emery and Emery, *History of a Genetic Disease*, 120, 153.
[86] Anthony P. Monaco et al., "Isolation of Candidate cDNAs for Portions of the Duchenne Muscular Dystrophy Gene," Nature 323, no. 16 (1986): 646-650, doi: 10.1038/323646a0; Eric P. Hoffman, Robert H. Brown, Jr., and Louis M. Kunkel, "Dystrophin: The Protein Product of the Duchenne Muscular Dystrophy Locus," Cell 51, no. 6 (1987): 919-928, doi: 10.1016/0092-8674(87)90579-4.

associated with the disease phenotype. The search for the DMD locus, on the other hand, was a blind hunt; all that was known was that the gene of interest was located on the X chromosome. As such, muscular dystrophy was the first disorder for which scientists located and identified the defective gene without having any prior knowledge about what kind of protein it might encode;[87] on the flip side, it was also the first time that a disease-related protein had been identified from analysis of its gene.[88] Kunkel's unprecedented success demonstrated the potential of genetics, scientists believed, to provide more "accurate" insight into the pathological source of any disease with a genetic component. This logic thus inspired arguably the most ambitious undertaking in the history of science: the Human Genome Project (HGP). The effort to identify each individual component of humanity's DNA would change the process of diagnosing MD once again.

Although some genetic tests for diagnosing muscular dystrophy existed before the completion of the HGP, these assays identified DMD in only about two-thirds of boys who exhibited clear clinical symptoms of the disease.[89] The successful completion of the HGP, however, led the National Human Genome Research Institute (NHGRI) to invest 70 million dollars in DNA sequencing technologies with the hope of making them cheaper, faster, and more widely available.[90] The rapid development of high-throughput sequencing was a step towards realizing a new diagnostic test that scientists

[87] Emery and Emery, *History of a Genetic Disease*, 195.
[88] Tom Wilkie, *Perilous Knowledge: The Human Genome Project and its Implications* (Berkeley: University of California Press, 1993), 24.
[89] Morrison, "Dystrophinopathies," 19.
[90] Jason A. Reuter, Damek V. Spacek, and Michael P. Snyder, "High-Throughput Sequencing Technologies," *Molecular Cell* 58, no. 4 (2015): 586, doi: 10.1016/j.molcel.2015.05.004.

hoped would capture all cases of both Duchenne *and* Becker muscular dystrophies: individual DNA sequencing. To understand the process of diagnosis following the HGP, I spoke with Dr. Kunkel himself. In a conversation over Zoom, he explained that today, MD sequencing is typically done via targeted exome sequencing, that is, sequencing of the parts of the gene that code for the dystrophin protein, because it is so cost-effective. For around $400, he estimated, a patient can receive a read-out of each dystrophin-encoding unit of their DNA.[91]

It is perhaps worth summarizing, then, the process of MD diagnosis in the present day. In an effort funded by the U.S. Centers for Disease Control and Prevention (CDC), 84 clinicians collaborated in 2009 to provide recommendations for healthcare providers on how to diagnose MD. The authors write that physicians should "suspect" a diagnosis of DMD if, first, they observe a child with abnormal muscle function, or second, if they happen to notice an abnormally high CK level when testing "for unrelated indications." The next and final step to confirm a diagnosis of DMD (or BMD) is to conduct some kind of genetic test, the type depending on local availability and/or reliability. If multiple molecular test options are available, however, dystrophin gene sequencing, the authors suggest, will provide the most accurate result.[92]

Diagnosing Disease, or Creating Diseases from Diagnoses?

On the surface, it seems that the advent of new diagnostic technologies would make it easier for clinicians to know whether a patient has or does not have one of the

[91] Louis M. Kunkel, in discussion with the author, March 8, 2021.
[92] Katharine Bushby et al., "Diagnosis and Management of Duchenne Muscular Dystrophy, Part I: Diagnosis, and Pharmacological and Psychosocial Management," *The Lancet Neurology* 9, no. 1 (2010): 81-82, doi: DOI:10.1016/S1474-4422(09)70272-8.

dystrophinopathies. But the evolving process of diagnosing muscular dystrophy instead reveals underlying epistemological concerns about legitimate ways of knowing, which in turn shapes what qualifies as legitimate knowledge. For example, although clinical symptoms and elevated CK levels may indicate that a patient has a muscular dystrophy, these tests by themselves no longer constitute legitimate ways of knowing if a patient has MD. My conversation with Dr. Kunkel further highlighted these points. When asked about how muscular dystrophy was diagnosed at the beginning of his career, he said:

> So we didn't know much at the time. Muscle biopsy was how it was diagnosed. Carrier females were detected by elevated CK levels, but it was very imprecise. And so many women didn't know they were carriers and frequently would have a child with Duchenne [muscular dystrophy] before they actually even knew that they were a carrier… You can't just use CK levels anymore, it's all molecularly done.[93]

Kunkel primarily mentioned CK levels in the context of screening for mothers carrying a dystrophin mutation that could be passed on to her children, only mentioning CK analysis for direct diagnostic purposes at the end of his response, rejecting it as something "you just can't" do anymore. This is a far cry from Dubowitz's bold statement that DMD could be "diagnosed with confidence before it is clinically apparent" using a CK assay alone. After the genomic revolution of the late 20th and early 21st centuries, CK serum analysis was not sufficient on its own to identify cases of MD.

In general, the history of MD diagnosis follows a larger "ways of knowing" trend in biomedicine – the trend of methodological reductionism. As philosopher of

[93] Louis M. Kunkel, in discussion with the author, March 8, 2021.

science Michael Ruse writes, "Inspired by the history of science since the Renaissance, the methodological reductionist argues that the triumphs of science come through the revealing and understanding of ever-smaller entities of nature."[94] In other words, scientists have come to believe that there is some higher, "more truthful" truth that can be elucidated by thinking on a smaller and smaller scale or by continually subdividing a whole into parts. The procedure for diagnosing MD perfectly encapsulates this theory. Over time, acceptable ways of confirming diagnosis shifted from a macroscopic scale (clinical symptoms) to a microscopic scale (histology) to an enzymatic scale (CK levels) to, finally, a molecular scale. And while it is tempting to view this sequence of events as a naturally progressing process from less to more accurate, it is more precise to see this "narrowing of the evidentiary terrain" as a new way of considering the boundaries of the dystrophinopathies as diseases.[95]

Indeed, these diagnostic changes have defined what muscular dystrophy *is*. At first, this style of thinking seems counterintuitive; it seems like biomedical professionals would have to define a disease first in order to diagnose their patients. But the history of muscular dystrophy demonstrates that the process can work in the reverse; diagnosis constructs the limits of a disease. When Conte, Gioja, Partridge, and Little came across instances of muscular dystrophy, their patients' outward signs of illness led them to conclude that they had observed a disease of weakened muscle. When histological

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[94] Michael Ruse, "Knowledge in Human Genetics: Some Epistemological Concerns," in *Genes and Human Self-Knowledge*, ed. by Robert F. Weir, Susan C. Lawrence, and Evan Fales (Iowa City: University of Iowa Press, 1994), 38.

[95] Bharat Jayram Venkat, "Cures," *Public Culture* 28, no. 3 (2015): Venkat, Bharat Jayram. "Cures." *Public Culture* 28, no. 3 (2015): 493, doi: 10.1215/08992363-3511502. While Venkat uses the phrase, "narrowing of the evidentiary terrain," in relationship to the concept of "cure," it applies equally well to discussions of diagnosis.

analysis emerged as the next authoritative mode to diagnose individuals, the definitions of DMD and BMD were slightly narrowed into "granular and fatty degeneration of the voluntary muscles." In the 20th century, after scientists like Dreyfus, Schapira, and Ebashi discovered that DMD and BMD patients had different serum enzyme levels than those unaffected by dystrophinopathies, MD became a disease at the biochemical level, an enzymatic defect.[96] And today, almost every clinician would say that muscular dystrophy is a result of a gene mutation. Every paper, book, and essay on muscular dystrophy published after the identification of dystrophin cited thus far has described MD as either a genetic disease or disorder, and when I asked Dr. Kunkel what he felt was the most accurate way to describe the pathological source of DMD, he looked obviously perplexed. "It's genetic." He replied without hesitation. "It's a gene mutation that causes the absence of dystrophin."[97]

Yet by coming up with new ways to *diagnose* MD, scientists were simultaneously generating new ways to *conceptualize* MD. The anthropologists Margaret Lock and Vinh-Kim Nguyen have more thoroughly described how diseases are "made real" by diagnostic procedures:

> Before objects and events can be made phenomenologically real, their very existence has to be recognized by a process of naming, ordering, and classification. Such recognition, including the diagnosis and management of episodes of illness, is the product of culture and does not emerge spontaneously from nature. In other words, what will count as disease and illness comes about as the result of particular practices embedded in specific historical, political, social, and technical relationships.[98]

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[96] Emery and Emery, *History of a Genetic Disease*, 165.
[97] Louis M. Kunkel, in conversation with the author, March 8, 2021.
[98] Lock, Margaret and Vinh-Kim Nguyen, *An Anthropology of Biomedicine* (United Kingdom: Wiley-Blackwell: 2010), 33.

In other words, shifting cultural contexts ascribe legitimacy to certain *methods* of knowledge production (i.e. methods of diagnosis), which in turn influences the knowledge *produced* (i.e. the definition of MD). That this phenomenon has shaped understandings of muscular dystrophy becomes clear when returning to the advent of the CK serum test. As Dubowitz stated, the CK serum assay not only allowed doctors to diagnose cases of muscular dystrophy before the onset of symptoms, but it also allowed them to *exclude cases that would have otherwise been categorized as DMD* based on clinical symptoms and histology alone.[99] Therefore, Duchenne MD was subdivided into even more categories of muscular dystrophy.

Dr. Kunkel's thoughts on diagnosis provide additional evidence for this theory of disease-creation. When elaborating on how the diagnostic process has changed since he first began studying muscular dystrophy, he said:

> Now they do targeted sequencing. Genome sequencing has become, I mean, exome sequencing has become so economically feasible. It's like 400 bucks and you get the whole gene, you get the whole gamut. So if you have a child who's a boy who presents with symptoms of muscular dystrophy, 90% of the time they will be Duchenne and a dystrophin mutation. About 5 to 10% of the time, they will be an autosomal recessive form of muscular dystrophy. There are now almost 20 known autosomal, recessive dystrophies that look almost identical to Duchenne, and they were all picked up. A lot of them are proteins that work with dystrophin in the muscle cell membrane.

It was only after the advent of sequencing technologies that scientists identified these other autosomal (i.e. not on the sex chromosomes) recessive muscular dystrophies; had acceptable methods for diagnosis not changed following the genomic revolution, they would have still been classified as Duchenne. This is particularly interesting because

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[99] Dubowitz, "Screening for Duchenne," 294.

although histology has taken a back seat to molecular techniques, it is still an acceptable way to diagnose MD. In their recommendations to physicians, Bushby et al. concede that when molecular testing is not readily available, a muscle biopsy can be performed (although they do argue that it is "mandatory" to conduct genetic tests on the tissue sample to confirm an MD diagnosis). However, if a doctor orders a genetic test, but the results do not reveal a known, MD-associated mutation, a muscle biopsy is sufficient to diagnose the disease.[100] This continued, if begrudging, acceptance of tissue analysis even in light of new molecular diagnostic assays is probably a safeguard for the instances when a patient symptomatically and histologically presents with muscular dystrophy but does not have a known mutation associated with the disease. When this conflict between two sanctioned ways of knowing occurs, however, scientists fall back on genetics and classify their findings as a novel disease. A case may present exactly like DMD at the clinical, microscopic, and enzymatic levels, but the authority of molecular technologies means that it is ultimately not classified as the Duchenne type of MD. Such a distinction would not have been possible before the naissance of high-throughput sequencing technologies or the identification of the dystrophin gene. Individualized sequencing, then, not only paved the way for another method of diagnosis, but further specified the pathological nature of Duchenne (and other forms of) muscular dystrophy.

Ultimately, the history of MD diagnosis demonstrates that at some level, disease classification is arbitrary; these categories of diseases are certainly not "natural" or "inevitable." Instead, the current classifications of MD exist because muscular

[100] Bushby et al., "Diagnosis and Management," 81.

dystrophy is one of Hans-Jörg Rheinberger's "epistemic things," which are "material entities or processes – physical structures, chemical reactions, biological functions – that constitute the objects of inquiry. As epistemic objects, they present themselves in a characteristic, irreducible vagueness. This vagueness is inevitable because, paradoxically, epistemic things embody what one does not yet know."[101] On the one hand, muscular dystrophy is the "target" of inquiry, yet it is simultaneously defined in relationship to the scientists' concerns. [102] As such, how biomedical professionals define the disease is intimately dependent on how they are influenced by the world around them.

[101] Hans-Jörg Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube* (Stanford: Stanford University Press, 1997), 28.
[102] Rheinberger, *Toward a History*, 225.

Conclusion

After describing his histological findings, Meryon prefaced his hypotheses about the pathological origin of this unfamiliar disease with the following comment: "In considering the complex phenomena of disease in the human body, the great difficulty is manifestly that of singling out one only of the antecedents which concur to produce a given effect, and to point to that as the physical cause."[103] Biomedical researchers are still bedeviled by the same challenge nearly two centuries later. Yet while scientists continue their search for increasingly more "accurate" biological truths, it is worthwhile to pause and consider why said "truths" exist, or why they are constructed in certain ways. Again, this is not to make any anti-science claims. This mode of analysis does *not* argue, for example, that scientists are incorrect in saying that the dystrophinopathies are linked to, or even caused by, mutations in the *dystrophin* gene. Rather, considering how and why certain "truths" are crystallized is simply a way of recognizing that cultural processes have profoundly shaped how scientists understand nature. As Lock and Nguyen summarize, "The approach to human disease that characterizes biomedicine was neither an inevitable development nor the result of an orderly uncovering of the 'true' causes of illness. Biomedicine is the product of particular historical circumstances."[104] This, ultimately, is the notion of "biosociality."

What, then, can be said about the biosocial nature of muscular dystrophy? An incredible amount – far more than has been covered in this thesis. However, it is clear that underlying the entire history of MD research is a narrative around emerging

[103] Meryon, "On Granular," 79.
[104] Lock and Nguyen, *An Anthropology of Biomedicine*, 32.

technologies. The development of microscopy, CK serum assays, and genetic tests, each of which emerged from their own sociopolitical contexts that are worth exploring with an STS lens, not only created and reflected changing attitudes about *how* to know, but also about what there *is* to know. These technologies quite literally changed what muscular dystrophy *is* at a fundamental level, as "muscular dystrophy" exists as a category only because biomedical professionals have declared it so.

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